Screening for Cervical Cancer

July 16, 2012

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Abstract

Background: Cervical cancer screening using Pap smears is a well-accepted intervention. Studies from across Canada and around the world show 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.

Purpose: To synthesize research evidence on cervical cancer screening to inform revisions to the Canadian Task Force Recommendations which were last updated in 1994.

Data Sources: For the Key Questions, Medline, EMBASE and Cochrane Central were searched from 1995 to April 2012. For the Contextual Questions the same databases were searched from 2005 to February 2011. Grey literature was searched in February 2011 for recent relevant Canadian data.

Study Selection: Eligible studies included women aged 15 to 70 years with a history of sexual activity. The screening methods included conventional Pap tests, liquid-based Pap tests and HPV DNA tests. For the Key Question on screening effectiveness the study designs included systematic reviews, randomized controlled trials (RCTs), and observational studies with comparison groups. For the Key Question on harms and the Contextual Questions any study design was considered. All included studies were in English or French.

Data Abstraction: To identify papers considered for Key Questions, titles and abstracts were reviewed in duplicate. Any article marked for inclusion by either reviewer went on to full text rating. Full text inclusion, quality assessment and data extraction were done by two people. For Contextual Questions and grey literature, inclusion screening and abstraction were done by one person.

Results: One RCT had data on both incidence of and mortality from cervical cancer to answer the question of screening effectiveness. Compared to no screening, a single lifetime screen by either HPV or cytology significantly reduced the eight year follow-up mortality rate by 35% (RR 0.65, 95% CI 0.47-0.90, p=0.01). Considering the tests separately, a single lifetime screen by HPV test significantly reduced eight year follow-up mortality (age adjusted HR 0.52, 95% CI 0.33-0.82, p=0.005); whereas a single lifetime cytology test had a positive but not significant impact on eight year mortality (age adjusted HR 0.89, 95% CI 0.62-1.28, p=0.53).

With respect to cervical cancer incidence, the RCT showed screening by a single lifetime HPV or cytology test had little influence after eight years of follow-up compared to no screening (RR 1.12, 95% CI 0.91-1.39, p=0.28). This finding was repeated with each screening test independently (HPV HR 1.05, 95% CI 0.77-1.43, p=0.76; cytology HR 1.34, 95% CI 0.99-1.81, p=0.06). Conversely, evidence from the observational studies, conducted in areas where organized screening programs are in place and/or where women are likely to participate in recurrent opportunistic screening, demonstrated positive effects of cytology. The pooled analysis of 12 case-control studies showed a significant protective effect of cytology screening (OR 0.35, 95% CI 0.30-0.41, p<0.00001). Similarly, the results of a large cohort study indicated a

significant benefit of cytology testing compared to no screening on the outcome of cervical cancer incidence (RR 0.38, 95% CI 0.23-0.63, p=0.0002).

The same RCT mentioned above also examined the impact of screening on the incidence of stage II or higher cancer. Screening by a single lifetime HPV or cytology test showed a decrease in advanced cervical cancer after eight years (RR 0.56, 95% CI 0.42-0.75, p=0.0001). However, when tests were examined separately and were compared to no screening, HPV testing significantly decreased the incidence of advanced cervical cancer (HR 0.47, 95% CI 0.32-0.69, p=0.0001) while cervical cytology showed a non-significant reduction for this outcome (HR 0.75, 95% CI 0.51-1.10, p=0.14).

Two RCTs compared HPV testing with conventional cytology on outcomes of cervical cancer incidence and/or mortality. In one study, the HPV test performed significantly better, reducing the risk of mortality by 41% (RR 0.59, 95% CI 0.39-0.91, p=0.02) and the risk of advanced cervical cancer by 37% (RR 0.63, 95% 0.42-0.95, p=0.03) when compared to cytology. Combining the results from the two RCTs the HPV test was also superior to cytology for reducing the incidence of cervical cancer with three to eight year follow-up (RR 0.78, 95% CI 0.62-0.99, p=0.04).

Another RCT investigated the impact of computer-assisted screening compared to conventional cytology screening on cervical cancer mortality and incidence. With four to eight year follow-up, results showed no difference between the two slide reading techniques on either outcome (mortality RR 1.10, 95% CI 0.63-1.94, p=0.73; incidence RR 0.99, 95% CI 0.76-1.29, p=0.96).

Studies that examined Pap test screening intervals consistently showed: the strongest protective effect with the shortest interval and decreasing benefits with longer intervals; intervals of five years or less offered substantial protection against cervical cancer, but even intervals of 10 or 15 years offered significant protection; and regardless of the specific interval, any screening was better than none.

There is no conclusive evidence for establishing optimal ages to start and stop cervical screening. A few studies looked at participation trends noting very high screening attendance among women ages 20 to 35 years, high attendance among women ages 35 to 49 years, and consistently lower participation in older groups of women. Despite high participation among younger women the benefit of screening women below age 30 is unclear. It appears that exposure to cytology screening provides a substantial protective effect in women 30 years and older and there is some evidence that this protective effect remains strong in women over 65 years.

The Key Question search for harms of cervical screening (overdiagnosis, false-positives, colposcopy rate, anxiety/depression, and sexual dysfunction) found evidence only for false-positives of cytology. There was wide variation in the rates reported in six studies (e.g., from <1% for all diagnoses to 23% for LSIL+, and from 4% to 19% for PAPNET read slides). Given the differences in this evidence it is difficult to draw solid conclusions about false-positives. A Contextual Question on the harms of

cervical screening and pre-cancer found no direct evidence for overdiagnosis but located studies reporting false-positive rates and specificity for cytology and HPV tests. In younger women false-positive rates are highest and test specificity is lowest. It appears cytology tests are more specific than HPV tests with most differences occurring among younger women.

Limitations: For the question on the effect of screening on mortality, all the data came from one RCT in rural India in which a single test was offered to a population of previously unscreened women who were followed for eight years. No studies reported on all-cause mortality and no studies met the inclusion criteria that compared the effectiveness of liquid-based versus slide-based screening or reflex HPV testing versus conventional cytology. Most of the evidence used to answer the other Key Questions was found in case-control studies rated low or very low using the GRADE approach for quality assessment. We searched only for papers in English or French.

Conclusions: The evidence supports the conclusion that screening offers protective benefits and is associated with a reduction in incidence of and mortality from invasive cervical cancer. An RCT in India showed that even a single lifetime HPV test significantly decreased incidence of and mortality from invasive cervical cancer compared to no screening. Cytology screening was shown to be beneficial in a cohort study that found Pap testing significantly reduced the incidence of invasive cervical cancer compared to no screening. Pooled evidence from a dozen case-control studies also indicated a significant protective effect of cytology screening. This review found no conclusive evidence for establishing optimal ages to start and stop cervical screening, or to determine how often to screen; however the evidence suggests substantial protective effects for screening women 30 years and older and for intervals of up to five years.

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APPENDICES

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List of Acronyms

ASC-US	Atypical Squamous Cells of Undetermined Significance
CADTH	Canadian Agency for Drugs and Technologies in Health
CC	Conventional Cytology
CCHS	Canadian Community Health Survey
CI	Confidence Interval
CIN	Cervical Intraepithelial Neoplasia (1, 2, 3)
CQ	Contextual Question(s)
CTFPHC	Canadian Task Force for Preventive Health Care
GP	General Practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HADS	Hospital Anxiety and Depression Scale
HC-II	Hybrid Capture II (HPV Test)
HPV	Human Papillomavirus
HR	Hazard Ratio
HSIL	High Grade Squamous Intraepithelial Lesions
ICER	Incremental Cost Effectiveness Ratio
IV	Inverse Variance
KQ	Key Question(s)
LBC	Liquid-Based Cytology
LEEP	Loop Electrosurgical Excision Procedure
LLETZ	Large Loop Excision of the Transformation Zone
LSIL	Low Grade Squamous Intraepithelial Lesions
MH	Mantel-Haenszel
NICU	Neonatal Intensive Care Unit
NNTH	Number Needed to Treat to observe Harm
OR	Odds Ratio
PCCSI	Pan-Canadian Cervical Screening Initiative
PCR	Polymerase Chain Reaction (HPV Test)
QALY	Quality Adjusted Life Years
RCT	Randomized Controlled Trial
RR	Risk Ratio
SE	Standard Error
TOMBOLA	Trial of Management of Borderline and Other Low-grade Abnormal smears
UK	United Kingdom
US	United States
USPSTF	United States Preventive Services Task Force

Chapter 1: Introduction

Purpose

This is a revision of the Canadian Task Force for Preventive Health Care (CTFPHC) recommendations for cervical cancer screening, last updated in 1994.[1]

Cytology screening is a well-accepted intervention for the prevention and early identification of cervical cancer. Many recommendations are for yearly screening[2] and "the annual Pap smear" has become a regular part of medical care in Canada. However, many other countries (e.g., US, Finland, Netherlands, UK, France, Spain, Italy) recommend longer screening intervals and/or start testing at a later age.[3-9] 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 women's preferences for longer screening intervals, the question arises of how few Pap tests can be done and how late they can be started without losing the preventive benefit.

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 link 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 to organized screening.[10]

In the last five years, with better understanding of the infectious nature of the disease and a change in screening test technology, there has been pressure to amend screening policy. Many Canadian pathology laboratories have switched from smear-based technology to liquid-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 work-pressures on cytotechnologists.[10] Given these changes we need to understand how liquid-based testing affects the process of screening and to what extent it impacts the diagnostic yield and performance measures of the Pap test.

There is recognition that particular populations have low Pap test participation rates and high incidence of cancer; this includes populations from countries that are a source of substantial immigration to Canada.[11] There are questions about how to effectively reach out to immigrant women and other groups with low Pap test rates and high risk for cervical cancer to increase screening uptake.

Screening efforts must also consider the influence of new HPV technologies. There are questions about the need for Pap tests in young women immunized with the HPV vaccine and the role of HPV testing in deciding whether cervical cancer is likely to develop.

Questions like those about the reach and uptake of screening programs and the impact of HPV technologies need answers in the Canadian context. The Canadian Partnership Against Cancer is supporting the Pan-Canadian Cervical Screening Initiative (PCCSI) to work on these and other relevant issues and the CTFPHC has partnered with PCCSI to develop a consistent approach to cervical cancer screening.

Condition Background

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.[12]

Pre-cancerous lesions, otherwise known as dysplasia, cervical intraepithelial neoplasia (CIN), or intraepithelial lesions, are epithelial proliferations of atypical cells that form 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 where squamous cells cover glandular cells as a result of hormonal changes during the lifetime. Some pre-cancerous lesions only involve the basal cells near the basement membrane (CIN 1). Other pre-cancerous lesions can involve half (CIN 2) or the whole (CIN 3) thickness of the epithelium which increases the risk that the lesions will progress to cancer over time.

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, 15% are adenocarcinoma, a small percentage are a combination of these types (adenosquamous carcinoma), and the remainder are rarer types (e.g., small cell neuroendocrine).[13]

An earlier classification of Pap test results describing dysplasia has largely been superseded by Bethesda terminology, which classifies smears as atypical squamous cells of undetermined significance (ASC-US), low grade squamous intraepithelial lesions (LSIL), and high grade squamous intraepithelial lesions (HSIL).[14] The histology classification system is similar, but is based on the structural detail available in biopsy material.[15] Table 1 presents the comparative terminology of the three classification systems.

Prevalence, Incidence and Burden of Disease

Recent global estimates indicate cervical cancer is the third most common form of cancer diagnosed in women and the fourth leading cause of death due to cancer in women.[16-18] In Canada, in 2006 there were 1,400 new cases of invasive cervical cancer and 375 women died from this disease.[19,20] A modest decrease in national incidence and mortality rates (1,300 new diagnoses and 350 deaths) were projected for 2011.[19] Since the mid-1970s the decline in

incidence rates has slowed, particularly among women under 50 years.[21] The 2011 age-standardized estimated incidence rate of cervical cancer in Canada is 7 per 100,000 (down from 14.2/100,000 in 1979 and 21.6/100,000 in 1969) and for mortality it is 2 per 100,000 (down from 4.2/100,000 in 1979 and 7.4/100,000 in 1969).[19,22,23]

Etiology and Natural History

Cervical cancer develops as a result of loss of cell cycle regulation which in turn is caused by incorporation of parts of the HPV (i.e., E6 and E7 regions) into the nucleus of an epithelial cell. There are over 100 HPV types; more than 40 of them affect the anogenital tract with 12 considered to be oncogenic (HPV-16, 18, 31, 33, 35, 45, 52, 58, 39, 51, 56, 59) and another 13 considered possibly oncogenic.[24,25] Oncogenic HPV is the etiologic agent for cervical cancer and HPV-16 and HPV-18 are responsible for 70% of all cervical cancers.[26,27] Over 80% of sexually active women will be infected with genital HPV at some point in their lifetime.[28] The peak incidence and prevalence of infection occurs in the late teenage years with a progressive decline and then stabilization in HPV prevalence rates at 30 years of age. Transient HPV infections are inconsequential whereas persistent infections with oncogenic HPV are associated with increasing rates of dysplasia and ultimately cervical cancer.[11]

Risk Factors

The risk factors for cervical cancer and infection with oncogenic HPV are similar. HPV infection has been associated with certain sexual behaviours including: early age of first intercourse,[29] multiple sexual partners,[29,30] and a male partner with a history of multiple partners.[29] While an oncogenic HPV infection is the cause of cervical cancer, this alone may be insufficient for the disease to manifest.[18] Additional conditions or behaviours may need to be present to stimulate the incorporation of HPV DNA into the host cervical cell. Although not a definitive list, some of these co-factors include: advancing age,[29] immunosuppression (e.g., HIV),[31] smoking,[30,32,33] multiparity,[30] and long term use of oral contraception.[34]

Consequences of Untreated Pre-cancer

An unethical observational cohort study took place in New Zealand several decades ago.[35] Of the 1,063 women diagnosed with CIN 3 (severe dysplasia or HSIL) between 1955 and 1976, 143 were not offered treatment between 1965 and 1974. Thirty-year follow-up data showed, of the women who were not treated, 31.3% (95% CI 22.7-42.3) developed invasive cervical or vaginal cancer. In the group that had appropriate treatment, only 0.7% (95% CI 0.3-1.9) went on to develop cancer.

Rationale for Screening

Cervical cancer is a treatable disease and tertiary interventions have contributed to reductions in cervical cancer mortality rates.[36] However when these downstream activities are combined with preventive efforts, there is a greater impact in terms of lives saved. There is widespread acceptance that regular cervical cancer screening is the single most important public health

strategy to reduce cervical cancer mortality. Cervical cytology identifies pre-cancer which, if treated, prevents the occurrence of cancer or leads to identification of the cancer at an earlier stage permitting more effective treatment.

Implementation of the Pap test in the 1950s was never evaluated using a randomized study. Rather ecological data has consistently demonstrated that in regions or countries with cervical cancer screening programs, the mortality from invasive cervical cancer decreased as cervical cancer screening became more widespread.[37-40] In the Nordic countries where organized, nationwide screening programs are well established, cervical cancer mortality has shown a dramatic decrease. For example, Iceland began a screening program in 1964 and achieved full coverage by 1969. Overall age adjusted mortality rates dropped by 77% in Iceland between 1966-1970 and 1986-1999.[41,42] Finland and Sweden have also implemented national screening programs with declines in mortality of 50% and 34% respectively since the 1960s.{22030} It should be noted however that while organized screening programs may be largely responsible for reductions in cervical cancer incidence and mortality in these countries, some of the success must still be attributed to opportunistic screening, particularly in younger women, which remains common practice.[39]

In Canada, cervical screening became available in the 1950s, but uptake was variable. By the 1970s there was greater reduction in cancer incidence and mortality in regions where more screening efforts were occurring.[44,45] Today, although organized programs for cervical cancer screening have been implemented in a few provinces, Canada does not have fully coordinated and monitored programs in all 13 provinces and territories. Instead, a large proportion of women undergo opportunistic cervical screening which means individuals request or are offered a Pap test when visiting their doctor or health professional for other services such as physical exams.[46] Whether in the context of organized or opportunistic approaches, screening uptake is high in most areas. Statistics Canada data for 2005 indicated 72.8% of women aged 18 to 69 years had at least one Pap smear within the previous three years.[47] A more recent national report (with data for seven provinces) indicated the percentage of women aged 20 to 60 years who had at least one Pap test between 2006 and 2008 ranged from 63.8% to 75.5% (uncorrected for hysterectomy) and from 72.4% to 79.6% (hysterectomy corrected).[48]

Screening Strategies

The Pap test is a screening strategy used to retrieve cells from the cervix which are sent to a cytology lab for testing. For a conventional Pap test the cervical sample is smeared directly onto the microscope slide by the health care professional who performs the test. For liquid-based testing, which is becoming more common,[49] the health care professional puts the collected sample into a preservative solution which is then sent to the cytology lab to be prepared by a technician for examination. A recent RCT involving Canadian women aged 30 to 69 showed for the outcome of CIN2+ the conventional Pap test had sensitivity of 55.4% (95% CI 33.6-77.2) and specificity of 96.8% (95% CI 96.3-97.3).[50] For the same outcome, pooled estimates from a

meta-analysis that included North American research put the sensitivity of liquid-based testing at 57.1% (95% CI 46.3-67.2) and the specificity at 97.0% (95% CI 93.8-98.6).[51]

The persistence of an oncogenic HPV increases the likelihood of progressive disease.[52] As such, the HPV DNA test has been evaluated as a possible screening strategy for cervical cancer. This test is not useful for routine screening of younger women given that HPV is common in this population and most of these infections will clear up on their own. However the HPV test is suitable for women aged 30 years and older, who are at increasing risk of cervical cancer and in whom HPV is less common, possibly persistent, and more likely to be a sign of pre-cancerous or cancerous disease.[53] While cytology looks for the presence of abnormal cells that may lead to cervical cancer, HPV DNA testing takes a precursor perspective and looks for evidence of the virus that causes abnormal cells. Primary HPV testing is performed on swabs taken from the cervix in much the same way as a Pap smear is taken. Reflex HPV testing is performed on the remaining aliquot of liquid-based cytology samples after abnormalities are detected. Findings from the same Canadian-based RCT mentioned above put the sensitivity of HPV testing for CIN2+ at 94.6% (95% CI 84.2-100) and the specificity at 94.1% (95% CI 93.4-94.8).[50]

Outcomes of cervical cancer screening such as identification of pre-cancers or early invasive disease and decreased mortality must be put into the context of costs to the individual and the health care system, including costs related to overdiagnosis and over-treatment. Consideration of benefits, harms and costs is complicated by variations in risk factors, type and stage of cancer. "Among 18 to 20 year old women screened through the Alberta Cervical Cancer Screening Program, approximately 15% receive at least one abnormal result. And while only 0.2% of cervical cancer cases occur among females younger than 21 years, 10% of all colposcopy referrals are among females in this age group."[54(p. 8)] Positive findings on screening tests can 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. Management of CIN reduces incidence of later stage disease but not all untreated CIN progresses to cancer which means many women undergo unnecessary treatment procedures.[55]

Interventions and Treatments

Roughly 8% of Canadian women are found to have varying degrees of abnormality which requires follow-up with a repeat Pap test, an HPV test, or a colposcopy exam which can be used as a diagnostic test.[56] 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. For this procedure, a microscope is used to enlarge the view of the cervix by five to 15 times. 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 CIN 3 lesions in order to prevent progression to cervical cancer.[15]

Removal of pre-cancer usually involves outpatient therapy using excisional or destructive techniques including freezing (cryotherapy), evaporation of abnormal cells (laser), removal of abnormal cells with a hot wire through a loop electrosurgical excision procedure (LEEP or LLETZ), or surgical excision (cold knife cone biopsy). Close follow-up over several years is recommended to ensure that the disease has been successfully eliminated.[15,57]

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 and PET scan. 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 (surgical removal of the cervix) and pelvic node dissection. As treatment becomes more radical, side effects become more complex. However, the goal is to cure the patient of the cervical cancer. Again, close follow-up is required to determine if the disease has been eliminated, to detect recurrence, and to deal with complications and/or survivorship issues.[58]

Current Clinical Practice Guidelines

Updating its 1996 recommendations,[59] in 2003 the United States Preventive Services Task Force (USPSTF) reported there was sufficient good quality evidence to recommend cervical cancer screening with cytology for all women who have been sexually active and who have a cervix.[60] The question of whether or not to screen was considered answered and subsequent USPSTF reviews[61,62] have focused on other issues such as when to begin cervical screening, screening for older women, screening for women who have undergone hysterectomy, new technologies for cytology, and the role of HPV testing. In March 2012 the USPSTF released updated cervical screening guidelines.[63] Assigning a high level of certainty to the supporting evidence (which unlike this review included CIN outcomes and designs with no comparison groups), the USPSTF currently recommends cytology screening every three years for women aged 21 to 65 and/or co-testing (cytology plus HPV testing) every five years for women aged 30 to 65. Considering the balance of benefits and harms, the USPSTF determined there was sufficient evidence to recommend against screening women less than 21 years of age and against using HPV testing either alone or as part of a co-testing approach to screen women less than age 30. Sufficient evidence was also found to recommend discontinuing testing women older than age 65 who have had adequate recent screening with normal Pap tests and who are not otherwise at high risk for cervical cancer. The USPSTF further concluded there was sufficient evidence to recommend against routinely screening women who have had a total hysterectomy for benign disease.

In Canada, several guidelines of varying quality have addressed various aspects of the cervical cancer screening program. Since health care is primarily a provincial responsibility, most guidelines are provincial in scope. On a national level, a Health Canada Programmatic Guideline

for screening for cancer of the cervix was published in 1998. The goal of this document was to address quality management in the cervical screening program in each province. While this is the only national document available, the recommendations are described as being "based on opinion and expertise" of the panel of members. For this reason and the fact that the document is more than a decade old, it will not be discussed here.[15]

Previous Review and CTFPHC Recommendations

The CTFPHC recommendations were last updated in 1994.[1] At that time, annual screening was recommended following initiation of sexual activity or at age 18 years. After two normal screens, testing was recommended every three years to age 69 years. More frequent screening intervals were suggested for women who presented with the following risk factors: sexual debut occurred at less than age 18 years, multiple sexual partners, smoking, or low socioeconomic status.

Chapter 2: Methods

Analytic Framework and Key Questions

The Analytic Framework and Key Questions are presented in Figure 1. The population of interest is asymptomatic women, aged 15 to 70 years, who are or have been sexually active. Much of the recent research has focused on reductions in precursor lesions. These lesions are more common and present earlier outcomes for measurement during trials, thus reducing the sample sizes and duration of follow-up needed. Based on these advantages many cervical screening trials use precursor lesions as their end-points. However, evidence from the New Zealand trial suggests only a third (31%) of cases with precursor lesions will advance to invasive cancer.[35] The Working Group took the view that the CTFPHC methods require identification of the reduction of incidence and mortality as the critical outcomes of screening. Consequently the outcomes of interest for this review are cervical cancer or all-cause mortality and incidence of invasive cervical cancer.

The Key Questions (KQ) considered for this review include:

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 cytology screening?
- KQ1c. Does computer-assisted screening reduce incidence of or mortality from invasive cervical cancer compared to conventional cytology screening?
- KQ1d. How does varying the screening interval affect incidence of or mortality from invasive cervical cancer?
- KQ1e. How does varying the age at which screening is started or stopped reduce incidence of or mortality from invasive cervical cancer?

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

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

The Contextual Questions (CQ) considered for this review are:

CQ1. What are the harms of cervical cancer screening for pre-cancer (i.e., overdiagnosis and false-positive rates, specificity)?

CQ2. What are the harms of treatment of cervical cancer? Harms include: (a) harms of colposcopy, (b) harms of biopsy: cone biopsy (immediate and late; pre-term labour, miscarriage) and LEEP/LEETZ (immediate and late effects), (c) harms of treatment of cervical cancer: total hysterectomy (incontinence, infection, hospitalization) and radiotherapy.

CQ3. What is the effect of cervical cancer screening in subgroups: reduction in mortality and/or morbidity, and harms? Subgroups include: (a) Aboriginal populations, (b) rural populations, (c) immigrants, (d) pregnant women, (e) women who have sex with women, (f) immunocompromised women (e.g., with HIV), (g) women who had a hysterectomy, (h) women who received the HPV vaccination, and (i) women who have multiple partners or a change in partners. 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?

CQ4. What are the resource implications and cost effectiveness of cervical cancer screening in Canada?

CQ5. What are patients' values and preferences regarding cervical cancer screening?

CQ6. What process and outcome performance measures or indicators have been identified in the literature to measure and monitor the impact of cervical screening?

CQ7. What is the evidence of the value of organized programs for cervical cancer screening?

CQ8. What is the evidence of using different categories of health care professionals to perform Pap smears in medical or different settings?

CQ9. What is the evidence of the value (acceptability, participation rates) of women self-sampling for HPV testing?

Search Strategies

Three separate search strategies were conducted using Medline, EMBASE and Cochrane Central databases. For KQ1 the search focused generally on cervical cancer screening, included both RCTs and observational studies, and covered the period from 1995 to April 2012 (see Appendix 1). The search for KQ2 focused on adverse events associated with cervical cancer screening, included any study design, and covered the period from 1995 to April 2012 (see Appendix 1). The third search focused on the Contextual Questions, included any study design, and covered the period from 2005 to February 2011 (see Appendix 1). All three search strategies combined subject heading and text word terms for cervical cancer and screening, adapted for each database. All citations were uploaded to a web-based systematic review software program[64] for screening and data extraction. A fourth search of websites was conducted in February 2011 to find grey literature with relevant Canadian statistics (see Appendix 2).

Study Selection

Eligible studies included women aged 15 to 70 years who were or had been sexually active. The cervical cancer screening methods of interest included conventional Pap tests, liquid-based Pap tests and HPV DNA tests. For the effectiveness of screening for cervical cancer (KQ1) the study designs included systematic reviews, randomized controlled trials (RCTs), and observational studies with comparison groups. Any study design was considered to answer the harms questions

(KQ2) and the Contextual Questions. All included studies were in English or French. Grey literature was included if recent relevant national Canadian data were reported. The list of inclusion/exclusion criteria for this review is provided in Table 2.

External Review

Before beginning the review, the protocol was reviewed by the Cervical Cancer Working Group which included members of the CTFPHC, Public Health Agency of Canada staff, and key stakeholder groups. The revised protocol was sent to external reviewers with systematic review methodology and/or cancer content expertise (see Appendix 3); feedback was received and revisions were made. A draft of the evidence review was sent to the Cervical Cancer Working Group, and then the revised review went out to external experts not affiliated with the CTFPHC (see Appendix 4).

Quality Assessment, Data Abstraction and Analysis

The titles and abstracts of papers considered for the Key Questions were reviewed in duplicate by members of the synthesis team; any article marked for inclusion by either team member went on to full text rating. Full text inclusion, quality assessment and data extraction were done by two people. All disagreements were resolved through discussions rather than relying on a particular level of kappa score to indicate when discussions were no longer necessary. The inclusion results were reviewed by a third person. Data were extracted by two people using a standard format. The exceptions to this process were studies related to the Contextual Questions and grey literature, for which title and abstract screening and data extraction was done by one person.

The strength of the evidence was determined based on the GRADE system of rating the quality of evidence using GRADEpro software.[65,66] This system of assessing evidence is widely used and is endorsed by over 40 major organizations including the World Health Organization, Centers for Disease Control and Prevention, and the Agency for Healthcare Research and Quality.[67] The GRADE system rates the quality of a body of evidence as high, moderate, low or very low; each of the four levels reflects a different assessment of the likelihood that further research will impact the estimate of effect (e.g., high quality: further research is unlikely to change confidence in the estimate of effect).[67] A GRADE quality rating is based on an assessment of five conditions: (1) limitations in study designs (risk of bias), (2) inconsistency (heterogeneity) in the direction and/or size of the estimates of effect, (3) indirectness of the body of evidence to the populations, interventions, comparators and/or outcomes of interest, (4) imprecision of results (few events/observations, wide confidence intervals), and (5) indications of reporting or publication bias. Grouped RCTs begin with a high quality rating which may be downgraded if there are serious or very serious concerns across the studies related to one or more of the five conditions. All groups of observational (e.g., case-control and cohort) studies begin with a low quality rating which may be further downgraded based on assessments of the same five criteria. All other types of evidence are assigned a very low quality rating. For this review,

key data were entered into the GRADEpro software along with the quality assessment ratings to produce two analytic products, the GRADE Evidence Profile Tables and the GRADE Summary of Findings Tables (presented in the Evidence Sets).

The Cervical Cancer Screening Working Group rated each of the outcomes and potential harms of screening using the GRADE process.[66] GRADE suggests a nine point scale (1 to 9) to judge the importance of the outcomes and harms. The upper end of the scale (7 to 9) identifies outcomes of critical importance for clinical decision making. Rankings of 4 to 6 represent outcomes that are important but not critical, while low ranked items (1 to 3) are deemed of limited importance to decision making or to patients. This rating process identified cervical cancer incidence, cervical cancer mortality and all-cause mortality as critical primary outcomes and overdiagnosis as a critical harm associated with screening. Table 3 lists the rankings for the outcomes and harms considered in this review in terms of their importance for clinical decision making.

Arriving at a GRADE rating for a body of evidence requires a preliminary assessment of the risk of bias or study limitations for the individual studies. The RCTs were assessed using the Cochrane Review Manager Risk of Bias tool.[68] All case-control studies and the one cohort study with exposed and unexposed groups (a requirement embedded in the assessment tool) were quality appraised with the Newcastle-Ottawa Scale.[69] Information to determine the quality of evidence was abstracted in duplicate from the primary methodology paper for each study. The two team members extracting the data were blind to each other's ratings. In cases of disagreement, final decisions were determined by consensus after consultation with a third reviewer. Tables 4 to 6 summarize the results of these assessments.

For each study used to answer the Key Questions, review team members extracted data about the patient population, the study design, analysis and results. The characteristics of the included studies are reported by review question in Tables 7 to 12.

For consistency the risk ratios (RRs) and hazard ratios (HRs) are reported for the screened group(s) with the unscreened group as the referent. For the case-control studies, even though study authors reported odds ratios (ORs) for the incidence of cervical cancer, technically the estimates of effect were for the participants' exposure to cervical screening. Consistent with how we reported the RRs and HRs, in this review all ORs are less than one which relates to the protective effect of screening. Some studies reported ORs in the opposite direction or provided ORs for the longest screening interval (KQ1d); in these cases we inverted the OR and the confidence interval (CI) to get results for the screened population or the group with the shortest interval. These data were used for calculations and presentation of the findings within the body of the review and the Evidence Sets.

Findings presented throughout the body of this review are rounded and/or reported to the second decimal. However, at the request of the CTFPHC, where possible we used four decimals in our calculations and in the presentation of results in the Evidence Sets. Most of the included studies reported findings with two decimals, but some offered none, one or three; none used four. The

additional decimals were generated using Open-Epi software[70] to compute unreported CIs, when inverting ORs and CIs, and/or when computing the natural logs and SEs required for Review Manager 5 (RevMan)[68] analyses. All of the ORs generated by RevMan match the ORs provided in the studies or computed by inversion. However, it is important to note that there were some minor differences between several of the numbers generated by RevMan and numbers given by authors or computed using Microsoft Excel[71] (usually with one of the confidence limits and at the second or third decimal). We investigated sources of and/or reasons for these discrepancies but did not arrive at a conclusive explanation. Possible explanations include rounding errors (particularly if studies provided one or no decimals), differences in statistical packages used to run analyses, and the potential for miscalculations in the original analyses and/or typos in the published manuscripts. Since we rely on RevMan to generate the overall estimates of effect, heterogeneity statistics, and forest and funnel plots, in this review we default to and report the values generated by RevMan.

With respect to data analysis, a single study[72] provided most of the data to inform KQ1. The study authors reported age adjusted HRs with 95% CIs for two comparisons (conventional cytology versus control; HPV testing versus control) and three outcomes of interest to this review (cervical cancer mortality, incidence of all cervical cancer, and incidence of stage II or higher cervical cancer). The analysis for the adjusted HRs was conducted using the generic inverse variance method. This method allows for log transformations of the data which were needed to account for the adjusted HRs. Using the adjusted HRs and CIs reported in the paper, the logs of the HRs and standard errors were calculated by the review team using Microsoft Excel 2010.[71] Analysis was then conducted using RevMan 5.[68] Forest plots were generated for each comparison and outcome. The study provided details that enabled conducting additional analyses of interest to the review that were not performed by the study authors. We combined the cytology and HPV testing groups into a single cervical screening group and compared this group against the control group on the same three outcomes mentioned above. The event rates were entered into RevMan and were used to compute the RR for each of the three outcomes. A fixed effects model was used given the analysis was being conducted on a single study (no heterogeneity). Forest plots were produced for each of the outcomes for the screening (combining cytology and HPV testing) versus no screening comparison.

For KQ1, the cytology versus no screening comparison was also analyzed using a meta-analysis of 12 case-control studies (13 data sets were entered because one study[73] reported separate results for organized and spontaneous screening). The meta-analysis was conducted using the generic inverse variance method which allows for log transformations of the data. Using the crude or adjusted ORs and CIs reported in the papers (as reported, inverted if not given for the screened group, and/or generated using Open-Epi software[70] if not reported) the natural logs of the ORs and CIs were used to calculate standard errors (SE) using Microsoft Excel.[71] The meta-analysis was performed using RevMan[68] with a random effects model proposed by DerSimonian and Laird.[74] The random effects model assumes the studies are a sample of all potential studies

and incorporates an additional between-study component to the estimate of variability. We used a test based on the deviations of the individual study estimates from the summary estimate of effect (the heterogeneity Chi^2) as our primary method to test for heterogeneity.[75] To supplement this test, RevMan calculates a statistic to quantify heterogeneity, the I^2, which describes the proportion of the variance in the point estimate due to heterogeneity rather than sampling error.[76] Although there are no strict rules for interpreting I^2 a rough guide is that an $I^2 > 50\%$ may represent substantial heterogeneity.[77] There was substantial heterogeneity across the pooled studies (Chi^2 $p<0.00001$, $I^2=76\%$). A forest plot was generated for the meta-analysis. RevMan was also used to produce a funnel plot of the 12 studies (13 data sets) to inform an assessment of publication bias. The funnel plot graphed the SE of the logs of the ORs against the ORs. Asymmetry in the funnel plot indicates the likelihood of publication bias (see Evidence Set 2).

GRADEpro software[65] was used to generate an Evidence Profile Table and a Summary of Findings Table for each of the three outcomes of interest [cervical cancer mortality, incidence of cervical cancer (or exposure to screening for case-control studies), incidence of stage II or higher cervical cancer] and incorporating the available comparisons [screening (HPV testing or cytology) versus no screening, HPV testing versus no screening, cytology versus no screening] (see Evidence Sets 1 to 3).

Data were available from two studies[72,78] to answer KQ1b (comparing HPV testing against conventional cytology). Only one study[72] provided data for the outcomes of cervical cancer mortality and incidence of advanced cervical cancer. For these two outcomes, the event rates and sample sizes for the HPV testing and cytology groups were entered into RevMan[68] and were used to compute the RR. A fixed effects model was selected given the analysis was conducted on a single study (no heterogeneity). Using RevMan, a forest plot was produced for each outcome. Both studies provided data for the outcome of incidence of cervical cancer. This data was pooled using a fixed effects model (given no significant heterogeneity between studies) to produce a combined RR for the outcome. A forest plot was generated. GRADEpro software[65] was used to produce an Evidence Profile Table and a Summary of Findings Table including the three outcomes of interest (cervical cancer mortality, incidence of cervical cancer, incidence of stage II or higher cervical cancer) for the comparison between HPV testing and cytology (see Evidence Set 4).

Data were available from one RCT[79] to answer KQ1c (comparing computer-assisted screening against conventional cytology screening) for the outcomes of cervical cancer mortality and incidence. For these two outcomes, the event rates and sample sizes for the computer-assisted and conventional cytology groups were entered into RevMan[68] and were used to compute the RR. A fixed effects model was selected given the analysis was conducted on a single study (no heterogeneity). Using RevMan, a forest plot was produced for each outcome. GRADEpro software[65] was used to produce an Evidence Profile Table and a Summary of Findings Table including the two outcomes of interest (cervical cancer mortality and incidence) for the comparison between computer-assisted and conventional cytology (see Evidence Set 5).

The data from the studies included for KQ1d on cervical cancer screening intervals could not be pooled. The details and findings of these studies are presented narratively below and in a summary table in Evidence Set 6.

The data from the studies included for KQ1e on ages to start and stop cervical cancer screening could not be pooled. The details and findings of these studies are presented narratively below and in a summary table in Evidence Set 7.

The data from the studies included for KQ2 on the harms (false-positives) of cervical cancer screening could not be pooled. The details and findings of these studies are presented narratively below and in a summary table in Evidence Set 8.

Chapter 3: Results

Summary of the Literature Search for Key Questions

Our search of EMBASE, Medline and Cochrane Central for systematic reviews, RCTs and observational studies located 15,145 potentially relevant citations (see Figure 2). At title and abstract screening 14,614 were excluded. A total of 531 papers were retrieved and assessed on inclusion criteria; 504 were eventually excluded (see on-line addendum for a list of excluded studies). The reference lists of all on-topic systematic reviews were searched to ensure that we had considered all relevant primary studies cited in those reviews that met our inclusion criteria. Following full text screening, three RCTs were included for data extraction for KQ1 and its sub-questions[72,78,79] and 21 observational studies (one study had four publications) were included for KQ1 and KQ2.[73,80-102]

In addition to our search of the literature we examined the 1996 and 2011 USPSTF evidence reviews[62,103] for relevant studies not captured in our search. Five studies[104-108] included in the 1996 USPSTF report[103] that pre-dated our search parameters were added to the evidence for this review. The 2011 USPSTF report[62] contained no studies that met our inclusion criteria that weren't already part of this review.

A total of 29 relevant studies (32 papers) were located and included to answer the Key Questions in this review. Some of the studies were used to answer more than one question.

Results for Key Questions

Key Question 1: What is the effect of cervical cancer screening on incidence of and mortality from invasive cervical cancer?

For KQ1 we found one RCT[72] and one cohort study[94] that provided cervical cancer incidence and/or mortality outcomes for women with a history of screening compared with women with no history of screening. Twelve case-control studies[73,80-86,104-107] were located that examined the odds of exposure to cytology screening among women with and without invasive cervical cancer. No studies reporting all-cause mortality were found. The characteristics of the 14 studies included for KQ1 are reported in Table 7.

Cervical Cancer Mortality

Evidence Set 1 provides the GRADE Evidence Profile Table (Table 13), the GRADE Summary of Findings Table (Table 14), and the forest plots (Forest Plots 1 to 3) generated for the outcome of cervical cancer mortality across three comparisons: (1) invited to screening with HPV testing or cytology versus no screening, (2) invited to screening with HPV testing versus no screening, and (3) invited to screening with cytology versus no screening.

One recent cluster randomized trial of moderate GRADE quality addressed KQ1.[72] Fifty-two villages in India, with a total of 131,746 healthy women ages 30 to 59 years, were randomly assigned to one of four groups. These groups received screening by a single lifetime HPV test (n=34,126), cervical cytology (n=32,058) or visual inspection by acetic acid (n=34,074), or standard care which involved giving women information on how to seek screening at local hospitals (n=31,488). In this review we focus on study results that address the two most relevant screening modalities for the Canadian context which are conventional cytology and HPV testing.

Compared to no screening, a single lifetime screen by either HPV or cytology significantly reduced the eight year follow-up mortality rate by 35% (RR 0.65, 95% CI 0.47-0.90, p=0.01). Considering the tests separately, a single lifetime screen by HPV test significantly reduced eight year follow-up mortality (age adjusted HR 0.52, 95% CI 0.33-0.82, p=0.005); whereas a single lifetime cytology test had a positive but not significant impact on eight year mortality (age adjusted HR 0.89, 95% CI 0.62-1.28, p=0.53).

Incidence of Invasive Cervical Cancer

Evidence Set 2 provides the GRADE Evidence Profile Table (Table 15), the GRADE Summary of Findings Table (Table 16) and the forest plots (Forest Plots 4 to 8) generated for the outcome of incidence of invasive cervical cancer (in RCT and cohort studies and for exposure to screening in case-control studies) across three comparisons: (1) invited to screening with HPV testing or cytology versus no screening, (2) invited to screening with HPV testing versus no screening, and (3) invited to screening with cytology versus no screening.

With respect to the impact of screening on the subsequent eight year incidence of cervical cancer, screening by a single lifetime HPV or cytology test did not influence cervical cancer incidence (RR 1.12, 95% CI 0.91-1.39, p=0.28). This finding was repeated with each test independently (HPV test: age adjusted HR 1.05, 95% CI 0.77-1.43, p=0.76; cervical cytology: age adjusted HR 1.34, 95% CI 0.99-1.81, p=0.06). The study's finding of a higher, though not significant risk for invasive cervical cancer among screened women is explained by the purposeful and active detection of disease in the screened groups and the fact that this was the first cervical screening procedure almost all of the eligible women had ever undergone (only 8 of the 131,806 women had been tested in the past). First time or prevalent screening will detect previously unknown disease that has accumulated from the past, while such disease in the unscreened group will only become known as it progresses to produce signs or symptoms which can take many years. If screening is accomplishing its goal of prevention, the incidence of advanced disease and disease-related mortality would be lower in the screened groups compared to the unscreened groups (as is demonstrated in the mortality outcome reported above and the incidence of stage II or higher disease outcome reported below).

On the other hand, the observational (case-control and cohort) studies that were conducted in nations or regions where organized screening programs are in place and/or in countries where women are likely to participate in recurrent opportunistic screening demonstrated significant protective effects of cytology screening.

Twelve very low GRADE quality case-control studies were found which examined exposure to cervical screening among women with invasive cervical cancer and women without the disease.[73,80-86,104-107] The pooled analysis showed the odds of having had at least one screening Pap test were higher among women without invasive cervical cancer (OR 0.35, 95% CI 0.30-0.41, p<0.00001). However, this result should be applied with caution given that the heterogeneity statistics for this group of studies were significant (Chi^2=50.98, df=12, p<0.00001; I^2=76%) and sensitivity analyses (based on differences in study designs, populations, interventions, organized/opportunistic approaches, length of exposure to screening) were not able to explain the variation. Although high heterogeneity presents a potential serious concern in the GRADE quality assessment,[109] the CTFPHC working group decided not to downgrade the evidence on inconsistency because the point estimates were similar across studies and all were in the same direction and the confidence intervals of most studies overlapped. Brief summaries of the 12 case-control studies are provided below.

Two studies were conducted in Canada.[81,106] The older study included 212 Toronto area residents, aged 20 to 69, admitted to a single large cancer centre, and diagnosed with cervical cancer between 1973 and 1976.[106] Five controls were obtained for each case; these women were matched to cases based on age (±10 years), neighbourhood, and type of dwelling. Results showed a protective effect of having had at least one Pap test in the previous 60 months (OR 0.37, 95% CI 0.27-0.50). The more recent study was conducted in Manitoba with 666 women aged 18 years and older, diagnosed with invasive cervical cancer between 1989 and 2001.[81] Five age (±1 year) and area of residence matched controls (n=3,343) were selected for each case. Consistent with the results of the previous study, there was a significant protective effect of having had a Pap test in the 6 to 60 month interval prior to diagnosis of the case (OR 0.36, 95% CI 0.30-0.43).

Four studies were conducted in Latin American countries.[82,84,104,107] In Colombia 204 newly diagnosed invasive cervical cancer patients reported to the Cali cancer registry between 1977 and 1981 and 73 patients diagnosed earlier (1971-1976) were compared to two sets of age matched (±2 years) controls.[104] Health centre controls were identified from outpatient facilities and neighbourhood controls were identified from within a block of where cases lived. The results showed cytology screening had an extremely strong protective effect (neighbourhood controls OR 0.10, 95% CI 0.05-0.19; health centre controls OR 0.04, 95% CI 0.02-0.08). Neighbourhood data was selected for the meta-analysis because this control group would likely be more representative of the general population than the group recruited from health centres. One of the studies conducted in Mexico looked at the screening histories of 397 residents of Mexico City, less than 75 years old, with newly diagnosed invasive cervical cancer.[82] An age stratified random sample (n=1,005) of female residents of Mexico City, between ages 25 and 80 was selected for the control group. Any lifetime spontaneous cervical cancer screening (except 12 months prior to a case diagnosis or 12 months preceding a control participant's interview) had a protective effect [adjusted (for age, age at sexual debut, number of normal births, number of sex partners,

socioeconomic level) OR 0.38, 95% CI 0.28-0.52]. In Guadalajara, Mexico 143 women, less than 70 years old, newly diagnosed with invasive cervical cancer were compared to 311 age matched (±3 years) hospital or health centre controls also residing in this metropolitan area.[84] Again, not including smears performed 12 months prior to case diagnosis, the results showed a significant protective effect of cytological screening (OR 0.30, 95% CI 0.21-0.42). In another study, researchers identified 759 women diagnosed with invasive cervical cancer in 1986 and 1987 from cancer treatment centres in Colombia, Costa Rica, Mexico and Panama.[107] Two age (five year groups) and hospital matched controls were selected for each case in Colombia and Mexico; one age and hospital matched control and one age and community matched control were selected for each case in Costa Rica and Panama. The findings indicated that any history of Pap testing offered a protective benefit (age adjusted OR 0.40, 95% CI 0.32-0.50).

The remaining case-control studies were conducted in a variety of locations including the United States,[86] Sweden,[80] Finland,[73] Japan,[85] Italy[105] and South Africa.[83] A small study in Pennsylvania compared the screening histories of 143 age (±5 years), neighbourhood, and race (black or white) matched pairs of cases (women diagnosed with invasive cervical cancer when they were less than 80 years old) and controls.[86] Excluding diagnostic Pap tests performed in the previous 12 months, any screening in the three year interval prior to case diagnosis had a protective effect (multivariate adjusted OR 0.32, 95% CI 0.15-0.69). In a nation-wide audit of Sweden's organized screening program, researchers examined the cytology histories of all women diagnosed with invasive cervical cancer (n=1,230) over a three year period (1999-2001) as well as a group of 6,124 population-based, age matched controls.[80] Excluding tests performed six months prior to case diagnosis, the results showed a protective effect of undergoing one or more Pap tests within the recommended interval (3.5 years for women 53 years and under; 5.5 years for women 54 to 65 years; 6.5 years for women 66 years and older) (OR 0.40, 95% CI 0.34-0.46). A Finnish study compared the lifetime screening histories (excluding tests performed 12 months prior to diagnosis) of 147 women aged 30 to 91 who were being treated for invasive cervical cancer between 1987 and 1994 with a population-based sample of 1,098 women with the same age range and who lived in the catchment area of the hospital where cases were being treated.[73] The study authors reported separate odds ratios for organized mass screening and spontaneous or opportunistic screening; these data were entered separately into the meta-analysis for this review. Any testing in the organized screening program offered a protective benefit (age adjusted OR 0.36, 95% CI 0.25-0.52). While the results were not as favourable as organized screening nor were they statistically significant, opportunistic screening did show some benefit (age adjusted OR 0.73, 95% CI 0.49-1.08). In a study conducted in Japan, 198 women 35 to 79 years who had been diagnosed with invasive cervical cancer were identified as cases.[85] For this analysis we only used the findings that pertained to the 65% of cases (n=129) with screen detected cervical cancer; we did not include the 69 outpatients who were diagnosed when they presented with gynecological symptoms. Two age (±5 years) and area matched controls were selected for each case. Excluding diagnostic tests, the results indicated any history of cervical screening had a strong protective effect (OR 0.14, 95% CI 0.08-0.26). Researchers in Italy

identified 121 women with newly diagnosed cervical cancer during 1978 in Milan using the Regional Hospital Discharge Diagnosis Information System.[105] Three controls were matched by age and hospital to each case; only married women were included and women with breast cancer were excluded. Findings indicated a non-significant benefit of a history of undergoing at least one Pap test (OR 0.61, 95% CI 0.36-1.04). One additional case-control study was conducted in the Western Cape of South Africa.[83] In this study, the lifetime screening histories of 524 coloured and African women less than 60 years old with newly diagnosed cervical cancer were compared with 1,540 age (decade), race, area of residence, and hospital matched controls. The results showed any opportunistic cervical screening offered significant protective benefits (multivariate adjusted OR 0.30, 95% CI 0.26-0.35).

The case-control evidence that cytology screening offers a substantial protective benefit is supported by results from a low GRADE quality cohort study of eligible women aged 25 to 69 years (n=116,022).[94] In this UK-based study, the incidence of invasive cervical cancer was significantly lower among women who participated in the country's comprehensive screening program (i.e., they had at least one Pap test in the preceding 6 to 66 months) than among women who were not screened during this interval (RR 0.38, 95% CI 0.23-0.63, p=0.0002).

Incidence of Stage II or Higher Cervical Cancer

Evidence Set 3 provides the GRADE Evidence Profile Table (Table 17), the GRADE Summary of Findings Table (Table 18), and the forest plots (Forest Plots 9 to 11) generated for the outcome of incidence of stage II or higher cervical cancer across three comparisons: (1) invited to screening with HPV testing or cytology versus no screening, (2) invited to screening with HPV testing versus no screening, and (3) invited to screening with cytology versus no screening.

The moderate GRADE quality cluster randomized trial conducted in India mentioned above also examined the impact of cervical screening on the incidence of advanced (stage II or higher) cancer.[72] Compared to the unscreened control group, women screened by a single lifetime cytology or HPV test showed a significantly lower risk of advanced cervical cancer (RR 0.56, 95% CI 0.42-0.75, p=0.0001). When tests were examined separately, HPV testing significantly decreased advanced cervical cancer compared to no screening (age adjusted HR 0.47, 95% CI 0.32-0.69, p=0.0001) while cytology produced a small non-significant effect (age adjusted HR 0.75, 95% CI 0.51-1.10, p=0.14). In summary, cervical screening decreased the subsequent eight year mortality rate and incidence of advanced staged cancer in this one study and it appears the single lifetime screen using HPV testing was the test contributing these advantages.

Key Question 1a: Do liquid-based methods of cytology reduce incidence of or mortality from invasive cervical cancer compared to slide-based techniques?

For sub-question KQ1a that looked at the comparison between liquid-based and slide-based techniques, we did not find any studies that examined the outcomes of cervical cancer incidence or mortality (cervical cancer or all-cause) that met the inclusion criteria for this review.

Key Question 1b: Does either primary or reflex HPV testing reduce incidence of or mortality from invasive cervical cancer compared to conventional cytology screening?

For sub-question KQ1b we found two RCTs[72,78] that reported on the outcomes of cervical cancer incidence and/or mortality. Both studies looked at primary HPV testing compared to conventional cytology. No studies were found that met the inclusion criteria for this review that examined reflex HPV testing compared to conventional cytology. No studies reporting all-cause mortality were found. The characteristics of the two included studies are reported in Table 8. Evidence Set 4 provides the GRADE Evidence Profile Table (Table 19), the GRADE Summary of Findings Table (Table 20), and the forest plots (Forest Plots 12 to 14) generated for three outcomes of interest (cervical cancer mortality, incidence of invasive cervical cancer, incidence of stage II or higher cervical cancer) across the comparison between primary HPV testing and conventional cytology.

The moderate GRADE quality cluster randomized trial conducted in India addressed cervical cancer mortality by comparing the benefits of a single lifetime HPV test to cytology.[72] The HPV test performed significantly better, reducing the risk of cervical cancer mortality by 41% of what it was for cytology (RR 0.59, 95% CI 0.39-0.91, p=0.02). Similar results were observed for the incidence of advanced (stage II or higher) cervical cancer outcome; HPV testing reduced the risk by 37% compared to cervical cytology (RR 0.63, 95% 0.42-0.95, p=0.03). Combining the results from the Indian study[72] with findings from another large randomized trial in Finland,[78] the HPV test was also superior to cytology for reducing the incidence of cervical cancer, with follow-up ranging from three to eight years (RR 0.78, 95% CI 0.62-0.99, p=0.04). Unlike the Indian trial which offered almost all of the women their first opportunity to receive screening, the Finnish study was conducted in a country where organized screening has been available nationally since the early 1960s and where all women between age 30 and 60 are invited to be screened every five years. Taken together, these RCTs were rated as moderate quality as per a GRADE analysis.

Key Question 1c: Does computer-assisted screening reduce incidence of or mortality from invasive cervical cancer compared to conventional cytology screening?

For sub-question KQ1c we found one RCT[79] that looked at the impact of computer-assisted screening compared to conventional cytology on the outcomes of cervical cancer incidence and mortality. No studies reporting all-cause mortality were found. The characteristics of the included study are reported in Table 9. Evidence Set 5 provides the GRADE Evidence Profile Table (Table 21), the GRADE Summary of Findings Table (Table 22), and the forest plots (Forest Plots 15 to 16) generated for two outcomes of interest (cervical cancer mortality, incidence of invasive cervical cancer) across the comparison between computer-assisted screening and conventional cytology.

One large, recent, high GRADE quality RCT of a population-based screening program in Finland investigated the impact of computer-assisted screening compared to conventional cytology on the outcomes of cervical cancer mortality and incidence.[79] Of over half a million women eligible for routine screening between 2003 and 2005, 169,159 were invited to attend computer-assisted screening and 334,232 were invited to attend screening using conventional cytology. With a range of follow-up from four to eight years, results showed no significant difference between these two slide reading techniques on either outcome. For cervical cancer mortality, the risk ratio slightly favoured conventional screening (RR 1.10, 95% CI 0.63-1.94, p=0.73) and for incidence of invasive cervical cancer the risk was even (RR 0.99, 95% CI 0.76-1.29, p=0.96).

Key Question 1d: How does varying the screening interval affect incidence of and mortality from invasive cervical cancer?

For the question of screening intervals, the search located 14 studies which included 12 case-control studies[80,83-85,87-89,91-93,102,105,107,108] (one study had three papers) that looked at exposure to cervical screening and two cohort studies[94,95] that reported incidence rates for cervical cancer. We found no studies that reported cervical cancer or all-cause mortality outcomes related to screening intervals. The 14 studies were conducted in 10 different locations including Sweden, the Netherlands, the US, the UK, Australia, Italy, Japan, Thailand, South Africa, and Latin America. In terms of screening test type, all the studies used or examined exposure to Pap tests. The characteristics of the 14 studies included for KQ1d are reported in Table 10.

Agreement was reached by two independent reviewers on quality assessment ratings using the Newcastle-Ottawa Scale.[69] The 12 case-control studies included for this question received between four and eight stars out of a possible nine stars (see Table 5). In terms of the "selection" (of cases and controls) category, all but one of the studies used adequate case definition with independent validation, some (n=5) studies did not discuss the representativeness of cases, many studies (n=8) recruited controls from medical care groups and hospital populations (as opposed to the community at large), and all but two of the studies specified that controls had no history of invasive cervical cancer (the two studies that were not awarded stars for this question indicated controls had no known hysterectomy but did not explicitly state these women had no history of cervical cancer). With respect to the two "comparability" questions, 11 studies received stars for matching cases and controls by age (the one study that did not get a star did not explicitly state whether all research sites used age matching) and six studies received a second star for matching on other important factors (primarily area of residence). In terms of the final assessment category, half of the studies (n=6) used secure records or structured and blinded interviews to ascertain exposure to cervical screening and all of the studies used the same method of ascertaining exposure and the same non-response rate for both cases and controls. Only one of the cohort studies[94] could be appraised with the Newcastle-Ottawa (Cohort) Scale[69] which bases assessment on the presence of exposed and unexposed cohorts; the second study[95] involved two age differentiated cohorts, both of which were exposed to screening. The Herbert study[94]

received eight of the nine available stars, missing only the point for comparability of cohorts on factors other than age. Based on the quality appraisal of the studies, there are no serious concerns in terms of study design. Thus, as a group these observational studies would be considered low quality evidence according to the GRADE system.[66]

Methodological variations across studies prevented pooling the data for this review question. The inconsistencies appeared in interval durations, groupings of intervals, and start times for intervals. For example, some studies used yearly intervals and others used bi-yearly; some studies looked at intervals less than three years, three to five years, five years and over, while others looked at intervals less than five years, five to 10 years, and 10 years and over; some studies looked at time since last smear while others specified time since last negative smear; some studies excluded tests within six months of the index date, some studies excluded tests within 12 months of the index date, and others did not mention such exclusions. While we were not able to perform a meta-analysis on these studies, we do provide descriptions of key findings from each study below (case-control studies followed by the cohort studies; Table 23 in Evidence Set 6 provides a summary of the data) and we were able to draw a few general themes or patterns from the data. First, the shortest screening interval offered the greatest protective effect. Second, screening intervals of five years or less appeared to offer women substantial protection against cervical cancer. Third, the protective effect of screening diminished with longer intervals between tests but even intervals of 10 to 15 years showed significant protective benefits. Finally, regardless of the specific screening interval, any screening was better than no screening.

In a nation-wide audit of Sweden's organized screening program, researchers examined the cytology histories of all women diagnosed with invasive cervical cancer (n=1,230) over a three year period (1999-2001) as well as 6,124 population-based, age matched controls.[80] Excluding tests performed six months prior to case diagnosis, the results showed a significant protective effect of having at least one Pap test within the recommended interval (3.5 years for women 53 years and under; 5.5 years for women 54 to 65 years; 6.5 years for women 66 years and older) (OR 0.40, 95% CI 0.34-0.46).

An older and smaller case-control study (cases n=121; hospital controls n=350) conducted in Italy investigated the interval between participants' last negative smear and the estimated time of invasion (or a corresponding date for controls).[105] The protective benefit of screening was greatest for intervals of 0 to 11 months (OR 0.14, no CI given) and 12 to 23 months (OR 0.16, no CI given). Higher odds ratios were reported for longer intervals: 24 to 35 months OR 1.16 (no CI given), 36 to 47 months OR 0.75 (no CI given), and 48 months or more OR 1.01 (no CI given).

Another Italian case-control study recruited women (n=191) from the Obstetrics and Gynecology Clinic of the University of Milan and the National Cancer Institute of Milan who were less than 75 years old and had been diagnosed with cervical cancer.[108] Controls (n=191) were patients without cancer or a gynecologic disorder admitted to one of the three Milan university hospitals in the prior year. Results showed the greatest benefit with the shortest interval since the last

smear. Excluding women with a positive smear result less than one year before diagnosis, the protective benefit of having a Pap test in the last 36 months (multivariate adjusted OR 0.12, 95% CI 0.07-0.20) was greater than the benefit observed for a screening interval of 36 to 60 months (multivariate adjusted OR 0.33, 95% CI 0.14-0.80) or for an interval of more than 60 months (multivariate adjusted OR 0.34, 95% CI 0.16-0.42).

A third small case-control study conducted in Italy looked at the screening histories of 208 women with cervical cancer and 832 age matched controls with no known hysterectomy.[93] Excluding Pap tests performed in the 12 months prior to case diagnosis and adjusting for civil status and place of birth, screening in the previous 36 months offered the most protective benefit (adjusted OR 0.25, 95% CI 0.15-0.42). However, longer screening intervals also showed significant beneficial effects (36 to 71 months adjusted OR 0.34, 95% CI 0.21-0.56; 72 months or more adjusted OR 0.56, 95% CI 0.38-0.82).

In another case-control study, researchers identified women diagnosed with invasive cervical cancer (n=759) in 1986 and 1987 from cancer treatment centres in Colombia, Costa Rica, Mexico and Panama.[107] Two age (five year groups) and hospital matched controls were selected for each case in Colombia and Mexico; one age and hospital matched control and one age and community matched control were selected for each case in Costa Rica and Panama. The effect of screening was the same for intervals of 12 to 23 months and 24 to 47 months (age adjusted OR 1.00, 95% CI 0.77-1.43). Although none of the results were significant, the age adjusted point estimates consistently showed greater protective benefits with shorter screening intervals (12 to 23 month interval compared to 48 to 71 month interval OR 0.59, 95% CI 0.40-1.00; 12 to 23 month interval compared to 72 to119 month interval OR 0.71, 95% CI 0.43-1.25; 12 to 23 month interval compared to an interval of 120 months or greater OR 0.56, 95% CI 0.40-1.00).

A South African case-control study examined the screening histories of 524 African/coloured women diagnosed with invasive cervical cancer and 1,540 African/coloured age, race, and place of residence matched hospital controls.[83] The findings indicated that the shorter the interval, the greater the protective effect of screening. Having at least one Pap test in the previous 60 months or previous 60 to 119 months offered the most protection (for both intervals multivariate adjusted OR 0.3, 95% CI 0.2-0.4). While still significant, the beneficial effect of screening declined with longer intervals (interval of 120 to 179 months multivariate adjusted OR 0.4, 95% CI 0.3-0.5; interval of 180 months or more multivariate adjusted OR 0.5, 95% CI 0.4-0.7).

A US study looked at the Pap testing histories of 482 women diagnosed with invasive cervical cancer who were matched (by age, race, and length of membership in a specific California-based health maintenance organization) with 934 controls.[87] Findings showed the protective effect of screening increased with shorter screening intervals. A screening interval of 12 months offered more protection than an interval of 24 months (OR 0.58, 95% CI 0.38-0.89) or an interval of 36 months (OR 0.49, 95% CI 0.29-0.83). There was no significant difference between the 24 and 36 month screening intervals (OR of 36 months relative to 24 months 1.20, 95% CI 0.65-2.21,

p=0.561). The authors reported additional odds ratios comparing annual Pap testing with three longer intervals since last negative smear. The 12 month screening interval offered significantly more protection than screening intervals of 37 to 60 months (OR 0.32, 95% CI 0.19-0.52), 60 to 120 months (OR 0.21, 95% CI 0.14-0.33) and 120 months or more (OR 0.11, 95% CI 0.07-0.19).

Based on their long-term case-control study of cervical screening in the UK, Sasieni et al. published three papers that provided data on the protective effect of cervical cancer screening associated with varied intervals.[88,89,91] The 1996 paper reported results of the initial study that investigated the screening histories of all 348 women diagnosed with invasive cervical cancer in 1992 in several UK health districts and 677 age and residency matched controls.[88] Results showed screening at any interval less than 48 months offered significantly greater protective benefits compared to no screening or screening more than 66 months previously. The odds were lowest for the shortest interval showing an increasing trend as intervals lengthened [all analyses excluded microinvasive cervical cancer: 0 to 11 month interval OR 0.18 (95% CI 0.09-0.35); 12 to 23 month interval OR 0.33 (95% CI 0.18-0.61); 24 to 35 month interval OR 0.26 (95% CI 0.14-0.47); 36 to 47 month interval OR 0.32 (95% CI 0.17-0.56); 48 to 65 month interval OR 0.64 (95% CI 0.36-1.14)].

Updated results presented in the 2003 Sasieni et al. paper were based on data gathered about the screening patterns of 1,305 women diagnosed with invasive cervical cancer (stage IB+) and 2,532 age and residency matched controls.[89] The authors presented odds ratios for three age groups according to two models with different interval divisions (see Table 23 for full details). For the youngest women (20 to 39 years), a screening interval of 0 to 35 months offered significant protection (OR 0.28, 95% CI 0.20-0.41) while no beneficial effects were observed with longer intervals (36 to 59 month interval OR 1.03, 95% CI 0.68-1.56; interval over 60 months OR 2.05, 95% CI 1.20-3.49). For women in the middle age group (40 to 54 years) screening every 35 months and every 36 to 59 months offered significant protection (35 month interval: OR 0.12, 95% CI 0.08-0.17; 36 to 59 month interval: OR 0.39, 95% CI 0.26-0.58). There was a small but not significant benefit when the interval was 60 months or more (OR 0.72, 95% CI 0.43-1.18). For the oldest women (55 to 69 years) screening had a protective effect at any interval. A 35 month interval offered the greatest protective effect (OR 0.13, 95% CI 0.08-0.19), followed closely by a 36 to 59 month interval (OR 0.20, 95% CI 0.12-0.33). For these women an interval of 60 months or more was also beneficial (OR 0.45, 95% CI 0.25-0.81).

In a 2009 publication Sasieni et al. presented another round of findings on the incidence of cervical cancer associated with various screening intervals.[91] In this update, cases included 3,305 women diagnosed with three different histological types of cervical cancer and 6,516 age matched controls. Compared to a screening interval of 66 months or more, having a Pap test within a 42 month interval offered significant protection against adenosquamous carcinoma (OR 0.17, 95% CI 0.09-0.32), squamous carcinoma (OR 0.25, 95% CI 0.21-0.29), and adenocarcinoma (OR 0.57, 95% CI 0.42-0.76). The protective benefit of screening declined but was still significant when the interval increased to between 42 and 66 months [adenosquamous

carcinoma OR 0.24 (95% CI 0.12-0.48), squamous carcinoma OR 0.39 (95% CI 0.33-0.45), and adenocarcinoma OR 0.63 (95% CI 0.46-0.85)].

An Australian study investigated the impact of different screening patterns on the incidence of invasive cervical cancer.[92] The study included 877 women (ages 20 to 69 years) diagnosed with invasive cervical cancer during a four year period (2000-2003) and 2,614 age matched controls. Compared to a screening interval of four years or more, regular Pap testing (two or more in four years) offered substantial protection (OR 0.04, 95% CI 0.03-0.06) as did irregular Pap testing (one in four years) (OR 0.15, 95% CI 0.12-0.19).

In a Japanese study, researchers investigated the screening histories of 198 women ages 35 to 79 years who had been diagnosed with invasive cervical cancer and 396 age and area matched controls.[85] A 12 month cytology screening interval offered significantly more protection than an interval of 60 months or more (OR 0.09, 95% CI 0.06-0.16). Significant protection was also observed with an interval of 24 months compared to 60 months or more (OR 0.17, 95% CI 0.08-0.34). Non-significant benefits were found for Pap testing intervals of 36 months (OR 0.67, 95% CI 0.26-1.73) and 48 months (OR 0.45, 95% CI 0.13-1.59) compared to 60 months or more.

Another case-control study in Mexico involved 143 women, less than 70 years old, living in Guadalajara, with newly diagnosed invasive cervical cancer and 311 age matched hospital or health centre controls also residing in this city.[84] Significant protective effects were found for screening intervals of 1 to 12 months (age adjusted OR 0.2, 95% CI 0.1-0.4) and 13 to 60 months (age adjusted OR 0.2, 95% CI 0.1-0.5) compared to no history of screening. Though not as great, an interval of 60 months or more also offered protective benefits (OR 0.5, 95% CI 0.3-0.9).

A recent case-control study was conducted in Thailand six years after the introduction of a national cervical cancer screening program in 2005.[102] Researchers compared the Pap test histories of 130 women aged 30 to 64 with a diagnosis of invasive cervical cancer against the screening histories of 260 women, age matched to cases within 10 years and with no history of gynecological diseases (130 hospital controls, 130 hospital patient companion controls). Excluding women who had tests performed in the previous six months (cases n=41; controls n=37), the results showed significant protective effects for screening intervals of 12 to 35 months (OR 0.27, 95% CI 0.13-0.56; adjusted for significant risk factors and number of Pap tests) and for 36 months or more (OR 0.42, 95% CI 0.20-0.88; adjusted for significant risk factors and number of Pap tests). No protective effect was found for the shortest interval of 6 to 11 months (adjusted OR 1.38, 95% CI 0.56-3.40). The authors suggest the slightly increased but non-significant risk associated with this interval may be attributed to Pap tests conducted for diagnostic purposes among women presenting with gynecological symptoms.

A large cohort study of screening eligible women aged 25 to 69 years living in the UK (n=116,022) also looked at the incidence of invasive cervical cancer according to short (6 to 42 months), long (43 to 66 months) and overdue (> 66 months) intervals.[94] The incidence of invasive cervical cancer was significantly lower among women who participated in the country's

comprehensive screening program (i.e., they had at least one Pap test in the preceding 6 to 66 months) than among women who were not screened during this time (RR 0.38, 95% CI 0.23-0.63). The risk of developing cervical cancer was also significantly lower for women screened in the short interval compared to those screened in the long interval (RR 0.45, 95% CI 0.26-0.77). Finally, even women who did not get screened during the program interval but who had a record of previous cytology testing reduced their risk of being diagnosed with cervical cancer by 66% of the risk for women with no history of screening (RR 0.34, 95% CI 0.14-0.82).

Finally, a large prospective cohort study conducted in the Netherlands investigated the 20-year cumulative incidence of cervical cancer after three consecutive negative smears in women 30 to 44 years (n=445,382; mean age 37.3) and women 45 to 54 years (n=218,847, mean age 48.7).[95] The three negative result Pap tests were conducted, on average, every 39 months in the younger group, and every 40 months in the older group. The cumulative incidence rate for cervical cancer did not differ significantly between the groups for any screening interval (<12 months, 13 to 36 months, 37 to 60 months, 61 to 120 months, 121 to 180 months, 181 to 240 months).

Key Question 1e: How does varying the age at which screening is started or stopped reduce the incidence of and mortality from invasive cervical cancer?

For the question on ages to start and stop screening, the search located four studies (one study had three papers) including three case-control studies[80,83,88-90] that examined exposure to screening among different age groups and one age comparison within a cohort study[95] that reported incidence rates for cervical cancer. No studies were found that looked specifically at the age to stop screening; only one study reported an OR for the protective benefit of screening among older women (after standard screening discontinuation ages for women with a cytology testing history). We found no studies that reported cervical cancer or all-cause mortality outcomes related to age and screening history. The four included studies were conducted in Sweden, South Africa, the UK, and the Netherlands. The characteristics of these studies are reported in Table 11.

Agreement was reached by two independent reviewers on quality assessment ratings for the three case-control studies using the Newcastle-Ottawa Scale[69] (see Table 5). The study by Hoffman and colleagues[83] received six out of a possible nine stars; missed points were for use of hospital controls, no statement regarding the representativeness of the cases, and no statement indicating whether interviewers were blind to participants' case/control status. The other two case-control studies received eight of the nine stars: Andrae et al.[80] matched cases and controls on age but no other important factors; Sasieni et al.[88-90] indicated controls had no known hysterectomy but did not explicitly state that controls had no history of cervical cancer. The cohort study included for this review question[95] could not be assessed with the Newcastle-Ottawa (Cohort) Scale because it involved two age differentiated cohorts, both of which were exposed to the intervention of interest. Based on the quality appraisal, there are no serious concerns in terms of overall study

design. Thus, as a group these observational studies would be considered low quality evidence according to the GRADE rating system.[66]

Methodological variations across studies (in overall age ranges and age groupings used for analysis) prevented pooling the data for this review question. While we did not perform a meta-analysis on these studies, we do provide descriptions of key findings from each study below (case-control studies followed by the cohort study; Table 24 in Evidence Set 7 provides a summary of the data). Given the available data we were not able to definitively answer the question regarding ages when to start or stop cervical cancer screening, however we were able to draw a few themes from the data. Participation trends showed very high screening attendance among young women 20 to 35 years, high attendance among women 35 to 49 years, and consistently lower participation in older groups of women. Despite high participation among younger women the benefit of screening women below age 30 is unclear. It appears that exposure to cytology screening provides a substantial protective effect in all age groups 30 years and older and there is some evidence that this protective effect remains strong in women over 65 years.

Results of a nation-wide audit of an organized screening program in Sweden indicated the odds of being exposed to cervical screening were consistently higher for women who were not diagnosed with invasive cervical cancer, regardless of age.[80] Screening within the recommended interval (42 months for women 53 years and under; 66 months for women 54 to 65 years; 78 months for women aged 66 years and older) offered a significant protective benefit (OR 0.40, 95% CI 0.34-0.46). The point estimates were similar across three age groups. In younger women, (aged 21 to 29 years at case diagnosis), the OR was 0.42 (95% CI 0.24-0.74). In the middle age group (aged 30 to 65 years at case diagnosis) the OR was 0.40 (95% CI 0.34-0.47). Finally, in the oldest group (66 years and older at case diagnosis) the OR was 0.36 (95% CI 0.24-0.53).

Unlike the previous study that investigated outcomes related to an organized screening program, another case-control study was conducted in an area where cervical cancer screening is limited (Western Cape, South Africa).[83] Across all women studied (n=2,064; 524 cases, 1,540 hospital controls), the odds of exposure to cervical screening were significantly higher among those not diagnosed with invasive cervical cancer [adjusted (for age, education, area of residence, race, education, parity, age of sexual debut, injectable contraceptive use, oral contraceptive use, cigarette smoking) OR 0.3, 95% CI 0.3-0.4]. The protective benefit of screening was observed in all age groups however statistically significant effects were observed only in women 30 years and older [<30 years OR 0.7 (95% CI 0.3-2.1); ages 30 to 39 OR 0.3 (95% CI 0.2-0.6); ages 40 to 49 OR 0.3 (95% CI 0.2-0.4); ages 50 to 59 OR 0.3 (95% CI 0.2-0.4)].

Drawing from their longitudinal study of cervical screening in the UK, Sasieni et al. published three papers that examined age and screening history.[88-90] The first paper reported results of the initial case-control study that investigated the screening histories of all 348 women diagnosed with invasive cervical cancer in 1992 in several UK health districts and 677 age and residency

matched controls.[88] Across ages, participation in screening declined with increasing age in both (fully invasive cancer) case and control groups. In the younger group (20 to 34 years) 86% of cases and 91% of controls had been screened; in the 35 to 49 year old group 71% of cases and 87% of controls were screened; in the 50 to 64 year old group 57% of cases and 74% of controls had been screened; in the 65 to 74 year old group 32% of cases and 40% of controls were screened; and in the oldest group (ages 75+) 10% of cases and 9% of controls had been screened. Except for the oldest group which showed no difference, in all age categories women with invasive cancer were significantly more likely to have no history of screening up to six months prior to diagnosis compared with women who did not have cervical cancer (p=0.002).

In 2003 Sasieni et al. presented updated results from their case-control study of the benefits of cervical cancer screening at different ages in the UK.[89] At this point in the study, cases included all women (n=1,305) aged 20 to 69 years diagnosed with invasive cervical cancer (stage IB+) between 1990 and 2001 (age matched to 2,532 controls). Results were similar to the previous round of analysis. Across age groups, participation in screening consistently declined with increasing age in cases (80% of cases aged 20 to 39; 68% of cases aged 40 to 54; 48% of cases aged 55 to 69). In the control group, participation rates remained constant for women aged 20 to 54 years (around 83-84%) and then declined in the 55 to 69 year old group (70.7%). In all three age categories more women with invasive cancer had no history of screening up to six months prior to diagnosis compared with women who did not have cervical cancer.

In 2009 Sasieni et al. presented another round of findings from their case-control study on the effectiveness of cervical cancer screening with age.[90] In this update, cases included all women (n=4,012) aged 20 to 69 years diagnosed with any stage of cervical cancer (including IA) between 1990 and 2008 (age matched to 7,889 controls). Considering cases diagnosed between the ages of 25 and 29 and their matched controls, study results showed no protective effect of cervical screening for women who were tested between ages 20 and 21 and not ages 22 to 24 (OR 1.51, 95% CI 0.95-2.38). Similarly, there was no protective benefit of screening women between ages 22 and 24 (OR 1.11, 95% CI 0.83-1.50). Examining cases diagnosed between the ages of 35 and 39 and their matched controls, the findings indicate a non-significant protective effect of screening women between ages 30 and 31 and not between ages 32 to 34 (OR 0.79, 95% CI 0.57-1.1) and a significant benefit of testing between ages 32 and 34 (OR 0.55, 95% CI 0.44-0.69). The protective benefit of screening continued to increase as age increased. For women diagnosed with cancer between ages 45 and 49 and their matched controls, the protective effect of screening between ages 40 and 41 and not ages 42 to 44 was significant (OR 0.40, 95% CI 0.27-0.58) as was the benefit for women screened between ages 42 and 44 (OR 0.37, 95% CI 0.29-0.48). Finally, for cases diagnosed between ages 55 and 59 and their matched controls, screening offered substantial protection both for women screened between ages 50 and 51 and not ages 52 to 54 (OR 0.27, 95% CI 0.17-0.43) and for women screened between ages 52 and 54 (OR 0.26, 95% CI 0.19-0.36).

Finally, a large prospective cohort study conducted in the Netherlands compared the 20-year cumulative incidence of cervical cancer after three consecutive negative smears in women aged

30 to 44 years (n=445,382; mean age 37.3) and women aged 45 to 54 years (n=218,847, mean age 48.7).[95] The cumulative incidence rate for cervical cancer did not differ between the two age groups at any stage during follow-up (p-values ranged from 0.09 to 0.85). Study authors report an overall hazard ratio of 0.84 (95% CI 0.59-1.21) for the comparison between older and younger women. After three consecutive negative smears, the use of cytological screening to detect and prevent cervical cancer produced the same outcomes in older and younger women.

Key Question 2: What are the harms of cervical cancer screening?

CTFPHC members ranked the identified harms of cervical cancer screening in terms of their importance for decision making (Table 3). Overdiagnosis was ranked as critical, and false-positives, colposcopy rate, anxiety/depression, and sexual dysfunction were rated as important. The search looked for studies (using any quantitative design) reporting on any of these harms. No evidence was found that met the inclusion criteria for the review (Table 2) for the harms of overdiagnosis (of invasive cancer), colposcopy rate, anxiety/depression, or sexual dysfunction. The only harm reported in the research included for this Key Question was false-positive rates for invasive cervical cancer by cytology screening tests. To supplement this data, in Contextual Question 1 (below) we summarize the research literature that examines overdiagnosis, false-positive rates and specificity of screening for pre-cancer using cytology and HPV tests.

A false-positive screening test result can lead to patient anxiety and potentially unnecessary follow-up either with repeat cervical testing at six months or a colposcopy examination to determine if higher grade disease or cancer is present. If there is a discrepancy between the cytology test and the biopsy result this often results in obtaining a larger cervical specimen through a loop electrosurgical excision procedure (LEEP) or cold knife conisation. Unnecessary testing/treatment may also lead to negative outcomes for future pregnancies (see Contextual Question 2 below).

Six small single-group retrospective studies that involved reviews of cervical specimens and/or test results were found that included data on cervical cytology false-positives rates for the outcome of cervical cancer.[96-101] The characteristics of these studies are reported in Table 12 and a summary of relevant false-positive findings is provided in Evidence Set 8 in Table 25. Given the observational status and the lack of comparison groups for these studies (a serious design limitation), this body of evidence would be rated as very low GRADE quality. Once again there was too much inconsistency across studies to pool the data. For example: studies looked at different screening tests and slide reading techniques; findings reported false-positive rates for different levels and types of cervical cancer and pre-cancers; sample compositions were different (some studies used only positive screening test results, some included negative results, some used consecutive smears); and there was variation in how authors computed the false-positive rates. The variation also showed up in the false-positive rates reported in the six studies. For instance the false-positive rate for conventional cytology ranged from less than 1%[97] for all diagnoses to over 22%[101] for LSIL+, and the false-positive rate for PAPNET read slides was 4% in one study[96] and

over 19% in another.[97] Given these differences it is difficult to draw any solid conclusions about the harm of false-positives from this evidence.

Key Question 2a: At what rates do these harms occur, by age and with different screening intervals?

For sub-question KQ2a that asked about rates of cervical cancer screening harms by ages and intervals, we did not find any studies that met the inclusion criteria for this review. None of the studies included for KQ2 (above) reported false-positive rates for specific age groups. Some of the studies included for Contextual Question 1 (below) reported false-positive rates and/or specificity for detecting pre-cancer by various age groups.

Results for Contextual Questions

We searched Medline, EMBASE and Cochrane Central from 2005 to February 2011 for any papers, with any study design, that might answer the Contextual Questions.

Contextual Question 1: What are the harms of cervical cancer screening for pre-cancer (i.e., overdiagnosis and false-positive rates and specificity)?

To supplement the minimal evidence available to answer KQ2 a Contextual Question was added to search for studies that report false-positive/specificity and overdiagnosis rates for pre-cancer.

Any invasive cervical cancer or pre-cancerous disease detected by screening that would not have been identified clinically or would not have resulted in symptoms or death in a woman's lifetime is considered overdiagnosis. Few studies directly addressed the topic of overdiagnosis but many authors agreed there is a need for more longitudinal study of this issue to be able to provide precise estimates. Four studies were located that addressed overdiagnosis including two recent systematic reviews[110,111] and two older primary studies.[112,113] The first systematic review reported finding no studies that quantified overdiagnosis of cervical cancer linked to screening.[110] The second systematic review also found no direct evidence of overdiagnosis; however indirect evidence from five studies was reported.[111] In one of these studies, over a period of a decade, mild and moderate dysplasia regressed by 87.7% and 82.9% respectively. The review authors used results from four other studies of HPV testing to postulate that the high rate of CIN detection using this screening approach may lead to overdiagnosis. In the mid-1990s a retrospective chart review was conducted on 145 Hong Kong women aged 19 to 72 years (mean age 35.6) who had cytological diagnoses of LSIL or HSIL and who had undergone colposcopies and colposcopic-directed biopsies.[112] An LSIL diagnosis by cytology alone was associated with an overdiagnosis rate of 11.7% (17/145). When the cytology diagnosis was combined with colposcopy the rate of overdiagnosis for LSIL was 6.9% (10/145). In addition, in the group of women with biopsy confirmed LSIL, spontaneous regression of the lesions occurred in 81.1% of the cases within two years and without treatment. Finally, to assess the effect of age

and HPV infection on the predictive value of cytology, an Austrian study compared the cytological and histological findings for a sample of 671 women (mean age 36.8 years) with Pap test results suggesting LSIL, HSIL or invasive cervical cancer.[113] Study results showed cellular changes associated with HPV led to significantly more overdiagnoses (9% for HPV positive women, 4% for HPV negative women) even with an adjustment for age (p=0.004). Though this study demonstrated an independent relationship between HPV changes and cytological overdiagnosis, the data also showed a trend toward a higher probability of overdiagnosis in younger women (≤35 years) compared to older women (>36 years).

Twenty-two studies were found that reported false-positive rates and/or specificity for pre-cancer, including eight systematic reviews or pooled analyses and 14 primary studies. The included studies were drawn from four databases for this review (main, observational, update 2011, contextual) and relevant studies included in the most recent USPSTF systematic review on cervical cancer screening which reported data on test specificity and computed false-positive values.[62] To be considered for this Contextual Question the studies had to meet several criteria: (1) cytology (conventional or liquid-based) or HPV DNA tests; (2) primary cervical screening (not secondary, repeat or triage testing); (3) diagnoses for CIN2+; (4) gold standard verification of disease status (colposcopy, histology) or adjustment for verification bias; (5) the study or studies were conducted in locations generalizable to Canadian context (North America, Europe). Particular emphasis was given to studies that reported results for different age ranges.

Evidence Set 9 contains data extraction and summary tables for specificity and false-positive rates from the 22 studies. Table 26 provides an overview of all studies including designs, locations, sample characteristics, cytology and histology cut points, screening tests, age groups, false-positive rates and specificity. To help organize and synthesize this data four additional tables were created. Table 27 provides specificity for all ages organized by cytology cut points, screening test types, and CIN levels. Table 28 provides screening test specificity for older women, primarily age 30 and above, organized by cytology cut points, screening test types, and CIN levels. Table 29 provides screening test specificity for younger women, primarily below age 30, organized by cytology cut points, screening test types, and CIN levels. Table 30 provides false-positive rates for all ages and varied age groups, organized by cytology cut points, screening test types, and CIN levels.

Looking across the data addressing this contextual question, recent systematic reviews have found no direct evidence for overdiagnosis linked to screening. It appears that cytology tests are more specific than HPV tests with the difference between screening tests most notable among younger women (under 30 years). Finally, test specificity is lowest for younger women (under 30 years) and false-positive rates are highest for women under 25 years.

Contextual Question 2: What are the harms of treatment of cervical cancer? Harms include: (a) harms of colposcopy, (b) harms of biopsy: cone biopsy (immediate and late effects; pre-term labour, miscarriage) and LEEP/LEETZ (immediate and late effects), (c) harms of treatment of cervical cancer: total hysterectomy (incontinence, infection, hospitalization) and radiotherapy.

a. Harms of Colposcopy

Our search located two primary studies that examined the harms of colposcopy.[114,115]

The TOMBOLA (Trial of Management of Borderline and Other Low-grade Abnormal smears) group (UK) conducted an observational study nested within their randomized controlled trial examining the frequency of post-colposcopy bleeding, pain, discharge and change in the first menstrual period post-colposcopy.[114] The study was divided between women who received colposcopy only, or colposcopy with either a punch biopsy or LLETZ. We are reporting data of the colposcopy only. There were 929 women eligible to participate in this study. Seven hundred and fifty-one women completed the survey at the six week post-procedure mark, and of those, 401 women had received a colposcopy only. Following the colposcopy 14-18% of these women reported they experienced pain, bleeding or discharge. The severity of the after-effects was rated by the women as very mild to moderate; no women in this group reported having very severe after-effects. Twenty-nine percent of the women reported a change in their first menstrual period following colposcopy. The authors note that this study is important because it asks women directly about their experiences as opposed to asking physicians for their interpretation of those experiences. As well the authors note that the experience of pain with colposcopy is an important deterrent to participation and adherence to follow-up.

A 2006 Canadian study explored colposcopy management of LSIL by surveying colposcopists from seven provinces.[115] The multiple choice instrument included questions that described clinical scenarios. Surveys were mailed to 252 colposcopists with a total of 120 (48%) surveys returned. The answers reflected the respondents' intentions for treatment rather than data from their actual practice. However, from the scenarios described, the colposcopists indicated that for women who receive a negative colposcopy result, 43% would be discharged and 53% would be referred for a second colposcopy. For women who receive a positive colposcopy result for LSIL, 65% would be referred for a repeat colposcopy, 16% would be referred to treatment and 13% would be discharged to cytological follow-up. These data demonstrate the wide variability in the management of LSIL in Canada.

b. Harms of Biopsy: Cone Biopsy and LEEP/LEETZ

Cone Biopsy: Pregnancy Outcomes

Two systematic reviews with meta-analyses were located that examined harms of cone biopsy (cold knife and laser conisation) in terms of pregnancy related outcomes.[116,117] The first meta-analysis

found cold knife conisation increased the risk of: perinatal mortality (7 studies: RR 2.87, 95% CI 1.42-5.81), severe pre-term (<32 to 34 weeks) delivery (5 studies: RR 2.78, 95% CI 1.72-4.51), extreme pre-term (<28 to 30 weeks) delivery (4 studies: RR 5.33, 95% CI 1.63-17.40), and severe (<2000g) low birth weight (1 study: RR 2.86, 95% CI 1.37-5.97).[116] Only one paper described the effects of laser conisation and this study showed significantly increased risks of severe (<2000g) and extreme (<1500g) low birth weight (RR 3.50, 95% CI 1.06-11.53; RR 10.00, 95% CI 1.19-83.84, respectively).[116] The second systematic review reported similar findings.[117] Cold knife conisation was associated with higher risks of: pre-term delivery (8 studies: RR 2.59, CI 95% 1.80-3.72), low birth weight (<2500g) (4 studies: RR 2.53, CI 95% 1.19-5.36), and caesarean section (4 studies: RR 3.17, 95% CI 1.07-9.40). No significant risk estimates were found for outcomes associated with laser conisation, although the risk of pre-term delivery approached significance (6 studies: RR 1.71, CI 95% 0.93-3.14).

One large retrospective cohort study conducted in Finland also looked at adverse pregnancy outcomes in 8,210 singleton births in women previously treated for CIN compared to singleton births in women with no history of treatment for CIN who delivered in the same time period (n=1,056,855).[118] In women treated using excisional therapies (cold knife conisation, laser conisation and LEEP) there were greater risks of pre-term delivery (RR 1.99, 95% CI 1.81-2.20), low birth weight (RR 2.06, 95% CI 1.83-2.31), and perinatal mortality (RR 1.74, 95% CI 1.30-2.32).

LEEP/LEETZ: Pregnancy Outcomes

Nine papers (two systematic reviews and seven primary studies) were located in the search that examined adverse effects on pregnancy outcomes associated with loop electrosurgical excision procedures (LEEP) or large loop excision of the transformation zone (LLETZ).

Two meta-analyses investigated the effects of LEEP/LLETZ on pregnancy outcomes.[116,117] In the 2006 meta-analysis, LLETZ was found to increase the risk of pre-term (<37 weeks) delivery (8 studies: RR1.70, 95% CI 1.24-2.35), low birth weight (<2500g 6 studies: RR 1.82, CI 95% 1.09-3.06) and spontaneous rupture of membranes (3 studies: RR 2.69, 95% CI 1.62-4.46), but had no adverse effects in terms of risks for caesarean section, precipitous labour, perinatal mortality and NICU admission.[117] The 2008 meta-analysis included some of the same studies covered in the 2006 review, however it also included more recently published data from two small and four large studies and it focused on more serious obstetrical outcomes not captured in previous reviews. Similar to the 2006 review the 2008 meta-analysis found no significant risk associated with LLETZ on the outcome of perinatal mortality (7 studies: RR 1.17, 95% CI 0.74-1.87), however in contrast, the 2008 analysis also found no significant risks for pre-term (<32 to 34 weeks) delivery (4 studies: RR 1.20, 95% CI 0.50-2.89) or severe low birth weight (<2000g 1 study: RR 1.29, 95% CI 0.42-4.00; <1500g 1 study: RR 0.81, 95% CI 0.11-5.81; <1000g 1 study: RR 0.39, 95% CI 0.02-6.35).[116]

One Canadian (Nova Scotia) retrospective cohort study was found that examined harms of LEEP in terms of future pregnancy outcomes.[119] Women (n=571) who underwent a LEEP procedure and later became pregnant and progressed to more than 20 weeks gestation were compared to women (n=571) with no history of cervical surgery who were matched on age, parity, smoking status and year of delivery. Women with a history of LEEP were more likely than comparison women to experience pre-term delivery at less than 37 weeks gestation (7.9% versus 2.5%; OR 3.5, 95% CI 1.90-6.95, p<0.001) but not at less than 34 weeks (OR 3.50, 95% CI 0.85-23.49, p=0.12). Pre-term premature rupture of membranes also occurred more frequently in the LEEP group than in the comparison group (3.5% versus 0.9%; OR 4.1, 95% CI 1.48-14.09, p=0.004). Likewise, significantly more low birth weight babies were born to women who had undergone LEEP than women who did not have the procedure (5.4% versus 1.9%; OR 3.00, 95% CI 1.52-6.46, p=0.003). There were no differences between the two groups on any other delivery outcomes (i.e., premature rupture of membranes, induction, augmentation, mode of delivery, or indication for cesarean section).

A Danish population-based cohort study investigated adverse outcomes in the pregnancies of women who had experienced one or two conisations.[120] Of the 710 women who had had one conisation, most (n=572) had LLETZ, while some had electroknife (n=71) or cold knife (n=67) procedures. Compared to women with no pre-pregnancy conisation (n=72,899), women who had any of the cervical procedures had a higher frequency of pre-term delivery [11.1% (one conisation) and 33.3% (two conisations) versus 4.1% (no conisation); one conisation versus no conisation adjusted HR 2.8 (95% CI 2.3-3.5), two conisations versus no conisation adjusted HR 9.9 (95% CI 6-17)]. Women with only one conisation were at higher risk of pre-term delivery regardless of which conisation procedure was used; however, LLETZ was associated with lower risk estimates across gestational ages than either electroknife or cold knife. Birth weight was lower in babies born to women in both conisation groups (3,411g) compared to the no conisation group (3,537g) (p<0.001). There were no perinatal deaths in the two conisations group. However, there were more deaths in children (particularly those delivered at <28 weeks) of women with one conisation (n=7, 1%) compared to women with no history of the procedure (n=312, 0.4%) (adjusted HR 2.8, 95% CI 1.3-5.9, p=0.007).

Two additional papers reported on prospective cohort studies of pre-term delivery following LEEP in the Danish population.[121,122] The 2007 paper included all eligible deliveries (n=14,981) by 8,134 of the women recruited to the study between 1991 and 1993; of these deliveries, 349 (2.3%) were preceded by LEEP. A significantly increased risk of pre-term birth (<37 weeks) was found in the deliveries of women with a history of LEEP compared to deliveries among women who did not have the procedure (6.6% versus 3.5%; adjusted OR 1.8, 95% CI 1.1-2.9). The 2009 study included all singleton deliveries (n=552,678) in Denmark between 1997 and 2005 (deliveries were made by 381,239 women). LEEP preceded 8,180 (1.5%) of all deliveries. Similar findings were reported for pre-term births. A greater risk of pre-term delivery was

associated with a prior history of LEEP as compared to no exposure to the procedure (6.5% versus 3.24%; adjusted OR 2.07, 95% CI 1.88-2.27).

One case-control study from the UK examined delivery outcomes in primigravida who had undergone LLETZ (n=119) compared with age and parity matched controls (n=119).[123] Findings showed LLETZ had no adverse effects on any measured pregnancy outcomes: miscarriage rates (cases 11.8%; controls 9.2%), pre-term (<37 weeks) delivery (cases 10.9%; controls 9.2%), mean weeks of gestation (cases 39.4, controls 39.7), spontaneous onset of labour (cases 85.1%, controls 73.3%), first stage labour more than 12 hours (cases 9.2%, controls 8.4%), mode of delivery (cesarean section: cases 14.3%, controls 23.5%; spontaneous vaginal: cases 71.4%, controls 63.9%; instrumental: cases 14.3%, controls 12.6%), and birth weight (cases 3.26 kg; controls 3.38 kg).

Another case-control study conducted in Greece compared 28 women who had been treated for microinvasive cervical cancer with LEEP who later became pregnant and progressed to more than 24 weeks gestation, with 28 same year and same delivery department control subjects who had no history of cervical treatment.[124] Except for duration of labour, which was significantly shorter for cases than controls (mean hours 5.5 versus 7.1, p=0.032), the results showed no statistically significant differences between the two groups on delivery outcomes (i.e., duration of gestation, birth weight, cesarean section rate, NICU admissions, precipitous labour). However, the sample size was very small.

Sadler and colleagues compared the risk of pre-term delivery among New Zealand women previously treated with colposcopy (n=652) with women who had no history of cervical treatments (n=426).[125] Almost half (n=278) of the women in the colposcopy group were treated with LEEP; the remaining women were treated with laser conisation (n=105) or ablation (n=223). Based on adjusted relative risks, none of the colposcopy procedures were associated with significantly increased pre-term delivery or spontaneous pre-term birth. However, compared to women with no treatment history, women who had undergone LEEP had almost two-fold greater odds for experiencing pre-term premature rupture of membranes leading to pre-term delivery (adjusted RR 1.9, 95% CI 1.0-3.8).

Number Needed to Harm: Pregnancy Outcomes

This review found only one study that reported harms of treatment in terms of absolute risks. In one of the systematic reviews on pregnancy related outcomes the authors pooled the absolute frequency of adverse obstetric outcomes in women who received treatment and women who did not receive treatment to derive the number needed to treat to observe obstetric harm in one treated woman (NNTH).[116] The meta-analysis generated several NNTH for procedures and outcomes of interest to this review. For the outcome of perinatal mortality the NNTH for cold knife conisation was 71 (6 studies), for laser conisation it was 67 (3 studies), and for LLETZ it was 500 (7 studies). For severe preterm delivery (<32 to 34 weeks) the NNTH for cold knife conisation was 30 (5 studies), for laser conisation it was 167 (1 study), and for LLETZ it was 143

(4 studies). For extreme pre-term delivery (<28 to 30 weeks) the NNTH for cold knife conisation was 53 (3 studies) and for LLETZ it was 250 (3 studies). For the outcome of severe low birth weight (<2000g) the NNTH for cold knife conisation was 16 (1 study), for laser conisation it was 14 (1 study), and for LLETZ it was 106 (1 study). For extreme low birth weight (<1500g) the NNTH for cold knife conisation was 36 (1 study), for laser conisation it was 16 (1 study), and for LLETZ it was 670 (1 study). Finally for extreme low birth weight (<1000g) the NNTH for cold knife conisation was 54 (1 study) and for LLETZ there were no reported events (1 study). Overall, the harms associated with LEETZ were much less common than those resulting from cold knife or laser conisation.

Physical Effects

Only one UK-based primary study was found that examined the physical effects of biopsy across three conditions: colposcopy exam only, colposcopy and cervical punch biopsies, and colposcopy and LLETZ.[114] Participants were women (n=751) aged 20 to 59 years with low grade abnormal cytology who had undergone their first colposcopic procedure. The women completed two surveys developed specifically for the TOMBOLA trial: one approximately six weeks post-procedure to assess physical after-effects (i.e., pain/discomfort, bleeding, discharge), and a second approximately four months post-procedure to assess menstrual changes (i.e., timing, flow, duration, discomfort). Women in the LLETZ group (n=185) experienced a higher frequency of all physical after-effects than women in the biopsy (n=165) or colposcopy exam only (n=401) groups. A large portion of women in the LLETZ group reported pain (crude prevalence 67%, 95% CI 59.7-73.7) and discharge (crude prevalence 64.9%, 95% CI 57.5-71.7) compared to women undergoing punch biopsies (pain crude prevalence 55.2%, 95% CI 47.2-62.9; discharge crude prevalence 45.5%, 95% CI 37.7-53.4) and colposcopy exam only (pain crude prevalence 19.7%, 95% CI 15.9-23.9; discharge crude prevalence 15.7%, 95% CI 12.3-19.6). Reports of bleeding were similar in the LLETZ (crude prevalence 85.4%, 95% CI 79.5-90.2) and biopsy (crude prevalence 79.4%, 95% CI 72.4-85.3) groups although women who underwent LLETZ reported longer durations of bleeding ($p<0.001$) as well as discharge ($p<0.001$).

Sexual Functioning

Two primary studies were found that examined the effect of LEEP on women's sexual functioning. A two-year prospective study compared psychosexual functioning in 47 Swedish women who were receiving LEEP for the first time with 53 women who were not referred for LEEP.[126] Participants completed the same seven-item (i.e., frequency of intercourse, spontaneous interest, sexual arousal, orgasm, lubrication, dyspareunia, negative feelings) psychosexual questionnaire at three points (referral for colposcopy, six month follow-up with colposcopy, two year follow-up with colposcopy). No significant differences were found between the mean scores of the LEEP and non-LEEP groups at any time or on any of the questions. In a study conducted in Thailand, 89 women, mostly married (94.4%), mostly premenopausal (91%; ages 24 to 57) and who had previously undergone LEEP for cervical dysplasia completed a questionnaire on

pre- and post-procedural sexual functioning.[127] The mean length of time between having the procedure and resuming sexual intercourse was 8.1 weeks; most of the interviews were conducted 20 weeks after this point. No statistically significant changes were reported in terms of the frequency of sexual intercourse, dysmenorrhea, dyspareunia, or post-coital bleeding. However, several aspects of sexual functioning did change significantly after LEEP, for the worse: overall satisfaction (p=0.01), vaginal elasticity (p=0.03) and orgasmic satisfaction (0.01).

Anxiety and Depression

An RCT was conducted in the UK to investigate the long-term psychosocial impacts of LEETZ compared to biopsy with post-colposcopy recall for women with low-grade abnormal cytology results.[128] Participants completed seven psychosocial assessments [including the Hospital Anxiety and Depression Scale (HADS)] at baseline, pre-procedure, six weeks post-procedure and 12, 18, 24 and 30 months post-recruitment to measure long-term anxiety and depression [n at recruitment: LLETZ 487, biopsy and recall 502; n at final follow-up: LLETZ 306 (62.8%), biopsy and recall 288 (57.4%)]. There were no differences in the prevalence of significant depression (as indicated by a score of eight or more on the HADS depression sub-scale) between the two groups at any outcome assessment point (cumulative prevalence multivariate OR 0.78, 95% CI 0.52-1.17). At recruitment 7.3% of all women had significant depression, falling to 6.7% at six weeks post-procedure and rising to between 7.9% and 10.7% over the follow-up period. Women about to undergo LLETZ had more significant anxiety (as indicated by a score of 11 or more on the HADS depression sub-scale) than women about to undergo biopsy (16.2% vs. 11.4%, p=0.033). Aside from this one assessment point, there were no differences between groups on anxiety (cumulative prevalence multivariate OR 0.83, 95% CI 0.57-1.19). Similar to the depression findings, across all women there was a higher prevalence of anxiety at recruitment (22.3%) followed by a reduction six weeks post-procedure (8.0%) and a subsequent increase in point prevalence (13.8% to 15.6%) during follow-up.

c. Harms of Treatment of Cervical Cancer: Total Hysterectomy and Radiotherapy

Total Hysterectomy

No evidence was identified that looked at harms of total hysterectomy as a treatment for cervical cancer.

Radiotherapy

One recent systematic review was located that examined the effectiveness and safety of adjuvant therapies including radiotherapy in women who had experienced radical hysterectomy for early stage cervical cancer (FIGO stages IB1, IB2, IIA).[129] Only two RCTs with a combined sample of 397 women met the inclusion criteria of the review, both of which compared adjuvant radiotherapy with no adjuvant radiotherapy. Pooled analysis showed no significant difference in the five-year mortality rates between the treatment and no treatment groups (RR 0.8, 95% CI 0.3-

2.4), although women who underwent radiotherapy demonstrated a significantly lower risk of disease progression after five years of follow-up (RR 0.6, 95% CI 0.4-0.9). The included trials provided minimal information about the side effects of radiotherapy. Summary statistics were computed for three types of adverse events, none of them were significant and all of them had wide confidence intervals [haematological adverse events (grade 3-4) RR 2.38, 95% CI 0.63-9.05; gastrointestinal adverse events (grade 3-4) RR 7.32, 95% CI 0.91-58.82; genitourinary adverse events (grade 3-4) RR 2.12, 95% CI 0.54-8.37]. Thus the review authors concluded the evidence pertaining to the harms of radiotherapy was unclear.

Contextual Question 3: What is the effect of cervical cancer screening in subgroups: reduction in mortality and/or morbidity, and harms? Subgroups include: (a) Aboriginal populations, (b) rural populations, (c) immigrants, (d) pregnant women, (e) women who have sex with women, (f) immunocompromised women, (g) women who had a hysterectomy, (h) women who received the HPV vaccination, and (i) women who have multiple partners or a change in partners. 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?

a. Aboriginal Populations

Two studies were found that looked at cervical cancer screening rates and incidence of cervical cancer in Canadian Aboriginal populations.[130,131] Using data from two waves of the Canadian Community Health Survey (CCHS) (2000-2001, 2004-2005) one study investigated differences in cancer related health services use, including uptake of cervical cancer screening, between various Aboriginal groups and other non-Aboriginal residents of Northern Canada.[130] Of the 6,412 women 21 to 65 years who completed the CCHS survey, 52.5% of Inuit women, 49.2% of Métis women, 55% of First Nations women and 55.4% of non-Aboriginal women had had a Pap test in the previous 12 months. In the previous three years, 75.4% of Inuit women, 80.2% of Métis women, 80.6% of First Nations women and 80.1% of non-Aboriginal women had a Pap test. The likelihood of having a Pap test in the previous three years was lower for Inuit women compared to non-Aboriginal women (adjusted OR 0.63, 95% CI 0.40-0.98). No incidence or mortality rates were reported. However, an epidemiological study was found that examined the incidence of cancers among Inuit groups from 1989 to 2003.[131] During this period cervical cancer was the fourth leading cancer site for all circumpolar Inuit women. Canadian Inuit women had a much lower incidence of cervical cancer (cases/year/100,000: 1.93; age-standardized incidence rate/100,000: 14.7, 95% CI 9.0-20.3) than Inuit women as a whole (cases/year/100,000: 11.77; age-standardized incidence rate/100,000: 20.1, 95% CI 17.1-23.2) and Inuit women living in Greenland (cases/year/100,000: 8.57; age-standardized incidence

rate/100,000: 33.7, 95% CI 27.5-39.9), but a slightly higher rate compared to American Inuit living in Alaska (cases/year/100,000: 1.60; age-standardized incidence rate/100,000: 8.2, 95% CI 4.9-11.5). The risk of developing cervical cancer remained three times higher for Inuit women than non-Inuit women; however between 1999 and 2003 the rate of cervical cancer among Inuit women in all regions was less than half the rates reported in the 1970s and 1980s. This study only looked at circumpolar Inuit populations in Canada, Alaska and Greenland; no incidence or mortality rates were reported for First Nations or Métis women.

b. Rural Populations

No evidence was identified that looked at mortality and/or morbidity outcomes specifically in women who live in rural/remote areas who have undergone cervical screening or that looked at harms of cervical cancer screening in women who live in rural/remote areas.

c. Immigrants

Two population-based cohort studies were found that addressed rates of cervical cancer screening (but not cervical cancer incidence or mortality) among urban immigrant women in Ontario, Canada.[132,133] Of the 2,273,995 screening eligible women aged 25 to 69 years residing in Ontario's metropolitan areas between 2003 and 2005, 61.1% had appropriate screening rates (a Pap test completed during the three year period).[132] Women who registered with Ontario's universal health insurance plan (OHIP) within the preceding five years or preceding 10 years were less likely than long-term residents (Canadian-born women or distant immigrants) to have been screened. Two separate age group analyses (25 to 49 years; 50 to 66 years) were conducted to compare screening rates among most recent immigrants, recent immigrants, and long-term residents. Women aged 25 to 49 years who registered with OHIP in the past five years had an adjusted RR of 0.95 (95% CI 0.94-0.95) for screening when compared with long term residents. Women in this age category who registered with OHIP in the preceding 10 years had an adjusted RR of 0.93 (95% CI 0.92-0.93) compared to long term residents. Women aged 50 to 66 years who registered with OHIP in the past five years had an adjusted RR of 0.70 (95% CI 0.67-0.72) compared to long term residents. Women in this age category who registered in the past 10 years had an RR of 0.75 (95% CI 0.74-0.76) compared to long term residents.

A subsequent study examined cervical screening rates among the 2,865,313 eligible women in Ontario's urban centers between 2006 and 2008.[133] Consistent with the findings of the previous study, 61.3% of women had been screened in the preceding three year period. Except for younger women (aged 18 to 49 years) of Latin American and Caribbean origin, immigrant women from all included regions had significantly lower cervical screening rates than Canadian-born or long-term residents (referent group). In both younger and older age groups (aged 18 to 49 years; aged 50 to 66 years), across all regions of origin, South Asian women had the lowest screening rates compared to the referent group (aged 18 to 49 years adjusted RR 0.81, 95% CI 0.80-0.82; aged 50 to 66 years adjusted RR 0.67, 95% CI 0.65-0.69).

d. Pregnant Women

No evidence was identified that looked at mortality and/or morbidity outcomes specifically in populations of women who are pregnant and who have undergone cervical screening or that looked at harms of cervical cancer screening in pregnant women. Contextual Questions 2d and 2e report evidence from studies that looked at adverse effects on pregnancy related outcomes (e.g., birth weight, duration of gestation, mode of delivery, infant mortality) associated with treatment of cervical cancer (i.e., cone biopsy, LEEP/LEETZ).

e. Women who have Sex with Women

No evidence was identified that looked at mortality and/or morbidity outcomes specifically in populations of women who have sex with women that have undergone cervical screening or that looked at harms of cervical cancer screening in women who have sex with women.

f. Immunocompromised Women

No evidence was identified that looked at mortality and/or morbidity outcomes specifically in populations of immunocompromised women who have undergone cervical screening or that looked at harms of cervical cancer screening in immunocompromised women.

g. Women who had a Hysterectomy

No evidence was identified that looked at mortality and/or morbidity outcomes specifically in populations of women who have had a hysterectomy who have undergone cervical screening or that looked at harms of cervical cancer screening in women who have had a hysterectomy.

h. Women who Received the HPV Vaccination

No evidence was identified that looked at mortality and/or morbidity outcomes specifically in populations of women who received the HPV vaccination who have undergone cervical screening or that looked at harms of cervical cancer screening in women who received the HPV vaccine.

i. Women who have Multiple Partners or a Change in Partners

No evidence was identified that looked at mortality and/or morbidity outcomes specifically in populations of women who have multiple partners or a change in partners who have undergone cervical screening or that looked at harms of cervical cancer screening in women who have multiple partners or a change in partners.

Contextual Question 4: What are the resource implications and cost effectiveness of cervical cancer screening in Canada?

The search identified six studies of costs related to cervical cancer screening; two of these, primarily assessing HPV testing, were US-based[134] and German-based;[135] leaving four that

contained Canadian information.[136-139] Three relevant reports were found in a grey literature search for Canadian data;[136,140,141] one of which was also in peer-reviewed form.[140]

The grey literature search found a Technology Report commissioned by the Canadian Agency for Drugs and Technologies in Health (CADTH) and published on-line in 2008.[141] The purpose of the report was to consider the more expensive liquid-based cytology (LBC) as an alternative to conventional cytology (CC) for cervical cancer screening. A systematic review, meta-analysis, economic analysis and budget impact analysis were done to compare CC and LBC with and without HPV triage at screening intervals of one, two and three years. CADTH concluded that LBC can be cost effective but this alternative also increases colposcopy referrals: compared to current screening practices (yearly CC at 40% coverage), LBC offered every two years increases colposcopy referrals by 48%, lowers average lifetime costs while the disease burden remains similar. Direct comparison of all screening and triage strategies showed that annual screening with CC or LBC is always more costly and less effective than when combined with HPV triage. Compared to annual screening with CC, LBC with HPV triage every two years could reduce disease burden (3,023 women screened would prevent one cancer related death; a gain of 0.0002 QALYs), and reduce the cost ($59 per person), while increasing colposcopy rates by 37.5%. All costs are in 2006 Canadian dollars. The budget impact of LBC with HPV triage was estimated for each province for the first year of implementation (with an expectation that subsequent years would be similar). The range was from $262,000 for PEI, to $22M for Ontario. LBC with HPV triage would cost an additional $6.35 per targeted individual compared to CC.[141]

Kulasingam et al. used a Markov model to assess the cost-effectiveness of 27 different screening strategies in three Canadian provinces (Ontario, Alberta, and Newfoundland) and for Canada overall.[138] The strategies varied with respect to the age at which screening was started, the screening interval (one, two, three, and five years), and whether screening was conducted before 25 years of age. The screening alternatives included Pap test only, HPV test only, or Pap plus HPV in various combinations (triage or co-testing). The base case scenario included screening every year between age 18 and 21, then every three years until age 70 by Pap test alone (at $28/screen in 2006 Canadian dollars). Compared with the base case, the authors found HPV with Pap triage, every three or five years was associated with incremental cost effectiveness ratios (ICERs) less than $50,000 per life year gained; Pap followed by HPV triage was also associated with ICERs that were less than $100,000 per life year gained.[138]

Rogoza and colleagues used Markov modelling of data from five countries to consider optimization of policies for cervical cancer screening including vaccination.[142] For Canada, the base case model included one year screening intervals for women aged 18 to 69 years; 21-48% coverage rate, 12% never screened; cytology test cost $57; colposcopy biopsy cost $144; all costs in 2006 Canadian dollars and discounted. Adding vaccination to current screening predicted reductions in cervical cancers and related deaths by 71-77%. The total per woman lifetime costs in the base case scenario were $906 and $1,163, respectively with and without vaccine; the cost per QALY was $22,532 and the cost per life year gained was $31,817.

Introducing vaccination predicted greater reductions in cervical cancers compared to no vaccination. The model also explored hypothetical policy changes to the screening programs (e.g., reducing recommended frequency of screenings in order to, at least partly, offset the cost of vaccination): in Canada, the least expensive strategy was found to be a five year screening program combined with vaccination whereby the cost would be $657 per woman as opposed to the base case with $1,163 (no vaccine with current yearly screening among ages 18 to 69 years); however, cancer cases would more than double going from 242 to 572 in a cohort of 100,000 women. Increasing the frequency of screenings from five to three years (for 18 to 69 year olds) yielded a QALY of $40,740, and moving to yearly screening for 25 to 60 year olds yielded a QALY of $77,434; both of these scenarios are economically attractive. However, moving back to the base case with vaccine scenario, that is, yearly screening for 18 to 69 year olds instead of 25 to 60 year olds was not economically attractive with a QALY of $1,075,935.[142]

Chuck et al. used a Markov model to compare the cost-effectiveness of seven alternative screening and testing algorithms in Alberta.[139] Each alternative was evaluated at one, two and three-year screening intervals, and assessed versus the current screening strategy (annual screening with Pap plus Pap – for every unsatisfactory specimen the Pap is re-done every three months until a satisfactory specimen is obtained). After eliminating alternatives that were determined to not be cost-effective or to not be acceptable from a cervical cancer policy perspective, the authors reported that three-year Pap plus HPV triage was less costly and more effective, with a cost savings of $16,078 per QALY gained compared to the current screening strategy.[139]

Vijayaraghavan et al. used a Markov model to compare costs, quality of life, and survival in several screening strategies in Québec, including cytology alone (annual and triennial), cytology with HPV triage (annual and triennial), HPV with cytology triage (triennial), HPV and cytology co-testing (triennial), and HPV only (triennial).[137] The estimated annual incidence of cervical cancer was lower in the HPV only versus the cytology only (triennial) arm (145 versus 339 cases), as it was for the estimated number of cervical cancer deaths (33 versus 129 cases). Compared with no screening, the cost-effectiveness ratios for annual cytology, triennial cytology, and triennial HPV testing were $12,653/QALY, $10,161/QALY, and $9,863/QALY, respectively. Compared with triennial cytology, most strategies were cost-effective (ICER range: $8,158/QALY to $27,460/QALY), and the cytology plus HPV triage (triennial) strategy was both less costly and more effective.[137]

Finally, a Québec report conducted a cost analysis that compared the current screening strategy which is based on opportunistic screening (varying between one and three years in frequency) to an organized screening strategy affecting all women aged 21 to 69 years. In the three scenarios hypothesized (two year participation at 75%, two year participation at 80% and three year participation at 80%) total annual Québec costs decreased by, respectively 32%, 28% and 51%.[136]

Contextual Question 5: What are patients' values and preferences regarding cervical cancer screening?

Thirty-five papers were found that addressed the question of patients' values and preferences regarding cervical cancer screening, including two systematic reviews.

Preferences Regarding Screening Intervals

Two studies were found that addressed patients' preferences concerning cervical cancer screening intervals.[143,144] Findings from an American cross-sectional survey of 2,206 women aged 18 to 75 years (with no history of cervical cancer or hysterectomy), suggested that in 2005, most women (78.8%) believed a woman should get a Pap test every year, yet a large percentage (63.1%) of respondents indicated they would be willing to attend for screening every three years.[143] Alternately, results of a discrete choice survey completed by 167 Australian women aged 18 to 69 years, with a history of at least one Pap test, showed that participants would be more likely to attend screening if it was offered annually rather than bi-annually, and less likely to attend for screening if the recommended interval was three or five years.[144]

Preferences Regarding Health Care Providers

Patients' preferences regarding who performs the screening test were addressed in six studies, including one systematic review.[144-149] In a cross-sectional study from Jordan, 674 women ages 17 and older attending family medicine clinics completed a questionnaire assessing factors affecting uptake of screening as well as attitudes towards screening.[146] In terms of gender and clinical specialty, the majority of respondents favored having Pap tests performed by a female physician (71.8%) and by a gynecologist (67.6%). The majority of Crow Indian women who completed a survey about their Pap test screening experience (n=101) also reported they felt more comfortable when a female health care provider performed the test or when another woman was in the exam room during the test.[147] Likewise, the results of qualitative focus groups involving 135 UK residents (85 women, 50 men; aged 20 to 75) of African Caribbean, African Gujarati, Pakistani, Greek, and Arabic origins, identified the gender of the physician as a key factor affecting screening uptake and conveyed a strong preference for female providers.[149] Some participants in a small US qualitative study (interviews with 24 African American women ages 18 to 60) agreed that the presence of a male physician increased their embarrassment and having a female provider makes the process of undergoing a Pap test easier.[145] Results of the discrete choice survey of 167 Australian women mentioned above showed women were less likely to choose to be screened if the provider was male or not their regular physician.[144] Similarly, in a systematic review of sociocultural factors affecting the participation of ethnic and immigrant women in cervical cancer screening in the United States, the presence of a male health care provider was reported as a barrier to screening in three papers.[148]

Cultural Views Affecting Participation in Screening

As well as those mentioned above, six studies examined the impact of cultural views/influences on women's uptake of screening.

One Canadian study[150] aimed to discover how cervical screening might be better utilized by examining the attitudes and beliefs of eight First Nation Cree women living in a reserve community. Results indicated that embarrassment associated with the testing procedure, fear of cancer and lack of adequate information about cervical cancer (e.g., about the disease, screening, diagnosis, treatment) were barriers to screening. The study discussed the traditional belief that loss of the cervix would mean loss of strength or power, as the soul is believed to reside in the cervix, as well as beliefs about who should see the female body and traditional and biomedical health services.

In a focus group study[149] with 135 African Caribbean, African Gujarati, Pakistani, Greek and Arabic women (n=85) and men (n=50), preference for a female GP was reported among Muslim men and women due to the cultural belief that Muslim women may only be seen naked by their husbands. Younger Pakistani women were amenable to the presence of a male GP due to the medical nature of screening, though a female practitioner was still preferred. A doctor who was not of the same cultural background was reported as a motivator in uptake of screening among younger Pakistani Muslim women, due to a fear of "being found out." Low uptake of screening may be linked to the desire to adhere to cultural norms surrounding the preservation of a young woman's virginity before marriage, as stated by Arabic and Pakistani Muslim participants.

Four studies[151-154] presented acculturation as a barrier to cervical cancer screening. In a Canadian cross-sectional study[151] 172 female university students (78 Caucasian; 93 Chinese) and their mothers completed questionnaires regarding Pap test behaviour, indicating that Chinese daughters and mothers attended Pap testing less often and held less accurate beliefs regarding cervical cancer screening than Caucasian women. Among Chinese women, higher heritage acculturation scores were significantly linked to less accurate beliefs and lower Pap testing rates. In a cross-sectional study involving 174 Indian women living in India and Canada, 267 East Asian women in Canada and 222 Euro-Canadian women,[152] a higher level of mainstream acculturation was significantly associated ($p<0.001$) with more accurate reproductive health knowledge in the Indo-Canadian and East Asian Canadian groups. In an American study involving 473 asymptomatic Chinese American women aged 50 years and older, predictors of regular screening included lower cultural views (OR 0.97, 95% CI 0.94-0.99) and greater English proficiency (OR 1.30, 95% CI 1.03-1.64).[153] Another American study of non-Hispanic white women and Asian American women reported the likelihood of being recently screened was higher in women with less Eastern cultural views (OR 1.08, 95% CI 1.00-1.16).[154]

Factors Related to Screening or Intention to be Screened

The majority of studies answering the question of patients' preferences and values focused on factors influencing women's decisions whether or not to be screened. We found two systematic

reviews,[148,155] one integrated review[156] and 24 primary studies[138,145,146,149,153,157-175] that addressed these influencing factors. The themes identified in the three reviews were representative of the themes in the primary studies, with a few unique exceptions: six primary studies identified time as a barrier to women's participation, including "not getting around to it," as well as lack of time due to other commitments or inconvenience of appointments;[157-161,173] three studies identified a history of trauma or abuse as a barrier;[145,164,173] and five studies presented negative health care or Pap test experiences as a barrier to attending screening.[145,159,163-165]

One systematic review reported factors influencing women's decisions to avoid or attend breast and cervical cancer screening.[155] Five of the included studies found women did not attend regular cervical cancer screening because they feared the test results would reveal cancer and they preferred not knowing. Conversely two of the included studies identified fear of not detecting the disease as a motivating factor to continue with regular screening. The review also found that misperceptions about the risks and benefits of cervical cancer screening influenced women's decisions. Reported misperceptions included beliefs that screening was no longer necessary due to age (in women in their mid-50s), reduced risk (due to current or past sexual activity, family history) or general good health (lack of symptoms, self-care). Additionally, support of a health care provider was deemed important, but did not predict adherence to guidelines.

In another systematic review, the sociocultural factors influencing participation rates of ethnic and minority women in the US were examined.[148] Of the 55 studies included in the review, common barriers reported for Asian, Hispanic, Middle Eastern, and African American populations included fatalistic attitudes (22 papers), embarrassment (13 papers), fear of pain, anxiety and stress related to diagnosis (17 papers), lack of provider's recommendation (5 papers), presence of male health care provider (3 papers), distrust of the health care system (7 papers), difficulty finding interpreters (3 papers), lack of knowledge (10 papers) and the belief that screening is not necessary without illness (7 papers). Beliefs unique to specific cultural groups included: body-focused notions among Hispanics, administrative processes in establishing health care among African Americans, and misconceptions concerning susceptibility to cancer as well as stigmatization imposed by community/providers among Asian immigrants.

In an integrated review, the extrinsic and intrinsic factors influencing cervical cancer screening practices of African American and Hispanic women were addressed.[156] Seven studies identified salient beliefs about cancer as a barrier to screening, including fatalistic attitudes and misconceptions about risks, causes and treatments of cervical cancer. The review also reports that if minority women did not perceive themselves as vulnerable they were less likely to obtain a Pap smear. Vulnerability for cervical cancer was believed to be related to physical trauma, an infected partner and lack of feminine hygiene. Without a physician recommendation, these women were also less likely to participate in cervical cancer screening.

Contextual Question 6: What process and outcome performance measures or indicators have been identified in the literature to measure and monitor the impact of cervical screening?

It is important to evaluate the uptake and implementation of clinical practice guidelines. Using performance indicators is one strategy for measuring the reach and application of a guideline into clinical practice and for assessing the impact of guideline implementation on patients' quality of care and health related outcomes. The CTFPHC has established a process for selecting appropriate performance indicators for each of its guidelines.[176] To support this process a search of the grey literature was conducted as part of this review to locate relevant documentation containing performance indicators for cervical cancer. This search located two sources[177,178] which identified a number of potential performance indicators (see Appendix 5). This list was given to the CTFPHC Performance Indicators Subcommittee to assess each item for its relevance, validity, actionability, and feasibility as per established procedures. The short list of indicators and results of this assessment are reported in the guideline document.

Contextual Question 7: What is the evidence of the value of organized screening programs for cervical cancer screening?

Opportunistic or spontaneous cervical screening is the predominant strategy used in some countries, including Canada.[46] Other countries have introduced organized, population-based programs which approach cervical screening in a systematic and coordinated manner. According to the International Agency for Research on Cancer there are eight essential features of an organized screening program: (1) a clearly defined target population, (2) eligible screening participants are identifiable (e.g., a list with names and addresses), (3) processes are in place to maximize reach and encourage participation (e.g., personalized invitation letters), (4) suitable field and lab facilities exist for collecting and analyzing specimens, (5) systematic quality control procedures are in place to assess how tests are performed and interpreted, (6) appropriate facilities exist for diagnosis, treatment and follow-up of patients with confirmed abnormalities, (7) an organized referral system is in place to manage any identified abnormalities and provide information about normal results, and (8) an organized performance measurement/monitoring system is in place to enable collection of relevant and timely epidemiological data.[179]

Evidence from countries with organized cytology screening programs including the Nordic countries and the Netherlands indicated a strong association between those organized programs and the reduction in the burden of cervical cancer disease.[180] In these countries invasive cervical cancer incidence and mortality rates have dropped. In Finland, the nationally organized screening program invites women ages 30 to 64 years for Pap smears every five years.[181] This program was introduced in the 1960s. Since that time there has been a 70% uptake of invitations with an 80% drop in both incidence of and mortality from invasive cervical cancer.[181] The decline in incidence is supported by the results of a case-control study conducted in Finland in the mid-1990s.[73] Based on screening histories provided by 147 women with diagnosed invasive cervical

cancer and 1,098 controls, the evidence showed a significant protective benefit for attending organized screening [OR (adjusted for age and type of screening activity) 0.38, 95% CI 0.26-0.56], and a much smaller, non-significant benefit for any lifetime spontaneous Pap testing [OR (adjusted for age and type of screening activity) 0.82, 95% CI 0.53-1.26]. Cervical cancer screening in Denmark is organized by county and offered to women aged 30 to 64 years. In counties with organized screening that started in 1973 or earlier, incidence of cervical cancer declined and then stabilized.[182] In one county where there was an eight year (1984-1992) disruption in the organized screening program, the incidence of cervical cancer and mortality experienced a corresponding (but temporary) increase.[182] In 1988 the Netherlands initiated a national organized screening program and all women aged 35 to 54 years were offered cervical cancer screening seven times at three year intervals. This program was revised and beginning in 1996 women ages 30 to 60 years were offered cytology screening six times at five year intervals. Rates of mortality from cervical cancer dropped in the Netherlands from 7.3 per 100,000 woman-years in 1970 to 1.9 per 100,000 woman-years in 2007.[183]

Contextual Question 8: What is the evidence of using different categories of health care professionals to perform Pap smears in medical or different settings?

Only one American case-control study was found that looked at the rate of unsatisfactory liquid-based Pap smears performed by different types of physicians practicing in the same university-based medical centre.[184] The non-gynecologists [internal medicine (78%); family practice (12%); geriatrics, pediatrics, occupational and student health (10%)] had significantly higher unsatisfactory Pap test results compared to gynecologists [3% (602/21,964) versus 1% (604/47,165); $p<0.001$]. These physicians were more than twice as likely to collect unsatisfactory cervical cytological specimens as their colleagues with gynecological expertise (OR 2.17, 95% CI 1.94-2.43).

Contextual Question 9: What is the evidence of the value (acceptability, participation rates) of women self-sampling for HPV testing?

Acceptability of Self-testing

A general acceptance of self-sampling, a preference for self-sampling over Pap testing, concerns about the ability to perform the self-test correctly, and preferences for physician-testing based on confidence in testing procedures and skills was reported in the findings of two systematic reviews.[185,186] One systematic review included 20 studies that reported on women's (aged 18 to 64 years) acceptance, preference, willingness and/or attitudes regarding self-sampling after either performing a self-test or having the procedure explained.[185] Self-testing was considered an acceptable screening option by women in seven of the eight studies assessing this outcome. In eight out of 13 studies, women who had experience with both screening approaches preferred self-sampling (63-94%) to physician-testing. Across methods (tampons, vaginal lavage, brush, swab) women reported testing procedures were relatively easy to complete, however in the seven

studies that assessed participants' concerns about self-sampling a key worry centered on whether women could or would take the test properly to provide an adequate specimen. The second systematic review included 25 studies from 14 countries that compared self-sampling to Pap testing.[186] Five of the six studies that asked about test preference found more women would choose a self-test over a physician-performed Pap test; in the remaining study while more women preferred self-testing (23%) to clinician-testing (14%), the majority of women (63%) expressed no preference for a particular collection method. In the four studies that sought explanations for test preference, a common reason for choosing the Pap test was greater confidence in physicians' ability to perform the procedure properly.

Three cross-sectional studies were found that assessed women's opinions of and experiences with self-sampling after performing the test.[187-189] In a small study from the Netherlands, 104 women aged 18 to 59 years, recruited from obstetrics and gynecology clinics, were mailed a self-sampling lavage device with instructions and an acceptability questionnaire.[187] Most participants used the self-sampling kit, completed the survey, and attended the clinic for a scheduled Pap exam (n=91). Of these women, 90 (99%) thought the lavage device was easy to use, although 17 (19%) were not sure if they had performed the test correctly. Sixty-eight (75%) of the women said they would opt for self-sampling over a Pap test for their next screening, primarily because of the time saved and convenience of being able to do the test at home. Eighteen (20%) of the women expressed a preference for clinic-based, physician-performed sampling to ensure correct procedure and accurate results. There were no age differences in testing preference. In another study, 1,213 Hispanic women living in California were recruited to provide unsupervised, self-collected vaginal samples for HPV testing.[188] Most of the participants (78.8%) were aged 18 to 49 years, and 97.2% had had at least one Pap smear. One-third (33.7%) of the women said their overall self-sampling experience was excellent and nearly two-thirds rated their experience as good (32.95%) or very good (30.8%). Almost all (99.2%) of the women thought the self-sampling kit was easy to use, with about half (48.7%) rating ease of use as excellent. Likewise, most of the participants (98.2%) agreed that self-sampling was a convenient option (rated good by 16.4%, very good by 36.5%, excellent by 45.3%) compared with attending clinics for tests performed by physicians. The third study was conducted to find out if self-sampling is an acceptable screening method for Haitian immigrant women living in Miami.[189] Respected community health workers of Haitian decent recruited participants and provided instruction on how to use the tampon-like self-sampling device. Most of the 246 women who completed unsupervised self-sampling felt comfortable using the test (97.6%) and reported the device was easy to use (95.1%). Among women with a history of Pap testing (n=189), 86.8% said they favoured self-sampling. Similar to participants in the Netherlands study[187] the women who preferred Pap smears (13.2%) were not sure they performed the self-sampling test properly and they were more confident that their physicians would collect acceptable specimens. Despite a common concern about whether they had performed the test correctly, women in all three studies reported generally positive experiences with self-sampling and the majority said they preferred self-sampling over clinic-based, physician-performed Pap testing.

The literature search also located three small qualitative studies, two which were conducted in Canada that asked women their opinions on self-sampling without having performed the test.[190-192] One of the Canadian studies included focus groups with 44 women (mean age 37 to 44 years) in three Ontario communities (one small under-serviced northern community, one large urban city, one medium under-serviced city) to explore beliefs about self-sampling.[191] A key concern about self-sampling was the woman's ability to perform the test correctly and safely. Other reservations about self-testing included: losing the benefit of an annual appointment, forgetting to do the test, and physicians blaming women who self-test and later develop cancer. Despite these concerns, some participants said they would opt for self-sampling as an alternative to Pap testing in order to save time, reduce inconvenience, and diminish discomfort and embarrassment. However, logistical questions were raised about the cost for self-sampling kits, whether these costs would be covered under universal health insurance, and where kits could be obtained. A second Canadian study recruited recently immigrated, married mothers, aged 35 to 65 years (n=77) to focus group discussions about self-sampling.[190] Although the women expressed a general interest in self-testing, most said they would not use it. Participants discussed barriers to using the self-sampling approach and provided reasons why they preferred physician-performed Pap tests. Many barriers/reasons reflected concerns about not performing the self-test properly (e.g., not collecting acceptable samples, spilling fluid, effects of menstruation on results, incorrect insertion of the swab). Some women said their cultural and religious norms would proscribe self-testing of the vagina. Nevertheless, participants did agree that self-sampling would be appropriate and more convenient for some groups of women (e.g., those with: limited access to health care; discomfort with or fear of Pap tests or male physicians; busy schedules). Finally, a UK-based study included 28 Muslim women in focus group discussions about their preferences for and attitudes towards self-sampling (all but one of the women had a history of Pap testing).[192] Similar to the study mentioned above, many women said they preferred Pap smears taken by health care providers because of concerns that self-sampling might not be done correctly.[191] Despite their personal preferences, the participants recognized that self-testing offers a good alternative for women who encounter barriers to conventional cervical screening.

Participation Rates for Self-testing

Three primary studies were found that looked at participation rates for HPV self-sampling. One study examined the participation rate among 2,829 Swedish women (30 to 58 years) who had not attended the country's organized screening program for six or more years who were invited to perform HPV self-sampling at home.[193] More than half of the women (n=1,609, 56.9%) ordered the sampling device, of which more than two-thirds (n=1,107, 68.8%) performed the procedure and returned a specimen for HPV testing. There were no significant age differences in participation rates. A cohort study from the Netherlands also investigated the uptake of self-sampling by women not attending organized screening programs.[194] Of 28,071 women who had not responded to two screening invitations, 27,792 were randomly assigned to receive a (lavage) self-sampling kit, and 281 were assigned to a control group that received a third invitation to

attend conventional screening. There was a significant difference in compliance rates between the self-sampling and control groups (after adjustment for prior hysterectomy) [self-sampling: 27.5% (7,404/26,886) vs. control: 16.6% (46/277); 95% CI 6.5-15.3%, p<0.001]. The self-sampling rate did not vary with age. Finally, of the 1,883 Chilean women who participated in the 2003 national household-based health survey that included a self-sampling kit, 1,219 (64.7%) provided a specimen.[195] No reasons were given by the 16.9% of women who declined to provide a vaginal sample, however rates of refusal were higher among younger (< 25 years), older (>60 years), lower education, single and widowed women.

Discussion

To address the questions of interest, this review used a systematic review process and the quality of the evidence provided by the included studies was evaluated using the GRADE system.[66]

The first Key Question looked at the effect of cervical screening on incidence of and mortality from cervical cancer. Our review located one large, recent RCT conducted in India that showed a single lifetime screen by HPV testing or cytology decreased the risks of mortality (RR 0.65, 95% CI 0.47-0.90) and incidence of stage II or higher disease (RR 0.56, 95% CI 0.42-0.75) based on an eight year follow-up and compared to women who were not screened.[72] For the outcome of incidence of invasive cervical cancer, Sankaranarayanan et al. found no protective effect of a single lifetime screen (HPV test or cytology compared with no screening: RR 1.12, 95% CI 0.91-1.39). However, this finding is not consistent with the results of a dozen case-control studies conducted in nations or regions where organized screening programs are in place and/or in countries where women are likely to participate in opportunistic screening. A meta-analysis of these studies clearly demonstrated the protective benefit of cytology (Pap) screening (pooled OR 0.35, 95% CI 0.30-0.41).

Sankaranarayanan et al.[72] produced a methodologically strong study; however this research was downgraded to a moderate quality GRADE rating due to serious concerns about indirectness of the evidence. The results of the study in rural India where the incidence of disease is higher[18] may not be generalizable to the Canadian context where a significant proportion of eligible women have had some form of cervical screening[47] and where the incidence of high grade dysplasia and/or cervical cancer is lower.[19] The quality of the cytology assessment in India compared to other jurisdictions has also been questioned but not assessed.[196] Moreover, concerns have been raised that differences in follow-up care among the four groups in the Indian study could account for the differences seen in mortality rates.[197] Finally, replicating this study (i.e., including a no-screen group) would not be ethical in a countries like Canada where screening services are in place.

Observational studies involve less rigorous methods than RCTs thus they start with a low quality rating in the GRADE system.[66] The group of case-control studies used to answer Key Question 1 were downgraded to a very low quality GRADE rating due to concerns about indirectness of the body of evidence to the Canadian context (five of the 12 studies were conducted in developing nations) as well as the strong likelihood of publication bias. It should also be noted that half of these papers contained data that is at least 20 years old and all of them were based on screening that occurred more than 10 years ago, prior to the introduction of HPV testing.

We found no evidence for liquid-based versus slide-based techniques on cervical cancer incidence or mortality that met the inclusion criteria for this review. There is literature that looks at these techniques with the outcome of pre-cancer but these studies are outside the scope of this review.

With regards to the question asking how primary HPV testing and conventional cytology screening compare in terms of reducing the incidence of or mortality from invasive cervical cancer, the evidence provided by the trial in India showed a single lifetime HPV test was superior to cervical

cytology for decreasing the risks of advanced stage cervical cancer (RR 0.63, 95% 0.42-0.95) and mortality from the disease (RR 0.59, 95% CI 0.39-0.91).[72] These results were supported by another outcome in the Indian study and a second RCT[78] that compared HPV testing against cervical cytology on incidence of all cervical cancer (pooled RR 0.78, 95% CI 0.62-0.99).

One large, recent, high GRADE quality RCT of a population-based screening program in Finland was found to answer the review question that asked how computer-assisted screening compared to conventional cytology screening on the outcomes of cervical cancer mortality and incidence.[79] With a range of follow-up from four to eight years, study results showed no significant difference between these two slide reading techniques on either outcome (cervical cancer mortality RR 1.10, 95% CI 0.63-1.94; incidence of invasive cervical cancer RR 0.99, 95% CI 0.76-1.29).

Methodological variations across studies addressing screening intervals and target ages prevented pooling the data; thus this review is unable to provide definitive answers on when to start screening, when to stop screening, or how often to screen. However the evidence does offer some indications that are useful for decision making. Studies that examined Pap test screening intervals consistently showed: the shortest screening interval offered the greatest protective effect; screening intervals of five years or less appeared to offer substantial protection against cervical cancer; the protective effect of screening diminished with longer intervals between tests but even intervals of 10 to 15 years showed significant protective benefits; and regardless of the specific interval, any screening was better than no screening. In terms of ages when to start and stop screening, a few studies looked at participation trends noting very high screening attendance among women 20 to 35 years, high attendance among women 35 to 49 years, and consistently lower participation in older women. Despite high participation among younger women the benefit of screening women below age 30 is unclear. Screening decisions for this age group must consider the balance between potential benefits and potential harms which appear to be greater in younger women. Alternatively, exposure to cytology screening provides a substantial protective effect in women 30 years and older and there is some evidence this protective effect remains strong in women over 65 years.

Overall the harms of cervical cancer screening have not been well researched. The search for Key Question 2 found evidence for only one of the identified harms, namely false-positives. False-positive test results may lead to additional tests, anxiety and treatment for women who do not have the disease. A small number of very low GRADE quality observational studies (n=6) reported false-positive rates for cervical screening tests for the outcome of invasive cervical cancer. Once again there was too much inconsistency across studies to pool the data. There was wide variation in the false-positive rates reported in the six studies. For instance the false-positive rate for conventional cytology ranged from less than 1%[97] for all diagnoses to over 19%[100] for LSIL, and the false-positive rate for PAPNET read slides was 4% in one study[96] and over 19% in another.[97] Given the differences in this evidence it is difficult to draw any solid conclusions about the harm of false-positives. To supplement this data a Contextual Question examined overdiagnosis, false-positive rates and specificity for cervical cancer screening of pre-cancerous disease. Two recent systematic reviews reported finding no direct evidence for

overdiagnosis linked to screening. Almost two dozen studies were located that reported false-positive rates and/or specificity. This evidence showed: false-positive rates are highest in younger women; cytology tests are more specific than HPV tests with most differences occurring among younger women; and test specificity is lower in younger women. Other evidence reviewed for the Contextual Question on the harms of screening suggests that, in general, women experience little anxiety related to having the procedure performed. However, this seems less the case for some immigrant women who have strong cultural beliefs about exposing the body.

Harms of treatment include the process of further diagnostic tests, some of which have their own set of harms. For example, following a colposcopy approximately 15% of women will experience pain, bleeding or other discharge.[114] Cone biopsy is associated with increased risk of several pregnancy outcomes including severe (<32 to 34 weeks) and extreme (<28 to 30 weeks) pre-term delivery (RR 2.78, 95% CI 1.72-4.51 and RR 5.33, 95% CI 1.63-17.40 respectively)[116], severe (<2000g) low birth weight (2.86, 95% CI 1.37-5.97)[116] and caesarian sections (RR 3.17, 95% CI 1.07-9.40).[117] Absolute risks for adverse obstetric events indicate greater harms associated with cold knife and laser conisation than with LLETZ procedures [e.g., NNTH for: perinatal mortality with cold knife conisation 71, laser conisation 67, LLETZ 500; extreme pre-term delivery with cold knife conisation 53, LLETZ 250; extreme (<1500g) low birth weight with cold knife conisation 36, laser conisation 16, LLETZ 670].[116]

One of the elements of an effective cervical screening program, regardless of the test that is used, is that the program is organized in contrast to an opportunistic approach. An organized program involves monitoring, recall and follow-up. There is no randomized trial comparing organized versus other types of screening strategies. Evidence from the Nordic countries, the Netherlands and the UK indicates a strong association between such programs and the reduction in the incidence of and deaths from cervical cancer.[73,180] In Canada, the degree to which cervical screening programs are organized varies across provinces and territories. The lack of programs and registries to remind women when screening is due or overdue may present a significant barrier to providers and women accepting and/or adapting to changes from annual to longer screening intervals.

Resource implications are important considerations. It appears that liquid-based cytology compared to conventional cytology reduces costs of screening but increases referrals to colposcopy.[141] However, it is difficult to draw conclusions based on the identified studies as all tested different strategies, with different inputs into the models.

Whether the program is organized or opportunistic, patients' values and preferences influence their screening intentions and follow-through. Patients' preferences concerning screening intervals are not consistent. In the older American study where the guidelines recommended annual screening, women requested less frequent testing (i.e., tri-annual).[143] In the more current Australian work where the guidelines recommended screening every two years, women preferred annual screening.[144] Concerning the provider of the test, six studies using survey or qualitative methodology showed a preference for a female practitioner.[144-149] Cultural beliefs also influence

participation in screening. In a Canadian study with First Nation Cree women, embarrassment, fear of cancer, and lack of adequate information were barriers to screening.[150] In a focus group study of Muslim women and men, it was articulated that women may only be seen naked by their husbands.[149] It appears screening uptake among immigrant populations varies based on English proficiency and lower cultural views.[151-154] Recently immigrated women are less likely than those who have had a long term residency in Canada to participate in screening.[132] Intention to be screened was addressed in one systematic review.[155] Here three factors were identified: fear of the test, misperception of risk and benefits, and confusing recommendations from health care providers. A second systematic review indicated that participation rates among ethnic and minority women in the US were associated with fatalistic attitudes, lack of knowledge, fear of the procedure threatening virginity, and a belief that screening is unnecessary.[148]

Limitations

The findings of this review are impacted by the biases and limitations of the literature and the included studies. For the question on the effect of cervical cancer screening on mortality, all of the data came from one RCT of a single lifetime screen offered to women in rural villages in India with follow-up limited to eight years. No studies reported on the outcome of all-cause mortality and there was no evidence that met our inclusion criteria for the effectiveness of liquid-based versus slide-based screening or reflex HPV testing versus conventional cytology. The bulk of the evidence used to answer the other Key Questions was taken from low or very low GRADE quality case-controls, the results of which need to be considered with caution. Finally, we restricted our search to papers in English or French, thus we may have missed the opportunity to analyze data from papers written in other languages.

Conclusion

The ultimate goal of cervical screening is to decrease the incidence of and mortality from invasive cervical cancer. The evidence presented in this systematic review supports the conclusion that screening does offer protective benefits and is associated with a reduction in these critical outcomes. Compared to the Canadian context where the majority of eligible women have been screened and most participate in routine testing, an RCT in India showed that even a single lifetime HPV test significantly decreased incidence of and mortality from invasive cervical cancer compared to no screening. Cytology screening was shown to be beneficial in a cohort study that found Pap testing significantly reduced the incidence of invasive cervical cancer compared to no screening. Pooled evidence from a dozen case-control studies conducted in North America and abroad also indicated a significant protective effect of cytology screening. This review found no conclusive evidence for establishing optimal ages to start and stop cervical screening, or to determine how often to screen; however the evidence suggests substantial protective effects for screening women 30 years and older and for intervals of up to five years.

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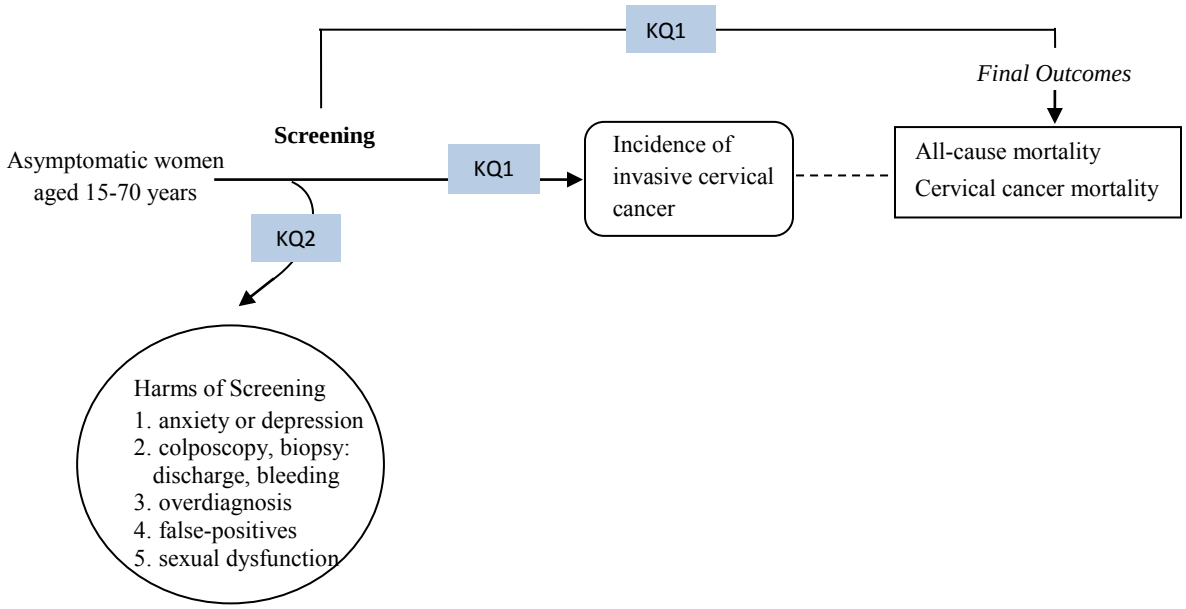
Figure 1: Analytic Framework and Key Questions



Key Questions (KQ) considered for this review include:

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

- 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 cytology screening?
- KQ1c. Does computer-assisted screening reduce incidence of or mortality from invasive cervical cancer compared to conventional cytology screening?
- KQ1d. How does varying the screening interval affect incidence of or mortality from invasive cervical cancer?
- KQ1e. How does varying the age at which screening is started or stopped reduce incidence of or mortality from invasive cervical cancer?

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

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

Additional Contextual Questions (CQ) are:

CQ1. What are the harms of cervical cancer screening for pre-cancer (i.e., overdiagnosis and false-positive rates and specificity)?

CQ2. What are the harms of treatment of cervical cancer? Harms include: (a) harms of colposcopy, (b) harms of biopsy: cone biopsy (immediate and late effects; pre-term labour, miscarriage) and LEEP/LEETZ (immediate and late effects), (c) harms of treatment of cervical cancer: total hysterectomy (incontinence, infection, hospitalization) and radiotherapy.

CQ3. What is the effect of cervical cancer screening in subgroups: reduction in mortality and/or morbidity, and harms? Subgroups include: (a) Aboriginal populations, (b) rural populations, (c) immigrants, (d) pregnant women, (e) women who have sex with women, (f) immunocompromised women (e.g., with HIV), (g) women who had a hysterectomy, (h) women who received the HPV vaccination, and (i) women who have multiple partners or a change in partners. 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?

CQ4. What are the resource implications and cost effectiveness of cervical cancer screening in Canada?

CQ5. What are patients' values and preferences regarding cervical cancer screening?

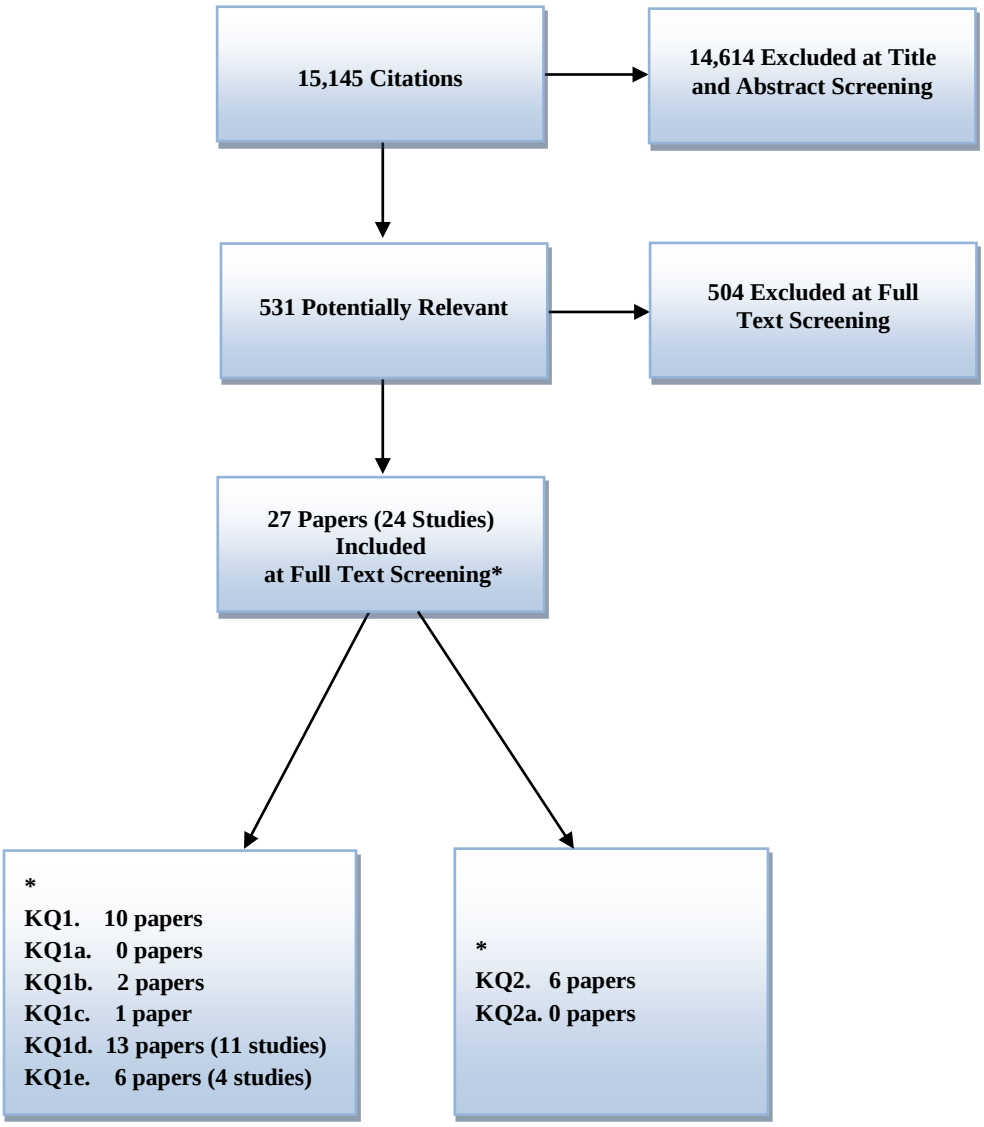
CQ6. What process and outcome performance measures or indicators have been identified in the literature to measure and monitor the impact of cervical screening?

CQ7. What is the evidence of the value of organized programs for cervical cancer screening?

CQ8. What is the evidence of using different categories of health care professionals to perform Pap smears in medical or different settings?

CQ9. What is the evidence of the value (acceptability, participation rates) of women self-sampling for HPV testing?

Figure 2: Search Results



*numbers of papers do not total 27 because papers/studies were used to answer more than one question

Table 1: Cervical Smear Classification Systems

Dysplasia (Cytology)	CIN (Histology)[15]	Bethesda (Cytology)[14]
Atypia	Atypia	ASC-US
HPV Effect	HPV Effect	LSIL
Mild Dysplasia	CIN 1	
Moderate Dysplasia	CIN 2	HSIL
Severe Dysplasia	CIN 3	
Carcinoma in Situ		
Invasive Cancer	Invasive Cancer	Invasive Cancer

Table 2: Inclusion/Exclusion Criteria

Population	Include women who are at risk for cervical cancer, between ages of 15 and 70 years, who are or who have ever been sexually active. Studies that examine age groups separately will be of great value.
Country	Include any country. 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	Include 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	Include incidence of invasive cervical cancer (squamous and adenocarcinoma); cervical cancer mortality and all-cause mortality. Exclude corpus uteri cancer.
Harms of Screening	Include anxiety and/or depression; sexual dysfunction; colposcopy and biopsy procedures (discharge, bleeding); overdiagnosis; false-positives
Study Design	Include meta-analyses, RCTs, observational studies (cohort studies, case-control studies).
Language	English or French

Table 3: Outcomes and Harms of Screening – Ranking of Importance for Clinical Decision Making

Outcome (O) / Harm (H)	Ranking	Importance
All-Cause Mortality (O)	9	Critical
Cervical Cancer Mortality (O)	9	Critical
Invasive Cervical Cancer (O)	8	Critical
Overdiagnosis (H)	7	Critical
False-Positive (H)	5	Important
Colposcopy Rate (H)	5	Important
Anxiety/Depression (H)	5	Important
Sexual Dysfunction (H)	5	Important

Table 4: Summary of Risk of Bias for RCT Studies*

Study	Random Sequence Generation (selection bias)	Allocation Concealment (selection bias)	Blinding of Participants and Personnel (performance bias)	Blinding of Outcome Assessment (detection bias)	Incomplete Outcome Data (attrition bias)	Selective Reporting (reporting bias)	Other Bias
Anttila[78]	High Risk	Unclear	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
	Probably not done	Does not specify	Not possible; unlikely to influence results	Probably not done; unlikely to influence results	Analysis by intention to screen	All outcomes of interest reported	No other sources of bias observed
Anttila[79]	High Risk	Unclear	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
	Personal identifiers used for allocation	Does not specify	Not possible; unlikely to influence results	Probably not done; unlikely to influence results	Analysis by intention to screen	All outcomes of interest reported	No other sources of bias observed
Sankaranarayanan[72]	Unclear	High Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
	Does not specify	Probably not done	Not possible; unlikely to influence results	Probably done	Analysis by intention to screen	All outcomes of interest reported	No other sources of bias observed

*Assessed using Cochrane Review Manager Risk of Bias Tool[198]

Table 5: Summary of Quality Assessment for Case-Control Studies*

Study	A: Selection				B: Comparability		C: Exposure			Total Stars
	A1: Adequate Case Definition	A2: Representative Cases	A3: Selection of Controls	A4: Definition of Controls	B1a: Controls for Age	B1b: Controls for Other Important Factors	C1: Ascertainment of Exposure	C2: Method of Ascertainment	C3: Non-response Rate	
Andrae[80]	Independently validated★	Consecutive cases★	Community controls★	No history of disease★	Yes★	No	Secure record★	Same for both groups★	Same for both groups★	8
Aristizabal[104]	Independently validated★	Representative cases★	Community and hospital controls★	Not stated	Yes★	Neighbourhood★	Secure record and non-blinded interview★	Same for both groups★	Not stated	7
Berrino[105]	Independently validated★	Consecutive cases★	Hospital controls	No history of disease★	Yes★	No	Secure record★	Same for both groups★	Same for both groups★	7
Clarke[106]	Independently validated★	Representative cases★	Community controls★	Not stated	Yes★	Neighbourhood and type of dwelling★	Secure record and non-blinded interview★	Same for both groups★	Non-respondents described	7
Decker[81]	Independently validated★	Consecutive cases★	Community controls★	No history of disease★	Yes★	Area of residence★	Secure record★	Same for both groups★	Same for both groups★	9
Hernández-Avila[82]	Independently validated★	Representative cases★	Community controls★	Not stated	Yes★	Age started sex, # normal births, # sex partners, SES★	Non-blinded interview	Same for both groups★	Rate different/no designation	6
Herrero[107]	Independently validated ★	Not stated	Hospital controls	No history of disease★	No	No	Non-blinded interview	Same for both groups★	Same for both groups★	4
Hoffman[83]	Independently validated★	Not stated	Hospital controls	No history of disease★	Yes★	Race, area of residence, hospital★	Interview	Same for both groups★	Same for both groups★	6
Jiménez-Pérez[84]	Independently validated★	Consecutive cases★	Hospital controls	No history of disease★	Yes★	Area of residence★	Non-blinded interview	Same for both groups★	Same for both groups★	7
Kasinpila[102]	Independently validated★	Consecutive cases★	Hospital controls	No history of disease★	Yes★	Significant risk factors★	Non-blinded interview	Same for both groups★	Same for both groups★	7
La Vecchia[108]	Independently validated★	Representative cases★	Hospital controls	No history of disease★	Yes★	No	Interview	Same for both groups★	Same for both groups★	6

Study	A: Selection				B: Comparability		C: Exposure			Total Stars
	A1: Adequate Case Definition	A2: Representative Cases	A3: Selection of Controls	A4: Definition of Controls	B1a: Controls for Age	B1b: Controls for Other Important Factors	C1: Ascertainment of Exposure	C2: Method of Ascertainment	C3: Non-response Rate	
Makino[85]	Independently validated★	Potential for selection bias	Community controls★	No history of disease★	Yes★	Area of residence★	Self-report	Same for both groups★	Same for both groups★	7
Miller[87]	Independently validated★	Potential for selection bias	Hospital controls	No history of disease★	Yes★	Length of membership in health program, race/ethnicity★	Secure record★	Same for both groups★	Same for both groups★	7
Nieminen[73]	Independently validated★	Consecutive cases★	Community controls★	Not stated	Yes★	Socio-demographic factor, parity, smoking★	Self-report	Same for both groups★	Rate different/no designation	6
Sasieni[88-91]	Independently validated★	Consecutive cases★	Community controls★	Not stated	Yes★	Area of residence★	Secure record★	Same for both groups★	Same for both groups★	8
Talbott[86]	Independently validated★	Consecutive cases★	Community controls★	Not stated	Yes★	Sex, race, street or neighbourhood★	Non-blinded interview	Same for both groups★	Same for both groups★	7
Yang[92]	Record linkage	Not stated	Hospital controls	No history of disease★	Yes★	No	Secure record★	Same for both groups★	Same for both groups★	5
Zappa[93]	Independently validated★	Consecutive cases★	Community controls★	Not stated	Yes★	No	Secure record★	Same for both groups★	Same for both groups★	7

*Assessed using Newcastle-Ottawa Scale[69]

Table 6: Summary of Quality Assessment for Cohort Study*

Study	A: Selection				B: Comparability		C: Outcome			Total Stars
	A1: Representative-ness of exposed cohort	A2: Selection of non-exposed cohort	A3: Ascertainment of exposure	A4: Outcome not present at outset	B1a: Comparability of cohorts: age	B1b: Comparability of cohorts on additional factor	C1: Assessment of outcome	C2: Length of follow-up	C3: Adequacy of cohort follow-up	
Herbert[94]	Truly representative ★	Same community★	Secure record★	Yes★	Yes★	No	Record linkage★	Yes★	Complete follow-up – all subjects accounted for★	8

*Assessed using Newcastle-Ottawa Scale[69]

Table 7: Characteristics of Included Studies for KQ1 - What is the effect of cervical cancer screening on incidence of and mortality from invasive cervical cancer?

First Author **Country**	Andrae[80] Sweden
Name of Study	Screening-preventable cervical cancer risks: Evidence from a nationwide audit in Sweden
Objective	To perform a nationwide audit of effectiveness of the Swedish national cervical cancer screening program
Methods	**Design**: Case-control **Selection:** Cases: all invasive cervical cancer cases diagnosed in Sweden (1 January 1999 – 31 December 2001) reported to Swedish Cancer Registry; Controls: 5 age matched controls per case randomly selected from National Population Register
Participants	**Sample**: Cases n=1,230; Controls n=6,124 **Characteristics:** Ages 20-99 years (age at diagnosis)
Intervention	**Type of test**: Pap test Recommended interval: 3.5 years for women aged 53 years and under; 5.5 years for women aged 54-65; 6.5 years for women aged 66 years and older
Outcomes	**Reported by study authors:** Women who did not have a Pap test within the recommended interval were significantly more likely to be diagnosed with cervical cancer than women who were screened (OR 2.52, 95% CI 2.19-2.91)
	Reported in this review (inverted values, odds of exposure to screening): Excluding tests performed six months prior to case diagnosis, results showed a significant protective effect of undergoing one or more Pap tests within the recommended interval (OR 0.40, 95% CI 0.34-0.46)
First Author **Country**	Aristizabal[104] Colombia
Name of Study	The impact of vaginal cytology on cervical cancer risks in Cali, Colombia
Objective	To investigate the role of cytology screening in preventing invasive cervical cancer
Methods	**Design**: Case-control **Selection**: Patients with newly-diagnosed invasive cervical cancer who were reported to the Cali cancer registry (1977-1981) and successfully traced for interview (22% of total), supplemented by 73 patients (diagnosed 1971-1976) currently under treatment

	and/or observation; two sets of controls, both age matched ±2 years, one identified at the clinic where case diagnosed and one residing in the same neighbourhood as case
Participants	**Sample:** Total=831; Cases n=277; Controls n=554 (277 neighbourhood, 277 health center) **Characteristics:** Ages 16-60 years
Intervention	**Type of test:** Cytology
Outcomes	**Reported by study authors:** Strong protective effect of cytology screening in reducing relative risks for invasive cervical cancer using neighbourhood controls (RR 9.9, no CI reported) Extremely strong protective effect of cytology screening in reducing relative risks for invasive cervical cancer using health center controls (RR 23.9, no CI reported)
	Reported in this review (inverted values, calculated CIs, odds of exposure to screening): Cytology screening had a strong protective effect (neighbourhood controls OR 0.10, 95% CI 0.05-0.19; health centre controls OR 0.04, 95% CI 0.02-0.08)
First Author **Country**	Berrino[105] Italy
Name of Study	Efficacy of screening in preventing invasive cervical cancer: A case-control study in Milan, Italy
Objective	To elucidate screening as a protective factor as well as a means of diagnosis for cervical cancer
Methods	**Design**: Case-control **Selection**: All invasive cervical cancer newly diagnosed in 1978 in Milan, identified through the Regional Hospital Discharge Diagnosis Information System and through a survey of gynecology and pathology departments of Milan hospitals; 3 hospital controls per case, hospitalized for reasons other than gynecological or breast cancer
Participants	**Sample:** Total=471; Cases n=121; Controls n=350
Intervention	**Type of test**: Pap test
Outcomes	**Reported by study authors:** The crude relative risk for developing cervical cancer with a history of at least one screen compared to no screening was 0.61 (no CI reported).
	Reported in this review (calculated CI, odds of exposure to screening): There is a non-significant benefit of a history of undergoing at least one Pap test (OR 0.61, 95% CI 0.36-1.04)

First Author **Country**	Clarke[106] Canada
Name of Study	Does screening by "Pap" smears help prevent cervical cancer? A case-control study
Objective	To test the hypothesis that Pap testing is an effective screening procedure for invasive cervical cancer
Methods	**Design:** Retrospective case-control **Selection:** Cases were women with newly diagnosed invasive cervical cancer admitted to the Princess Margaret Hospital 1 October 1973 to 30 September 1976; 5 age matched (±10 years) controls for each case, also matched by neighbourhood and type of dwelling, recruited by door-to-door calls
Participants	**Sample**: Total=1,272; Cases n=212; Controls n=1,060 **Characteristics:** Cases mean age 52.4 years; Controls mean age 51.5 years; Highest mean grade achieved in school was 9.9 in cases and 11.1 in controls ($p<0.05$); 54% of cases had family income below $10,000 compared with 41% of controls ($p<0.001$)
Intervention	**Type of test:** Pap test
Outcomes	**Reported by study authors:** Results showed a relative risk for invasive cervical cancer of 2.7 (95% CI 2.0-3.7, $p<0.0001$) in women who had not been screened by a Pap smear compared to those who had been screened
	Reported in this review (inverted values, odds of exposure to screening): Results showed a significant protective effect of having had at least one Pap test in the previous 60 months (OR 0.37, 95% CI 0.27-0.50)
First Author **Country**	Decker[81] Canada
Name of Study	Papanicolaou test utilization and frequency of screening opportunities among women diagnosed with cervical cancer
Objective	To examine the screening history of women in Manitoba diagnosed with invasive cervical cancer and to explore whether opportunities for screening were missed
Methods	**Design:** Case-control **Selection:** Cases were women aged 18 and older who resided in Manitoba and were diagnosed with invasive cervical cancer between 1989 and 2001, identified through Manitoba Cancer Registry; 5 controls for each case matched by age (±1 year) and area of residence, identified through the Manitoba Health Insurance Plan Registration file
Participants	**Sample**: Cases n= 666; Controls n=3,343

	Characteristics: Mean age at the time of diagnosis of invasive cervical cancer was 50 years; the mean income was $39,175 for cases and $42,280 for controls
Intervention	**Type of test**: Pap test
Outcomes	**Reported by study authors:** Women with no Pap test within the specified interval (5 years prior to case diagnosis) were more likely to be diagnosed with invasive cervical cancer than women who were tested (adjusted OR 2.77, 95% CI 2.30-3.30)
	Reported in this review (inverted values, odds of exposure to screening): There was a significant protective effect of having had a Pap test in the 6 to 60 month interval prior to diagnosis of the case (OR 0.36, 95% CI 0.30-0.43)
First Author **Country**	Herbert[94] UK
Name of Study	Relation between the incidence of invasive cervical cancer and the screening interval: Is a five year interval too long?
Objective	To examine the incidence of invasive cervical cancer per 100,000 women years at risk and relative risk according to screening history among eligible women aged 25-69 in Southampton and South West Hampshire during the three years after completion of the first round of comprehensive screening
Methods	**Design:** Cohort **Selection:** Study group comprised 116,022 women aged 25-69, registered with general practitioners in Southampton and South West Hampshire and eligible for screening, obtained from local cancer registry data, histology records at Southampton General Hospital, Wessex radiotherapy and oncology units, and records from adjacent district general hospitals and local private hospitals Excluded: women who had hysterectomies for unrelated disease
Participants	**Sample:** 116,022 women **Characteristics:** Ages 25-69
Intervention	**Type of test**: Pap test Four study groups: a) short interval - women screened within 3.5 years; b) long interval - women screened within 3.5-5.5 years; c) overdue - women who had a cytology record but had not been screened within 5.5 years; d) no cytology record
Outcomes	**Reported by study authors:** The incidence of invasive cervical cancer was significantly higher among women who did not participate in the country's comprehensive screening program (i.e., they had no Pap tests in the preceding 6 to 66 months) than among women who were screened during this interval (RR 2.622, 95% CI 1.586-4.334)

	Reported in this review (inverted values): The incidence of invasive cervical cancer was significantly lower among women who participated in the country's comprehensive screening program (i.e., they had at least one Pap test in the preceding 6 to 66 months) than among women who were not screened during this interval (RR 0.38, 95% CI 0.23-0.63, p=0.0002)
First Author **Country**	Hernández-Avila [82] Mexico
Name of Study	Evaluation of the cervical cancer screening programme in Mexico: A population-based case-control study
Objective	To determine the preventive effect of the cervical cancer screening program among women in Mexico City between September 1990 and December 1992
Methods	**Design:** Case-control **Selection:** Cases were women with newly incident cervical cancer, <75 years of age, residents of Mexico City for at least 2 years, identified from six hospitals, attending the gynecological clinic for histological confirmation of cervical neoplasm; controls were age-stratified (25-80) random sample of residents of Mexico City (for at least 2 years), identified from 3,694 randomly selected households
Participants	**Sample:** Cases (cancer in situ) n=233; Cases (invasive cervical cancer) n=397; Controls n=1,005 **Characteristics:** Age range was 25-80; Mean age was 48 (standard deviation [SD] = 13.5) for controls, 47.6 (SD=13.1) for invasive cervical cancer cases and 44.7 (SD=12.6) for in situ cases
Intervention	**Type of test**: Pap test
Outcomes	**Reported by study authors:** Significant and strong protective effect of Pap screening; adjusted OR for women with no previous Pap test compared to those who sought the Pap test spontaneously 0.38 (95% CI 0.28-0.52) (adjusted for age, age at start of sex life, number of normal births, number of sex partners, socioeconomic level)
	Reported in this review (odds of exposure to screening): Same as above
First Author **Country**	Herrero[107] Latin America
Name of Study	Screening for cervical cancer in Latin America: A case-control study
Objective	To examine cervical cancer screening patterns in Latin America
Methods	**Design**: Case-control

	Selection: Cases were women with newly diagnosed invasive cervical cancer, <70 years of age; Bogota and Mexico City controls - two age matched hospital controls, excluding psychiatric diagnoses or diseases related to the exposures of interest; Costa Rica and Panama Controls – one hospital control and one community control randomly chosen from current census listings of the country of residence of the case
Participants	**Sample:** Total=2,189; Cases n=759; Controls n=1,430 **Study recruitment years:** 1986-1987
Intervention	**Type of test:** Pap test
Outcomes	**Reported by study authors:** The age adjusted relative risk associated with never being screened and developing cervical cancer was 2.5 (95% CI 2.1-3.3)
	Reported in this review (inverted values, odds for exposure to screening): The findings indicated that any history of Pap testing offered a protective benefit (age adjusted OR 0.40, 95% CI 0.32-0.50)
First Author **Country**	Hoffman[83] South Africa
Name of Study	Limited Pap screening associated with reduced risk of cervical cancer in South Africa
Objective	To investigate the effect of Pap smear screening on the incidence of invasive cervical cancer in the Western Cape, South Africa
Methods	**Design**: Case-control **Selection**: Incident cases of invasive cervical cancer who presented at 2 tertiary hospitals; control subjects matched for age, race, place of residence and hospital
Participants	**Sample:** Cases n=524; Controls n=1,540 **Characteristics:** Women <60 years of age who lived within 150 km of Cape Town, South Africa for 6 or more months of the preceding year
Intervention	**Type of test**: Pap test
Outcomes	**Reported by study authors:** The OR of cervical cancer for women with any history of screening, regardless of the specific interval, was significantly reduced compared to women who had never had a Pap test (adjusted OR 0.3, 95% CI 0.3-0.4)
	Reported in this review (extra decimals calculated, odds of exposure to screening): The results showed any opportunistic cervical screening offered significant protective benefits (multivariate adjusted OR 0.30, 95% CI 0.26-0.35)

First Author **Country**	Jiménez-Pérez [84] Mexico
Name of Study	Has the use of pap smears reduced the risk of invasive cervical cancer in Guadalajara, Mexico?
Objective	To estimate the magnitude of the association between utilization of Pap smears and risk of invasive cervical cancer in women living in the metropolitan area of Guadalajara
Methods	**Design:** Case-control **Selection:** Cases were women diagnosed with invasive cervical cancer from Aug 1991 through March 1994, either histologically confirmed or diagnosed with clinical disease stage IB through IV, <70 years of age, residing for at least the past year in Guadalajara, referred for treatment or consultation to the study hospitals; 2.2 controls for each case (±3 years) with similar restrictions on place of residence, obtained from among women currently attending the same health center in which the case was first seen for reasons unrelated to cervical screening or gynecologic or obstetric condition, or, if the case was initially evaluated at a hospital, the health center closest to the case's area of residence
Participants	**Sample:** Cases n=143; Controls n=311 **Characteristics:** Cases average age 49.5 years; Controls average age 49.1 years; Cases and controls had very similar residence histories
Intervention	**Type of test**: Pap test
Outcomes	**Reported by study authors:** Age adjusted OR of invasive cervical cancer for women who have a history of Pap testing compared to those who have never been tested 0.3 (95% CI 0.2-0.4)
	Reported in this review (extra decimals calculated, odds of exposure to screening) Not including smears performed 12 months prior to case diagnosis, the results showed a significant protective effect of cytological screening (OR 0.30, 95% CI 0.21-0.42)
First Author **Country**	Makino[85] Japan
Name of Study	Evaluation of the effectiveness of cervical cancer screening: A case-control study in Miyagi, Japan
Objective	To estimate the effectiveness of screening for invasive cervical cancer
Methods	**Design:** Case-control **Selection:** Cases included mass-screen detected cases and outpatient detected cases (women with genital bleeding, discharge, or pelvic pain who had documented cervical smears) identified through cytology files of the Center for Clinical Cytology; 2 controls matched for each case by age (±5 years) and district of residence; controls for the mass screen-detected cases were selected from women who participated in the mass

	screening program, controls for the outpatient-detected cases selected from women who had visited gynecologists and had cervical smear examinations (record numbers were the nearest to the cases on the cytology file)
Participants	**Sample:** Cases n=198 cases (129 mass screen-detected and 69 outpatient-detected); Controls n=396 **Characteristics:** Cases 35-79 years
Intervention	**Type of test**: Pap test
Outcomes	**Reported by study authors:** Compared with women who had no prior screening, women who were tested through mass screening had an OR for invasive cervical cancer of 0.14 (95% CI 0.077-0.263)
	Reported in this review (odds of exposure to screening): Using only the findings that pertained to the 65% of cases (n=129) with screen detected cervical cancer and excluding diagnostic tests, the results indicated any history of cervical screening had a strong protective effect (OR 0.14, 95% CI 0.08-0.26)
First Author **Country**	Nieminen[73] Finland
Name of Study	Organised vs. spontaneous Pap-smear screening for cervical cancer: A case-control study
Objective	To compare the effect of organized Pap smear screening for cervical cancer against spontaneous screening on the incidence of invasive cervical cancer
Methods	**Design:** Case-control **Selection:** Cases were all 179 incident cases of invasive cervical cancer treated during the years 1987-1994 in the Department of Obstetrics and Gynaecology, Helsinki University Central Hospital (HUCH), and alive in 1994; controls were sampled from the Finnish Population Registry restricted to the HUCH catchment area
Participants	**Sample:** Cases n=179 cases; Controls n=1,507; Complete data on Pap histories for 147 cases and 1,098 controls) **Characteristics:** Mean age of cases and the controls 60 years (range 30-91 years); Cases almost the same overall socio-economic status as controls; Cases smoked significantly more often than controls (OR 3.42, 95% CI 2.32-5.05 for smoking in the age adjusted model); No observed differences in parity between cases and controls
Intervention	**Type of test**: Pap test
Outcomes	**Reported by study authors:** The age adjusted OR of invasive cervical cancer among those ever participating in the organized screening program was 0.36 (95% CI 0.25-0.53) Any lifetime spontaneous Pap smear had also a favourable, however weaker effect with an OR of 0.73 (95% CI 0.49-1.07)

	Reported in this review (odds of exposure to screening): Any testing in the organized screening program offered a protective benefit (age adjusted OR 0.36, 95% CI 0.25-0.52) Opportunistic cervical screening showed a non-significant benefit (age adjusted OR 0.73, 95% CI 0.49-1.08)
First Author **Country**	Sankaranarayanan[72] India
Name of Study	HPV screening for cervical cancer in rural India
Objective	To measure the effect of a single round of screening by testing for HPV, cytology or visual inspection on the incidence of cervical cancer and the associated rates of death in Osmanabad district in India
Methods	**Design**: RCT with cluster randomization **Selection:** 52 villages randomly assigned to one of 4 groups (HPV testing, cytology testing, visual inspection, or standard care); 13 villages in each group
Participants	**Sample**: Total: 131,746; HPV testing (34,126 invited; 27,192 attended); Cytology (32,058 invited; 25,549 attended); Visual inspection (outside scope of this review); Control/standard care: 31,488 **Characteristics:** Ages 30-59 years, healthy, currently or previously married, not pregnant, intact uterus, no history of cervical cancer, living in one of the study clusters
Intervention	**Intervention groups:** HPV test, cytology, visual inspection; women informed of the causes of cervical cancer, signs and symptoms, prevention, early detection and treatment and given a card indicating the date, time and place of screening **Control group:** No screening offered but women were told how to seek screening at local hospitals **Length of follow-up:** 8 years (January 2000 to December 2007)
Outcomes	**Mortality from cervical cancer (reported by study authors and in this review):** • Age adjusted HR 0.52 (95% CI 0.33-0.82) for mortality in HPV group compared to no screening; non-significant reduction in risk of death in the cytology group (age adjusted HR 0.89, 95% CI 0.62-1.28) **Incidence of cervical cancer (reported by study authors and in this review):** • Age adjusted HR 1.05 (95% CI 0.77-1.43) for detection of cervical cancer in HPV group compared to no screening; non-significant reductions in incidence in the cytology group with age adjusted HR 1.34 (95% CI 0.99-1.81) **Incidence of stage II or higher cervical cancer (reported by study authors and in this review):** • Age adjusted HR 0.47 (95% CI 0.32-0.69) for detection of advanced cervical cancer in HPV group compared to no screening; non-significant reductions in incidence in the cytology group with age adjusted HR 0.75 (95% CI 0.51-1.10)

First Author **Country**	Talbott [86] USA
Name of Study	Refining preventive strategies for invasive cervical cancer: A population-based case-control study
Objective	To investigate the protective effect of Papanicolaou test screening and contacts with the medical care system when considered in conjunction with established risk factors for cervical cancer
Methods	**Design:** Case-control **Selection:** Women diagnosed with invasive cervical cancer from July 1, 1984 through June 30, 1985 were identified through the Pennsylvania Cancer Registry; control matched sex, race and age (within 5 years) living on the same street or in same neighbourhood at time of diagnosis; cross-referenced telephone directories were used to identify households on the same street as the case Excluded: unknown race or stage at diagnosis, race other than white or black, deceased at entry into the registry and aged 80 years or older at time of diagnosis because of the difficulty in enrolling and interviewing older individuals
Participants	**Sample:** 143 matched pairs **Characteristics:** Cases average age 45.2 years; Controls average age 44.6 years
Intervention	**Type of test:** Pap test
Outcomes	**Reported by study authors:** Adjusted OR 3.10 (95% CI 1.45-6.64, p=0.0003) for women with no Pap test within 3 years compared to women who were screened within that interval
	Reported in this review (inverted values, odds for exposure to screening): Excluding any diagnostic Pap tests performed in the previous 12 months, any screening in the three year interval prior to case diagnosis had a protective effect (multivariate adjusted OR 0.32, 95% CI 0.15-0.69)

Table 8: Characteristics of Included Studies for KQ1b - Does either primary or reflex HPV testing reduce incidence of or mortality from invasive cervical cancer compared to conventional cytology screening?

First Author **Country**	Anttila[78] Finland
Name of Study	Rate of cervical cancer, severe intraepithelial neoplasia, and adenocarcinoma in situ in primary HPV DNA screening with cytology triage: Randomised study within organised screening programme
Objective	To assess performance and impact of HPV DNA screening with cytology triage compared with conventional cytology on cervical cancer and severe pre-cancerous lesions
Methods	**Design**: RCT **Selection:** Follow-up in women randomized (1:1) to primary HPV DNA screening with cytology triage (intervention group) or conventional cytological screening (control group) within the population-based screening program; record linkage between files from screening registry and national cancer registry during 2003-2007
Participants	**Sample:** HPV testing n=29,037; Cytology n= 29,039 **Characteristics:** Ages 30-64 years **Study recruitment years:** 2003-2005
Intervention	**Type of test:** Primary HPV DNA test (Hybrid Capture II) with cytology triage if result was positive (experimental arm) or conventional cytological screening (control arm) **Length of follow-up:** Mean 3.3 years; maximum 5 years
Outcomes	**Reported by study authors:** RR of cervical cancer in women invited to attend screening with HPV testing compared to women invited to attend for cytology testing: 0.75 (95% CI 0.26-2.16)
	Reported in this review: Same as above
First Author **Country**	Sankaranarayanan[72] India
Name of Study	HPV screening for cervical cancer in rural India
Objective	To measure the effect of a single round of screening by testing for HPV, cytology or visual inspection on the incidence of cervical cancer and the associated rates of death in Osmanabad district in India

Methods	**Design:** RCT with cluster randomization **Selection:** 52 villages randomly assigned to one of 4 groups (HPV testing, cytology, visual inspection, or standard care); 13 villages in each group
Participants	**Sample:** Total: 131,746 HPV testing: 34,126 invited; 27,192 attended Cytology: 32,058 invited; 25,549 attended Visual inspection: 34,074 invited; 26,765 attended (outside the scope of this review; results not reported) Control/standard care: 31,488 **Characteristics:** Ages 30-59 years; All women were healthy, currently or previously married, not pregnant, had an intact uterus, no history of cervical cancer, and were living in one of the study clusters
Intervention	**Intervention groups:** HPV test, cytology, visual inspection; women informed of the causes of cervical cancer, signs and symptoms, prevention, early detection and treatment and given a card indicating the date, time and place of screening **Control group:** No screening offered but women were told how to seek screening at local hospitals **Length of follow-up:** 8 years (January 2000 to December 2007)
Outcomes	**Study authors did not compute comparisons; results calculated for this review:** **Mortality from cervical cancer** • The HPV test significantly decreased the risk of mortality from cervical cancer when compared to cytology (RR 0.59, 95% CI 0.39-0.91) **Incidence of cervical cancer** • The HPV test significantly decreased the incidence of cervical cancer when compared to cytology (RR 0.78, 95% CI 0.62-0.99) **Incidence of stage II or higher cervical cancer** • The HPV test significantly decreased the risk of mortality from cervical cancer when compared to cytology (RR 0.63, 95% CI 0.42-0.95)

Table 9: Characteristics of Included Studies for KQ1c - Does computer-assisted screening reduce incidence of or mortality from cervical cancer compared to conventional cytology screening?

First Author **Country**	Anttila [79] Finland
Name of Study	Cervical cancer patterns with automation-assisted and conventional cytological screening: A randomized study
Objective	To evaluate alternative cytological screening methods in population-based screening for cervical cancer for incidence and mortality outcomes
Methods	**Design:** RCT **Selection:** Women randomized to automation-assisted or conventional cytological screening (1:2) within the Finnish population-based screening program for cervical cancer during January 1, 1999 to December 12, 2003 **Excluded:** excluded from follow-up because of emigration, death or diagnosis of cervical cancer occurring before the onset of follow-up
Participants	**Sample:** Automation-assisted screening: n=169,159; Conventional cytological screening: n=334,232
Intervention	**Type of test:** Automation-assisted vs. conventional cytology
Outcomes	**Reported by study authors:** The RR of cervical cancer incidence was 1.00 (95% CI 0.76-1.29) for automation-assisted screening in comparison with conventional screening among all invited The RR of cervical cancer mortality was 1.11 (95% CI 0.62-1.92) for automation-assisted screening in comparison with conventional screening among all invited
	Reported in this review (RevMan calculated slightly different values): For incidence of invasive cervical cancer the risk was even (RR 0.99, 95% CI 0.76-1.29, p=0.96) For cervical cancer mortality, the risk ratio slightly favoured conventional screening (RR 1.10, 95% CI 0.63-1.94, p=0.73)

Table 10: Characteristics of Included Studies for KQ1d - How does varying the screening interval affect the incidence and mortality of invasive cervical cancer?

First Author **Country**	Andrae[80] Sweden
Name of Study	Screening-preventable cervical cancer risks: Evidence from a nationwide audit in Sweden
Objective	To perform a nationwide audit of effectiveness of the Swedish national cervical cancer screening program
Methods	**Design:** Case-control **Selection:** Cases: all invasive cervical cancer cases diagnosed in Sweden (1 January 1999 – 31 December 2001) reported to Swedish Cancer Registry; Controls: 5 age matched controls per case randomly selected from National Population Register
Participants	**Sample:** Cases n=1,230; Controls n=6,124 **Characteristics:** Ages 20-99 years (age at diagnosis)
Intervention	**Type of test:** Pap test **Recommended interval:** 3.5 years for women aged 53 years and under; 5.5 years for women aged 54 to 65 years; 6.5 years for women 66 years and older
Outcomes	**Reported by study authors:** Women with no Pap smear history in the recommended interval had a higher OR for cervical cancer than women who were tested during the interval (OR 2.52, 95% CI 2.19-2.91)
	Reported in this review (inverted values, odds of exposure to screening) Excluding tests performed six months prior to case diagnosis, the results showed a significant protective effect of having at least one Pap test within the recommended interval (OR 0.40, 95% CI 0.34-0.46)
First Author **Country**	Berrino[105] Italy
Name of Study	Efficacy of screening in preventing invasive cervical cancer: A case-control study in Milan, Italy
Objective	To elucidate screening as a protective factor as well as a means of diagnosis for cervical cancer
Methods	**Design:** Case-control **Selection:** All invasive cervical cancer newly diagnosed in 1978 in Milan, identified

	through the Regional Hospital Discharge Diagnosis Information System and through a survey of gynecology and pathology departments of Milan hospitals; 3 hospital controls per case, hospitalized for reasons other than gynecological or breast cancer
Participants	**Sample:** Total=516; Cases n=121; Controls n=350
Intervention	**Type of test:** Pap test
Outcomes	**Reported by study authors:** ORs for comparison between screening interval and no previous negative smear (no CIs reported) • 0 to 11 months – OR 0.14 • 12 to 23 months – OR 0.16 • 24 to 35 months – OR 1.16 • 36 to 47 months – OR 0.75 • 48+ months – OR 1.01
	Reported in this review: Same as above
First Author **Country**	Herbert[94] UK
Name of Study	Relation between the incidence of invasive cervical cancer and the screening interval: Is a five year interval too long?
Objective	To examine the incidence of invasive cervical cancer per 100,000 women years at risk and relative risk according to screening history among eligible women aged 25-69 in Southampton and South West Hampshire during the three years after completion of the first round of comprehensive screening
Methods	**Design:** Cohort **Selection:** Study group of women at risk comprised 116,022 women aged 25-69, registered with general practitioners in Southampton and South West Hampshire and eligible for screening. Cases obtained from local cancer registry data, histology records at Southampton General Hospital, Wessex radiotherapy and oncology units, and records from adjacent district general hospitals and local private hospitals **Excluded:** women who had hysterectomies for unrelated disease
Participants	**Sample:** 116,022 women **Characteristics:** Ages 25-69
Intervention	**Type of test**: Pap test **Four study groups:** a) a short interval group, comprising women screened within 3.5 years; b) a long interval group, consisting of women screened within an interval of 3.5-5.5 years; c) an overdue group, consisting of women who had a cytology record but had not been screened within 5.5 years; d) a group with no cytology record

Outcomes	**Reported by study authors:** RR for no screening during interval of 6-66 months compared to screening during interval 2.622 (95% CI 1.586-4.334) RR for overdue for screening compared to no cytology record 2.970 (95% CI 1.215-7.260) RR for screening during a long interval compared to a short interval 2.223 (95% CI 1.298-3.806)
	Reported in this review (inverted values): The incidence of invasive cervical cancer was significantly lower among women who participated in the country's comprehensive screening program than among women who were not screened during this time (RR 0.38, 95% CI 0.23-0.63) The risk of developing cervical cancer was significantly lower for women screened in the short interval compared to those screened in the long interval (RR 0.45, 95% CI 0.26-0.77) Women who did not get screened during the program interval but who had a record of previous cytology testing reduced their risk of being diagnosed with cervical cancer by 66% of the risk for women with no history of screening (RR 0.34, 95% CI 0.14-0.82).
First Author **Country**	Herrero[107] Latin America
Name of Study	Screening for cervical cancer in Latin America: A case-control study
Objective	To examine cervical cancer screening patterns in Latin America
Methods	**Design:** Case-control **Selection:** Cases were newly diagnosed with invasive cervical cancer, <70 years of age; Bogota and Mexico City controls - two age matched hospital controls, excluding women with psychiatric diagnoses or diseases related to the exposures of interest; Costa Rica and Panama Controls – one hospital control and one community control randomly chosen from current census listings of the country of residence of the case
Participants	**Sample:** Total=2,189; Cases n=759, Controls n=1,430 **Study recruitment years:** 1986-1987
Intervention	**Type of test:** Pap test
Outcomes	**Reported by study authors:** Age adjusted relative risks for comparisons between specific screening intervals and interval of 12-23 months • 12 to 23 months – RR 1.00 (referent) • 24 to 47 months – RR 1.00 (95% CI 0.7-1.3) • 48 to 71 months – RR 1.7 (95% CI 1.0-2.5) • 72 to 119 months – RR 1.4 (95% CI 0.8-2.3) • ≥120 months – RR 1.8 (95% CI 1.0-2.5) • Never screened – RR 3.0 (95% CI 2.3-4.0)

	Reported in this review (inverted values, odds of exposure to screening) The effect of screening was the same for intervals of 12 to 23 months and 24 to 47 months (age adjusted OR 1.00, 95% CI 0.77-1.43) Although none of the results were significant, the age adjusted point estimates consistently showed greater protective benefits with shorter screening intervals • 12 to 23 month interval compared to 48 to 71 month interval OR 0.59, 95% CI 0.40-1.00 • 12 to 23 month interval compared to 72 to119 month interval OR 0.71, 95% CI 0.43-1.25 • 12 to 23 month interval compared to an interval of 120 months or greater OR 0.56, 95% CI 0.40-1.00)
First Author **Country**	Hoffman[83] South Africa
Name of Study	Limited Pap screening associated with reduced risk of cervical cancer in South Africa
Objective	To investigate the effect of Pap smear screening on the incidence of invasive cervical cancer in the Western Cape, South Africa
Methods	**Design**: Case-control **Selection**: Incident cases of invasive cervical cancer who presented at 2 tertiary hospitals; control subjects matched for age, race, place of residence and hospital.
Participants	**Sample:** Cases n=524; Controls n=1,540 **Characteristics:** Women <60 years of age who lived within 150 km of Cape Town, South Africa for 6 or more months of the preceding year
Intervention	**Type of test**: Pap test
Outcomes	**Reported by study authors:** ORs for comparison between screening interval and never screened • Never screened – OR 1.00 (referent) • < 5 years – OR 0.3 (95% CI 0.2-0.4) • 5 to 9 years – OR 0.3 (95% CI 0.2-0.4) • 10 to 14 years – OR 0.4 (95% CI 0.3-0.5) • ≥ 15 years – OR 0.5 (95% CI 0.4-0.7)
	Reported in this review: Same as above
First Author **Country**	Jiménez-Pérez[84] Mexico
Name of Study	Has the use of pap smears reduced the risk of invasive cervical cancer in Guadalajara, Mexico?

Objective	To estimate the magnitude of the association between utilization of Pap smears and risk of invasive cervical cancer in women living in the metropolitan area of Guadalajara
Methods	**Design:** Case-control **Selection:** Cases were women diagnosed with invasive cervical cancer from August 1991 through March 1994, either histologically confirmed or diagnosed with clinical disease stage IB through IV, <70 years of age, who had been residing for at least the past year in metropolitan Guadalajara and who were referred for treatment or consultation to the study hospitals; 2.2 controls for each case (±3 years) with similar restrictions on place of residence, obtained from among women currently attending the same health center in which the case was first seen for reasons unrelated to cervical screening or gynecologic or obstetric condition, or, if the case was initially evaluated at a hospital, the health center closest to the case's area of residence
Participants	**Sample:** Cases n=143; Controls n=311 **Characteristics:** Cases average age 49.5 years; Controls average age 49.1 years
Intervention	**Type of test**: Pap test
Outcomes	**Reported by study authors:** Age adjusted relative risks of invasive cervical cancer for comparison between screening interval and never screened • Never screened – OR 1.00 (referent) • 1 to 12 months – OR 0.2 (95% CI 0.1-0.4) • 13 to 60 months – OR 0. 2 (95% CI 0.1-0.5) • >60 months – OR 0.5 (95% CI 0.3-0.9)
	Reported in this review (odds for exposure to screening): Significant protective effects were found for screening intervals of 1 to 12 months (age adjusted OR 0.2, 95% CI 0.1-0.4) and 13 to 60 months (age adjusted OR 0.2, 95% CI 0.1-0.5) compared to no history of screening Though not as great, a screening interval of 60 months or more also offered protective benefits (OR 0.5 95% CI 0.3-0.9)
First Author **Country**	Kasinpila[102] Thailand
Name of Study	Evaluation of the nationwide cervical screening programme in Thailand: A case-control study
Objective	To evaluate the effectiveness of the national cervical cancer screening (Pap smear) program in Thailand for preventing invasive cervical cancer
Methods	**Design:** Case-control **Selection**: Cases were women diagnosed with invasive cervical cancer (histologically confirmed) within the preceding three months, identified from one of four tertiary

	hospitals in north-east Thailand, residents of the north-east region, aged 30-64; two controls for each case (10 year age matched) including one patient control randomly selected from the same hospital where the case was recruited and one woman visiting or accompanying a patient other than the case in the same hospital
Participants	**Sample:** Cases n=130 (135 were invited); Controls n=260 (130 patients of 137 invited agreed to participate; 130 patient-visitors of 140 invited agreed to participate) **Characteristics:** Cases average age 48.6 (SD=8.0); Patient controls average age 48.9; Visitor controls average age 47.6 **Study recruitment years:** May to December 2009
Intervention	**Type of test:** Pap test
Outcomes	**Reported by study authors:** Analysis excluded women with smears performed < 6 months prior to case diagnosis • 89/130 cases had smears ≥ 6 months prior to diagnosis • 223/260 controls had smears ≥ 6 months before matched case diagnosis ORs (adjusted for significant risk factors and number of Pap tests) for comparison between screening interval and never screened • Never screened – OR 1.00 (referent) • 6 to 11 months – OR 1.38 (95% CI 0.56-3.40) • 12 to 35 months – OR 0.27 (95% CI 0.13-0.56) • ≥ 36 months – OR 0.42 (95% CI 0.20-0.88)
	Reported in this review: Same as above
First Author **Country**	La Vecchia[108] Italy
Name of Study	"Pap" smear and the risk of cervical neoplasia: Quantitative estimates from a case-control study
Objective	To review the relationship between Pap smear and risk of cervical neoplasia
Methods	**Design:** Case-control **Selection:** Cases with invasive cancer recruited from Obstetrics and Gynaecology Clinic, University and National Cancer Institute of Milan; controls for invasive cancer were women admitted to 6 wards of 3 university hospitals in Milan which served a catchment area similar to that of the hospitals where cases were identified
Participants	**Sample:** Invasive Cervical Cancer Cases n=191; Controls n=191 **Characteristics:** Cases ages 23-74 years; Controls ages 22-74 years **Study recruitment years:** 1981-1983
Intervention	**Type of test:** Pap test

Outcomes	**Reported by study authors:** Multivariate adjusted relative risks of invasive cervical cancer for comparison between screening interval and never screened • Never screened – OR 1.00 (referent) • < 3 years (excluding cases with positive smear < 1 year prior to diagnosis) – OR 0.12 (95% CI 0.07-0.20) • 3 to 5 years – OR 0.33 (95% CI 0.14-0.80) • > 5 years – OR 0.34 (95% CI 0.16-0.42)
	Reported in this review (odds for exposure to screening): Excluding women with a positive smear result less than one year before diagnosis, the protective benefit of having a Pap test in the last 36 months (multivariate adjusted OR 0.12, 95% CI 0.07-0.20) was greater than the benefit observed for a screening interval of 36 to 60 months (multivariate adjusted OR 0.33, 95% CI 0.14-0.80) or for an interval of more than 60 months (multivariate adjusted OR 0.34, 95% CI 0.16-0.42)
First Author **Country**	Makino[85] Japan
Name of Study	Evaluation of the effectiveness of cervical cancer screening: A case-control study in Miyagi, Japan
Objective	To estimate the effectiveness of screening for invasive cervical cancer
Methods	**Design:** Case-control **Selection:** Cases included mass-screen detected cases and outpatient detected cases (women with genital bleeding, discharge, or pelvic pain who had documented cervical smears) identified through cytology files; 2 controls matched for each case by age (±5 years) and district of residence; controls for mass screen-detected cases were selected from women who participated in the screening program, while controls for outpatient-detected cases were selected from women who visited gynecologists and had cervical smear examinations; their record numbers were nearest to the cases on the cytology file
Participants	**Sample:** Cases n=198 cases (129 mass screen-detected and 69 outpatient-detected); Controls n=396 **Characteristics:** Cases 35-79 years
Intervention	**Type of test**: Pap test
Outcomes	**Reported by study authors:** OR for a 1 year interval compared to ≥5 years 0.09 (95% CI 0.055-0.163), p<0.001 OR for a 2 year interval compared to ≥5 years 0.17 (95% CI 0.083-0.335), p<0.001 OR for a 3 year interval compared to ≥5 years 0.67 (95% CI 0.259-1.727) OR for a 4 year interval compared to ≥5 years 0.45 (95% CI 0.125-1.593)

	Reported in this review: Same as above
First Author **Country**	Miller[87] United States
Name of Study	Screening interval and risk of invasive squamous cell cervical cancer
Objective	To compare risks of developing invasive squamous cell cervical cancer associated with screening intervals of 1, 2, and 3 years after a negative cervical smear
Methods	**Design**: Case-control **Selection**: Cases were cervical cancer patients diagnosed between 1983-1995 among long term members of a large HMO; women with a prior history of total hysterectomy or radiation therapy to the pelvis were excluded; controls were matched for age, length of membership in health organization, and race
Participants	**Sample:** Cases n=482; Controls n=934 **Characteristics:** Cases mean age 49.5 years; Controls mean age 48.8 years
Intervention	**Type of test**: Pap test
Outcomes	**Reported by study authors:** ORs for comparison between annual screening interval and other screening intervals • 1 year – OR 1.00 (referent) • 2 years – OR 1.72 (95% CI 1.12-2.64), p=0.13 • 3 years – OR 2.06 (95% CI 1.21-3.50), p=0.007 • 3 to 5 years – OR 3.16 (95% CI 1.93-5.18), p<0.001 • 5 to 10 years – OR 4.73 (95% CI 3.03-7.38), p<0.001 • >10 years – OR 8.86 (95% CI 5.29-14.82), p<0.001
	Reported in this review (inverted values, odds for exposure to screening): A screening interval of 12 months offered more protection than an interval of 24 months (OR 0.58, 95% CI 0.38-0.89) and an interval of 36 months (OR 0.49, 95% CI 0.29-0.83) There was no significant difference between the 24 and 36 month screening intervals (OR of 36 months relative to 24 months 1.20, 95% CI 0.65-2.21, p=0.561) The 12 month screening interval offered significantly more protection than screening intervals of 37 to 60 months (OR 0.32, 95% CI 0.19-0.52), 60 to 120 months (OR 0.21, 95% CI 0.14-0.33) and 120 months or more (OR 0.11, 95% CI 0.07-0.19)
First Author **Country**	Rebolj[95] Netherlands
Name of Study	Incidence of cervical cancer after several negative smear results by age 50: Prospective observational study

<table>
<tr><td>Objective</td><td>To determine the incidence of cervical cancer after several negative cervical smear tests at different ages</td></tr>
<tr><td>Methods</td><td>Design: Prospective observational (cohort) study
Selection: Women with three consecutive negative smear results identified from a national registry of histopathology and cytopathology</td></tr>
<tr><td>Participants</td><td>Sample: Two groups of women at the time of third negative smear test
Cohort 1: Women aged 30-44 years (mean age 37.3 years) n=445,382
Cohort 2: Women aged 45-54 years (mean age 48.7 years) n=218,847</td></tr>
<tr><td>Intervention</td><td>Type of test: Pap test
Length of follow-up: 20 years</td></tr>
<tr><td>Outcomes</td><td>Reported by study authors:
• The three negative result Pap tests were conducted, on average, every 39 months in the younger group, and every 40 months in the older group
• The cumulative incidence rate (CIR) for cervical cancer did not differ significantly between the two groups for any screening interval
<table>
<tr><th>Time (years) since third negative smear</th><th>30-44 year olds CIR (95% CI)</th><th>45-54 year olds CIR (95% CI)</th><th>P value</th></tr>
<tr><td>≤1</td><td>1 (0-3)</td><td>2 (1-5)</td><td>0.66</td></tr>
<tr><td>>1 to ≤3</td><td>6 (4-10)</td><td>11 (7-17)</td><td>0.09</td></tr>
<tr><td>>3 to ≤5</td><td>16 (12-21)</td><td>14 (10-21)</td><td>0.65</td></tr>
<tr><td>>5 to ≤10</td><td>41 (33-51)</td><td>36 (24-52)</td><td>0.48</td></tr>
<tr><td>>10 to ≤15</td><td>70 (51-95)</td><td>73 (39-135)</td><td>0.85</td></tr>
<tr><td>>15 to ≤20</td><td>128 (79-207)</td><td>105 (50-219)</td><td>0.27</td></tr>
</table>
Reported in this review:
Same as above</td></tr>
<tr><td>First Author
Country</td><td>Sasieni[89]
United Kingdom</td></tr>
<tr><td>Name of Study</td><td>Benefit of cervical screening at different ages: Evidence from the UK audit of screening histories</td></tr>
<tr><td>Objective</td><td>To contribute to knowledge regarding the relative merits of 3-year versus 5-year screening for invasive cervical cancer</td></tr>
<tr><td>Methods</td><td>Design: Case-control
Selection: Cases: women diagnosed with invasive cervical cancer identified from pathology laboratories and confirmed residents of the Health Authority region at diagnosis; Controls: age matched women with no known hysterectomy registered with a group practice in the same Health Authority area</td></tr>
</table>

<table>
<tr><td>Participants</td><td>Sample: Cases n=1,305; Controls n=2,532
Characteristics: Ages 20-69 years</td></tr>
<tr><td>Intervention</td><td>Type of test: Pap test</td></tr>
<tr><td>Outcomes</td><td>Reported by study authors:
ORs for frankly invasive cancer comparisons between no previous negative smear and specific screening intervals
<table>
<tr><td>Time since last smear</td><td>Ages 20-39
OR (95% CI)</td><td>Ages 40-54
OR (95% CI)</td><td>Ages 55-69
OR (95% CI)</td></tr>
<tr><td>No previous negative</td><td>1.00</td><td>1.00</td><td>1.00</td></tr>
<tr><td>0-2.9 years</td><td>0.28 (0.20-0.41)</td><td>0.12 (0.008-0.17)</td><td>0.13 (0.08-0.19)</td></tr>
<tr><td>3.0-4.9 years</td><td>1.03 (0.68-1.56)</td><td>0.39 (0.26-0.58)</td><td>0.20 (0.12-0.33)</td></tr>
<tr><td>Over 5 years</td><td>2.05 (0.73-1.46)</td><td>0.72 (0.43-1.18)</td><td>0.45 (0.25-0.81)</td></tr>
</table>
Reported in this review (odds for exposure to screening):
Same as above</td></tr>
<tr><td>First Author
Country</td><td>Sasieni[91]
United Kingdom</td></tr>
<tr><td>Name of Study</td><td>Screening and adenocarcinoma of the cervix</td></tr>
<tr><td>Objective</td><td>To investigate the effect of screening intervals on detection of adenocarcinoma and adenosquamous carcinoma of the cervix</td></tr>
<tr><td>Methods</td><td>Design: Case-control
Selection: Cases with invasive cancer identified from histopathology records; Age matched controls registered with a general practitioner in same administrative district</td></tr>
<tr><td>Participants</td><td>Sample: Cases n=3,305 (Adenocarcinoma n=641, Squamous Carcinoma n=2,531, Adenosquamous n=133); Controls n=6,516
Characteristics: Ages 20-69 years</td></tr>
<tr><td>Intervention</td><td>Type of test: Pap test</td></tr>
<tr><td>Outcomes</td><td>Reported by study authors:
ORs of invasive cervical cancer for comparison between specific screening intervals and longest interval
<table>
<tr><td>All cases</td><td>Adenocarcinoma
OR (95% CI)</td><td>Squamous
OR (95% CI)</td><td>Adenosquamous
OR (95% CI)</td></tr>
<tr><td>0 to 3.5 years</td><td>0.57 (0.42-0.76)</td><td>0.25 (0.21-0.29)</td><td>0.17 (0.09-0.32)</td></tr>
<tr><td>3.5 to 5.5 years</td><td>0.63 (0.46-0.85)</td><td>0.39 (0.33-0.45)</td><td>0.24 (0.12-0.45)</td></tr>
<tr><td>>5.5 years</td><td>1.00 (referent)</td><td>1.00 (referent)</td><td>1.00 (referent)</td></tr>
</table></td></tr>
</table>

	Reported in this review (odds of exposure to screening): Same as above
First Author **Country**	Sasieni[88] United Kingdom
Name of Study	Estimating the efficacy of screening by auditing smear histories of women with and without cervical cancer
Objective	To estimate the efficacy of screening for cervical cancer
Methods	**Design:** Case-control **Selection**: Cases of invasive cervical cancer were obtained from local pathology laboratories; Two residency and age matched controls per case were selected from the computerized registry held by the local family health services authority
Participants	**Sample**: Cases n=348; Controls n=677
Intervention	**Type of test:** Pap test
Outcomes	**Reported by study authors:** ORs for cervical cancer comparison between women with specific screening intervals and longest interval or no prior testing • 0 to11 month interval OR 0.18 (95% CI 0.09-0.35) • 12 to 23 month interval OR 0.33 (95% CI 0.18-0.61) • 24 to 35 month interval OR 0.26 (95% CI 0.14-0.47) • 36 to 47 month interval OR 0.32 (95% CI 0.17-0.56) • 48 to 65 month interval OR 0.64 (95% CI 0.36-1.14) • >66 months or no previous test OR 1.00 (referent)
	Reported in this review (odds of exposure to screening): Same as above
First Author **Country**	Yang[92] Australia
Name of Study	A case-control study of the protective benefit of cervical screening against invasive cervical cancer in NSW women
Objective	To examine the effects of different Pap screening patterns in preventing invasive cervical cancer among women in New South Wales, Australia
Methods	**Design**: Case-control **Selection:** 877 invasive cervical cancer cases diagnosed in 2000-2003; three age matched controls per case drawn from the state-wide Pap Test Register

Participants	**Sample**: Cases n=877; Controls n=2,614 **Characteristics:** Ages 20-69 years
Intervention	**Type of test:** Pap test
Outcomes	**Reported by study authors:** Relative risk of invasive cervical cancer for comparison between women who received regular Pap testing (2 or more tests in last 4 years) and women who were not tested during this interval 0.043 (95% CI 0.033-0.057) Relative risk of invasive cervical cancer for comparison between women who received irregular Pap testing (1 test in previous 4 years) and women were not tested during this interval 0.152 (95% CI 0.119-0.194)
	Reported in this review (odds of exposure to screening): Same as above
First Author **Country**	Zappa[93] Italy
Name of Study	Lower protection of cytological screening for adenocarcinomas and shorter protection for younger women: The results of a case-control study in Florence
Objective	To evaluate the efficacy of cytological screening in preventing cervical adenocarcinoma as compared to squamous cell cancer
Methods	**Design**: Case-control **Selection:** All women < 70 years registered at the Tuscany Tumour Registry as having cervical cancer diagnosed between 1994 and 1999, excluding micro-invasive tumours and those resident in the area < 5 years; For each case, 4 age matched controls with no known hysterectomy randomly selected from municipality residence database
Participants	**Sample**: Cases n=208 (148 squamous carcinoma, 53 adenocarcinoma, 7 other or unspecified type); Controls n=832 **Characteristics**: Ages < 70 years
Intervention	**Type of test:** Pap test
Outcomes	**Reported by study authors:** Adjusted ORs for comparison between specific screening intervals and no screening • No screening – OR 1.00 (referent) • <3 years – OR 0.25 (95% CI 0.15-0.42) • 3-6 years – OR 0.34 (95%CI 0.21-0.56) • ≥6 years – OR 0.56 (95% CI 0.38-0.82)
	Reported in this review (odds for exposure to screening): Same as above

Table 11: Characteristics of Included Studies for KQ1e - How does varying the age at which screening is started or stopped reduce the incidence of mortality from invasive cervical cancer?

First Author **Country**	Andrae[80] Sweden
Name of Study	Screening-preventable cervical cancer risks: Evidence from a nationwide audit in Sweden
Objective	To perform a nationwide audit of effectiveness of the Swedish national cervical cancer screening program
Methods	**Design:** Case-control **Selection:** Cases: all invasive cervical cancer cases diagnosed in Sweden (1 January 1999 – 31 December 2001) reported to Swedish Cancer Registry; Controls: 5 age matched controls per case randomly selected from National Population Register
Participants	**Sample:** Cases n=1,230; Controls n=6,124 **Characteristics:** Ages 20-99 years (age at diagnosis)
Intervention	**Type of test:** Pap test **Recommended interval:** 3.5 years for women aged 53 years and under; 5.5 years for women aged 54 to 65 years; 6.5 years for women aged 66 and older
Outcomes	**Reported by study authors:** ORs of cervical cancer for women without a Pap test compared to women with a Pap test • Age at diagnosis 21-29 years OR 2.37 (95% CI 1.36-4.13) • Age at diagnosis 30-65 years OR 2.51 (95% CI 2.14-2.94) • Age at diagnosis ≥66 years OR 2.79 (95% CI 1.89-4.11)
	Reported in this review (inverted values, odds for exposure to screening): Screening within the recommended interval offered a significant protective benefit (OR 0.40, 95% CI 0.34-0.46) with similar point estimates across three age groups • In younger women, (aged 21 to 29 years at case diagnosis), the OR was 0.42 (95% CI 0.24-0.74) • In the middle age group (aged 30 to 65 years at case diagnosis) the OR was 0.40 (95% CI 0.34-0.47) • In the oldest group (66 years and older at case diagnosis) the OR was 0.36 (95% CI 0.24-0.53)
First Author **Country**	Hoffman[83] South Africa
Name of Study	Limited Pap screening associated with reduced risk of cervical cancer in South Africa

Objective	To investigate the effect of Pap smear screening on the incidence of invasive cervical cancer in the Western Cape, South Africa
Methods	**Design:** Case-control **Selection:** Incident cases of invasive cervical cancer who presented at 2 tertiary hospitals; control subjects matched for age, race, place of residence and hospital.
Participants	**Sample:** Cases n=524; Controls n=1,540 **Characteristics:** Women <60 years of age who lived within 150 km of Cape Town, South Africa for 6 or more months of the preceding year
Intervention	**Type of test:** Pap test
Outcomes	**Reported by study authors:** ORs for cervical cancer for comparison between women with a history of screening compared to women with no history of Pap testing • Ages <30 years adjusted OR 0.7 (95% CI 0.3-2.1) • Ages 30-39 years adjusted OR 0.3 (95% CI 0.2-0.6) • Ages 40-49 years adjusted OR 0.3 (95% CI 0.2-0.4) • Ages 50-59 years adjusted OR 0.3 (95% CI 0.2-0.4)
	Reported in this review (odds of exposure to screening): Same as above
First Author **Country**	Rebolj[95] Netherlands
Name of Study	Incidence of cervical cancer after several negative smear results by age 50: Prospective observational study
Objective	To determine the incidence of cervical cancer after several negative cervical smear tests at different ages
Methods	**Design**: Prospective observational (cohort) study **Selection**: Women with three consecutive negative smear results identified from a national registry of histopathology and cytopathology
Participants	**Sample**: Two groups of women at the time of third negative smear test Cohort 1: Women aged 30-44 years (mean age 37.3 years) n=445,382 Cohort 2: Women aged 45-54 years (mean age 48.7 years) n=218,847
Intervention	**Type of test:** Pap test **Length of follow-up**: 20 years
Outcomes	**Reported by study authors:** The overall hazard ratio was 0.84 (95% CI 0.59-1.21) for the older group compared with the younger group

CIR: Cumulative Incidence Rate

Time (years) since third negative smear	30-44 year olds CIR (95% CI)	45-54 year olds CIR (95% CI)	P value
≤1	1 (0-3)	2 (1-5)	0.66
>1 to ≤3	6 (4-10)	11 (7-17)	0.09
>3 to ≤5	16 (12-21)	14 (10-21)	0.65
>5 to ≤10	41 (33-51)	36 (24-52)	0.48
>10 to ≤15	70 (51-95)	73 (39-135)	0.85
>15 to ≤20	128 (79-207)	105 (50-219)	0.27

Reported in this review:

Same as above

First Author Country	Sasieni[88] United Kingdom
Name of Study	Estimating the efficacy of screening by auditing smear histories of women with and without cervical cancer
Objective	To estimate the efficacy of screening for cervical cancer
Methods	**Design:** Case-control **Selection:** Cases of invasive cervical cancer were obtained from local pathology laboratories; Two residency and age matched controls per case were selected from the computerized registry held by the local family health services authority
Participants	**Sample:** Cases n=348; Controls n=677
Intervention	**Type of test:** Pap test
Outcomes	**Reported by study authors:** Percentage of women with no screening history up to six months prior to diagnosis

Age (Years)	Fully Invasive %	Controls %
20-34	14	9
35-49	29	13
50-64	43	26
65-74	68	60
75+	90	91
All Ages	45	29

<table>
<tr><td></td><td>Reported in this review (reversed %):
Percentage of women with a screening history up to six months prior to diagnosis
<table>
<tr><th>Age (Years)</th><th>Fully Invasive %</th><th>Controls %</th></tr>
<tr><td>20-34</td><td>86</td><td>91</td></tr>
<tr><td>35-49</td><td>71</td><td>87</td></tr>
<tr><td>50-64</td><td>57</td><td>74</td></tr>
<tr><td>65-74</td><td>32</td><td>40</td></tr>
<tr><td>75+</td><td>10</td><td>9</td></tr>
<tr><td>All Ages</td><td>55</td><td>71</td></tr>
</table></td></tr>
<tr><td>First Author
Country</td><td>Sasieni[89]
United Kingdom</td></tr>
<tr><td>Name of Study</td><td>Benefit of cervical screening at different ages: Evidence from the UK audit of screening histories</td></tr>
<tr><td>Objective</td><td>To examine relative merits of 3- versus 5-year screening for invasive cervical cancer</td></tr>
<tr><td>Methods</td><td>Design: Case-control
Selection: Cases: women with invasive cervical cancer identified from pathology labs, residents of the Health Authority region at diagnosis; Controls: age matched with no known hysterectomy registered with a group practice in the same Health Authority</td></tr>
<tr><td>Participants</td><td>Sample: Cases n=1,305; Controls n=2,532
Characteristics: Ages 20-69 years</td></tr>
<tr><td>Intervention</td><td>Type of test: Pap test</td></tr>
<tr><td>Outcomes</td><td>Reported by study authors:
Across age groups, participation in screening consistently declined with increasing age in cases (79.5% of cases aged 20-29; 67.6% of cases aged 40-54; 48.2% of cases aged 55-69)
In the control group, participation rates remained constant for women aged 20-54 years (around 83-84%) and then declined in the 55-69 year old group (70.7%)
In all age categories more women with invasive cancer had no history of screening up to six months prior to diagnosis compared with women who did not have cervical cancer</td></tr>
<tr><td></td><td>Reported in this review:
Same as above</td></tr>
<tr><td>First Author
Country</td><td>Sasieni[90]
United Kingdom</td></tr>
<tr><td>Name of Study</td><td>Effectiveness of cervical screening with age: Population-based case-control study of prospectively recorded data</td></tr>
</table>

Objective	To study the effect of cervical cancer screening on incidence of cervical cancer as a function of age, with particular focus on women < 25 years
Methods	**Design**: Case-control **Selection:** Cases were women diagnosed with cervical cancer identified from histology laboratory records between January 1990 and April 2008; Controls were women who registered with a National Health Service general practitioner (and had not subsequently died or emigrated), matched by age and place of residence
Participants	**Sample:** Cases n=4,012; Controls n=7,889 **Characteristics:** Ages 20-69 years
Intervention	**Type of test:** Pap test
Outcomes	**Reported by study authors:** ORs for women screened at particular ages versus not screened For diagnosis between ages 25-29 • Screened at age 20-21 (not 22-24) OR 1.51 (95% CI 0.95-2.38) • Screened at age 22-24 OR 1.11 (95% CI 0.83-1.50) For diagnosis between ages 35-39 • Screened at age 30-31 (not 32-34) OR 0.79 (95% CI 0.57-1.1) • Screened at age 32-34 OR 0.55 (95% CI 0.44-0.69) For diagnosis between ages 45-49 • Screened at age 40-41 (not 42-44) OR 0.40 (95% CI 0.27-0.58) • Screened at age 42-44 OR 0.37 (95% CI 0.29-0.48) For diagnosis between ages 55-59 • Screened at age 50-51 (not 52-54) OR 0.27 (95% CI 0.17-0.43) • Screened at age 52-54 OR 0.26 (95% CI 0.19-0.36)
	Reported in this review (odds for exposure to screening): Same as above

Table 12: Characteristics of Included Studies for KQ2 - What are the harms of cervical cancer screening?

First Author **Country**	Abali[101] Turkey
Name of Study	Histopathological correlation of squamous cell abnormalities detected on cervical cytology
Objective	To investigate correlation between cytology and histology in patients with squamous cell abnormalities in smear results
Methods	**Design:** Single-group, retrospective design involving test results/specimen review **Selection:** Patients who underwent Pap tests at the Istanbul Training and Research Hospital Department of Obstetrics and Gynecology between 2005 and 2008 and whose smear results were positive for squamous cell abnormalities
Participants	**Sample:** 374 women **Characteristics:** mean age 45.15 years (SD=10.78, range 23 to 78)
Intervention	**Type of test**: Pap test
Outcomes	**False-positives** False-positive rate for all squamous cell abnormalities was 43.04% (161/374) False-positive rate for squamous cell abnormalities excluding atypical squamous cells was 22.68% (22/97) Authors suggest reasons for the high false-positive rates including: high mean age of the sample and the presence of aging related physiological changes that are difficult to differentiate from neoplasia; the lack of hospital personnel who specialize in histopathology; low socioeconomic patient demographic and unlikely patient follow-up leading to more biopsies with colposcopies performed after single positive smears
First Author **Country**	Doornewaard [96] Netherlands
Name of Study	The diagnostic value of computer-assisted primary cervical smear screening: A longitudinal cohort study
Objective	To assess computer-assisted (neural network-based) cervical smear screening as a primary tool for the early detection of cervical dysplasia
Methods	**Design:** Sample Review – longitudinal cohort study **Selection:** All women with first positive smears in 1988, all women with a negative smear in 1988, but in seven consecutive years ever had an abnormal smear or positive histology selected from the national pathology database, random sample from remaining women with negative smear and no positive cytology or histology 1988-1995

Participants	**Sample:** 6,063 women; 846 with (pre-)neoplasia at follow-up; 5,217 with negative cytology at follow-up **Length of follow-up:** 7 years
Intervention	**Type of test**: Computer-assisted (neural network based), Pap smear screening
Outcomes	**False-positives** 210 conventional (LSIL 204, HSIL/carcinoma 6) 207 PAPNET (LSIL 195, HSIL/carcinoma 12) False-positive rate: 4% conventional; 4% PAPNET
First Author **Country**	Levine[99] USA
Name of Study	False-positive squamous cell carcinoma in cervical smears: Cytologic-histologic correlation in 19 cases
Objective	To compare and correlate the findings of 19 false-positive squamous cell carcinomas to define which type of dysplasia is more prone to diagnostic errors on Pap smears
Methods	**Design:** Single-group, retrospective design involving test results/specimen re-review **Selection**: Review of tissue sections from 19 false-positive cases for cytologic features of squamous cell carcinoma (of 128 patients diagnosed with invasive squamous-cell carcinoma from 1994-2000; records from New York University cytology files)
Participants	**Sample:** 19 false-positives from among 128 patients diagnosed with invasive squamous cell carcinoma **Characteristics:** Mean age 50.5 years; 12 (63%) were menopausal; 6 (30%) were cyclic (one with intrauterine device); 1 (5%) was pregnant; 3 (15%) were HIV positive
Intervention	**Type of test**: Pap test
Outcomes	**False-Positives** 19 cases with follow-up cone biopsies or hysterectomy specimens were false-positives for invasive squamous-cell carcinoma (14.8% of the 128 diagnoses); re-review indicated only cervical intraepithelial neoplasia (CIN)
First Author **Country**	Lorenzin [100] Italy
Name of Study	Histologic correlates of positive pap-smear results
Objective	To estimate the reliability of the pap smear for the correct identification of the degree of intraepithelial lesions and its accuracy in revealing the presence of invasive cervical cancer

Methods	**Design:** Sample review **Selection:** From January 1981 to December 1997 at the Cytological Center of the Oncologic Department in Busto Arsizio Hospital 1,016 cytological specimens characterized by cervical pathology were selected
Participants	**Sample:** 1,016 cytological specimens
Intervention	**Type of test**: Pap test
Outcomes	**False-positives** LSIL: 110 false-positive diagnosis out of 561 cases; HSIL: 65 false-positive diagnosis out of 361 cases; 1 carcinoma False-positive rate: 19.6% LSIL; 18% HSIL; 1.3% carcinoma
First Author **Country**	Mount[98] USA
Name of Study	False-positive diagnosis in conventional and liquid-based cervical specimens
Objective	To examine conventional and liquid-based cervical smears falsely diagnosed as malignant and investigate through cytologic-histologic correlation, factors influencing false-positive diagnoses
Methods	**Design**: Single-group, retrospective design involving test results/specimen re-review **Selection:** False-positive cases from records of cytologic diagnoses of malignancy between 1 May 1995 to 30 April 2001 retrieved through computer search were reviewed and correlated with histologic follow-up specimens
Participants	**Sample:** Total sample n=68 patients with malignancies; 32 from conventional smears, 36 from liquid-based samples **Characteristics:** Mean age 61 years (SD=14, range 25-84); 77% were post-menopausal and half were tobacco users
Intervention	**Type of test:** Liquid-based or conventional cytology
Outcomes	**False-Positives** 7 false-positives identified (10.3%); 4 from conventional smears (12.5%), 3 from liquid-based samples (8.3%) No significant difference (p value not specified) in the rates of false-positive diagnoses between conventional and liquid-based samples
First Author **Country**	Slagel [97] USA
Name of Study	Efficacy of automated cervical cytology screening

Objective	The goals of this study are to: 1) determine sensitivity, specificity, and false negative rates using this system for detection of possible premalignant and malignant lesions on cervicovaginal smears and 2) determine its utility as a rescreening quality control tool in review of previous negative Pap stained smears
Methods	**Design:** Sample review **Selection:** A retrospective review of conventionally prepared Pap smears form 500 consecutive unselected patients from the University of Iowa Hospitals and Clinics from October 1 to October 30, 1990 were used. These slides were evaluated by the PAPNET cytologic screening system
Participants	**Sample:** 500 patients
Intervention	**Type of test**: Pap test
Outcomes	**False-positive** False-positives: PAPNET: 19% (82/423); Laboratory (conventional): <1% (3/423)

Evidence Set 1: KQ1 - What is the effect of cervical cancer screening on mortality from invasive cervical cancer?

Table 13: GRADE Evidence Profile Table for Effect of Screening on Mortality from Invasive Cervical Cancer
- Invited to Screening with HPV Testing or Cytology versus No Screening
- Invited to Screening with HPV Testing versus No Screening
- Invited to Screening with Cytology versus No Screening

Table 14: GRADE Summary of Findings Table for Effect of Screening on Mortality from Invasive Cervical Cancer
- Invited to Screening with HPV Testing or Cytology versus No Screening
- Invited to Screening with HPV Testing versus No Screening
- Invited to Screening with Cytology versus No Screening

Forest Plots
- Forest Plot 1: Effect of Screening on Mortality from Invasive Cervical Cancer - Invited to Screening with HPV Testing or Cytology versus No Screening
- Forest Plot 2: Effect of Screening on Mortality from Invasive Cervical Cancer - Invited to Screening with HPV Testing versus No Screening
- Forest Plot 3: Effect of Screening on Mortality from Invasive Cervical Cancer - Invited to Screening with Cytology versus No Screening

Table 13: GRADE Evidence Profile Table for Effect of Screening on Mortality from Invasive Cervical Cancer

Quality Assessment							No. of Participants		Effect		Quality	Importance
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Screening	Control	Relative (95% CI)	Absolute per Million (Range)		
Cervical Cancer Mortality (invited to screening with HPV testing or cytology versus no screening; Follow-up: 8 years; Assessed with: district death registrations, hospital records, annual house visits)												
1[1]	randomized trials	no serious risk of bias[2]	no serious inconsistency[3]	serious[4]	no serious imprecision[5]	none[6]	88/66,184 (0.1330%)[7]	64/31,488 (0.2033%)[7]	RR 0.6542 (0.4742 to 0.9024)[8]	703 fewer (from 198 fewer to 1,069 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Cervical Cancer Mortality (invited to screening with HPV testing versus no screening; Follow-up: 8 years; Assessed with: district death registrations, hospital records, annual house visits)												
1[1]	randomized trials	no serious risk of bias[2]	no serious inconsistency[3]	serious[4]	no serious imprecision[5]	none[6]	34/34,126 (0.0996%)[7]	64/31,488 (0.2033%)[7]	HR 0.5200 (0.3300 to 0.8194)	975 fewer (from 367 fewer to 1,361 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Cervical Cancer Mortality (invited to screening with cytology versus no screening; Follow-up: 8 years; Assessed with: district death registrations, hospital records, annual house visits)												
1[1]	randomized trials	no serious risk of bias[2]	no serious inconsistency[3]	serious[4]	no serious imprecision[5]	none[6]	54/32,058 (0.1684%)[7]	64/31,488 (0.2033%)[7]	HR 0.8900 (0.6201 to 1.2775)	223 fewer (from 772 fewer to 563 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] Sankaranarayanan[72]

[2] Random sequence generation is unclear and allocation concealment is not discussed, however study limitations were not downgraded for these risks/uncertainties.

[3] Single study, therefore inconsistency not applicable.

[4] Directness downgraded due to concerns regarding population characteristics (rural women living in a low income country) and intervention characteristics [one-time opportunistic screening; short duration (3 months) of training received by lab technicians responsible for processing and reading the samples].

[5] The number of events is small (<300, a threshold rule of thumb value for dichotomous outcomes), however considering the specific outcome the evidence is not downgraded.

[6] Insufficient number of studies to assess publication bias.

[7] Rates were adjusted for age by study authors.

[8] Study authors do not provide a Hazard Ratio for the HPV testing and cytology groups combined versus the control group. Using sample and event data we computed a Relative Risk.

Table 14: GRADE Summary of Findings Table for Effect of Screening on Mortality from Invasive Cervical Cancer

Outcomes	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk Number per Million **Control**	Corresponding Risk Number per Million **Screening**			
Cervical Cancer Mortality (invited to screening with HPV testing or cytology versus no screening) Assessed with: district death registrations, hospital records, annual house visits; Follow-up: 8 years	**2,033**[1]	**1,330** (964 to 1,834)[1]	**RR 0.6542** (0.4742 to 0.9024)[2]	97,672 (1 study[3])	⊕⊕⊕⊖ **moderate**[4,5,6,7,8]
Cervical Cancer Mortality (invited to screening with HPV testing versus no screening) Assessed with: district death registrations, hospital records, annual house visits; Follow-up: 8 years	**2,033**[1]	**1,057** (671 to 1,666)[1]	**HR 0.5200** (0.3300 to 0.8194)	65,614 (1 study[3])	⊕⊕⊕⊖ **moderate**[4,5,6,7,8]
Cervical Cancer Mortality (invited to screening with cytology versus no screening) Assessed with: district death registrations, hospital records, annual house visits; Follow-up: 8 years	**2,033**[1]	**1,809** (1,261 to 2,596)[1]	**HR 0.8900** (0.6201 to 1.2775)	63,546 (1 study[3])	⊕⊕⊕⊖ **moderate**[4,5,6,7,8]

*The **assumed risk** is the median control group risk. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence Interval; **RR:** Risk Ratio; **HR:** Hazard Ratio

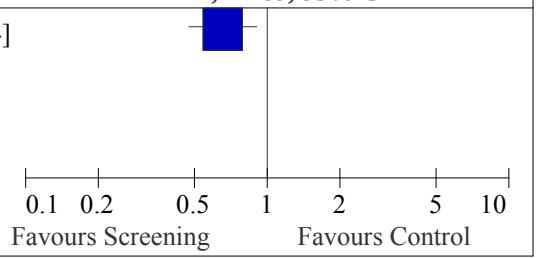
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Rates were adjusted for age by study authors.
[2] Study authors do not provide a Hazard Ratio for the HPV testing and cytology groups combined versus the control group. Using sample and event data we computed a Relative Risk.
[3] Sankaranarayanan[72]
[4] Random sequence generation is unclear and allocation concealment is not described, however study limitations were not downgraded for these risks/uncertainties.
[5] Single study, therefore inconsistency not applicable.
[6] Directness downgraded due to concerns regarding population characteristics (rural women living in a low income country) and intervention characteristics [one-time opportunistic screening; short duration (3 months) of training received by lab technicians responsible for processing and reading the samples].
[7] The number of events is small (<300, a threshold rule of thumb value for dichotomous outcomes), however considering the specific outcome the evidence is not downgraded.
[8] Insufficient number of studies to assess publication bias.

Forest Plot 1: Effect of Screening on Mortality from Invasive Cervical Cancer - Invited to Screening with HPV Testing or Cytology versus No Screening

Study	Screening Events	Screening Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sankaranarayanan et al. 2009	88	66,184	64	31,488	100.0%	0.6542 [0.4742, 0.9024]

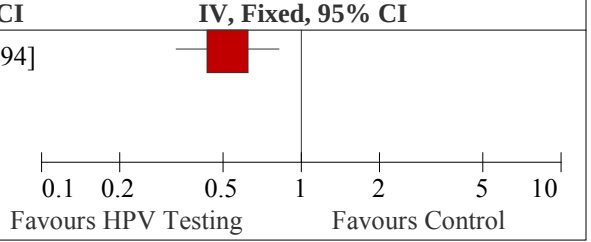
Test for overall effect: Z = 2.59 (P = 0.010)
(M-H: Mantel-Haenszel)



Forest Plot 2: Effect of Screening on Mortality from Invasive Cervical Cancer - Invited to Screening with HPV Testing versus No Screening

Study	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Sankaranarayanan et al. 2009	-0.6539	0.232	100.0%	0.5200 [0.3300, 0.8194]

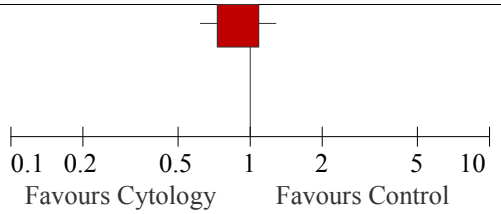
Test for overall effect: Z = 2.82 (P = 0.005)
(IV: Inverse Variance)



Forest Plot 3: Effect of Screening on Mortality from Invasive Cervical Cancer - Invited to Screening with Cytology versus No Screening

Study	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Sankaranarayanan et al. 2009	-0.1165	0.1844	100.0%	0.8900 [0.6201, 1.2775]

Test for overall effect: Z = 0.63 (P = 0.53)
(IV: Inverse Variance)



Evidence Set 2: KQ1 – What is the effect of cervical cancer screening on incidence of invasive cervical cancer?

Table 15: GRADE Evidence Profile Table for Effect of Screening on Incidence of Invasive Cervical Cancer
- Invited to Screening with HPV Testing or Cytology versus No Screening (RCT)
- Invited to Screening with HPV Testing versus No Screening (RCT)
- Invited to Screening with Cytology versus No Screening (RCT)
- Exposure to Cytology Screening (Case-Control Studies)
- Screening with Cytology versus No Screening (Cohort Study)

Table 16: GRADE Summary of Findings Table for Effect of Screening on Incidence of Invasive Cervical Cancer
- Invited to Screening with HPV Testing or Cytology versus No Screening (RCT)
- Invited to Screening with HPV Testing versus No Screening (RCT)
- Invited to Screening with Cytology versus No Screening (RCT)
- Exposure to Cytology Screening (Case-Control Studies)
- Screening with Cytology versus No Screening (Cohort Study)

Forest Plots
- Forest Plot 4: Effect of Screening on Incidence of Invasive Cervical Cancer - Invited to Screening with HPV Testing or Cytology versus No Screening (RCT)
- Forest Plot 5: Effect of Screening on Incidence of Invasive Cervical Cancer - Invited to Screening with HPV Testing versus No Screening (RCT)
- Forest Plot 6: Effect of Screening on Incidence of Invasive Cervical Cancer - Invited to Screening with Cytology versus No Screening (RCT)
- Forest Plot 7: Effect of Screening on Incidence of Invasive Cervical Cancer - Exposure to Cytology Screening (Case-Control Studies)
- Forest Plot 8: Effect of Screening on Incidence of Invasive Cervical Cancer - Screening with Cytology versus No Screening (Cohort Study)

Funnel Plot
- Funnel Plot 1: Effect of Screening on Incidence of Invasive Cervical Cancer - Exposure to Cytology Screening (Case-Control Studies)

Table 15: GRADE Evidence Profile Table for Effect of Screening on Incidence of Invasive Cervical Cancer

Quality Assessment							No. of Participants		Effect		Quality	Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Screening	Control	Relative (95% CI)	Absolute per Million (Range)		
Incidence of Invasive Cervical Cancer (invited to screening with HVP testing or cytology versus no screening; Follow-up 8 years; Assessed with: cancer registry data)												
1[1]	randomized trials	no serious risk of bias[2]	no serious inconsistency[3]	serious[4]	no serious imprecision	none[5]	279/66,184 (0.4216%)[6]	118/31,488 (0.3747%)[6]	RR 1.1249 (0.9075 to 1.3945)[7]	468 more (from 347 fewer to 1,478 more)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of Invasive Cervical Cancer (invited to screening with HPV testing versus no screening; Follow-up 8 years; Assessed with: cancer registry data)												
1[1]	randomized trials	no serious risk of bias[2]	no serious inconsistency[3]	serious[4]	no serious imprecision[8]	none[5]	127/34,126 (0.3722%)[6]	118/31,488 (0.3747%)[6]	HR 1.0500 (0.7705 to 1.4309)	187 more (from 859 fewer to 1,610 more)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of Invasive Cervical Cancer (invited to screening with cytology versus no screening; Follow-up 8 years; Assessed with: cancer registry data)												
1[1]	randomized trials	no serious risk of bias[2]	no serious inconsistency[3]	serious[4]	no serious imprecision[8]	none[5]	152/32,058 (0.4741%)[6]	118/31,488 (0.3747%)[6]	HR 1.3400 (0.9899 to 1.814)	1,271 more (from 38 fewer to 3,040 more)	⊕⊕⊕O MODERATE	CRITICAL
Exposure to Cytology Screening (cases: women diagnosed with invasive cervical cancer; controls: women with no cervical cancer); Exposure ranged from within previous 3 years to lifetime history; Assessed with: self-reports, hospital, clinic and registry records)												
13[9]	observational studies[10]	no serious risk of bias[11]	no serious inconsistency[12]	serious[13]	no serious imprecision	reporting bias[14]	4,781 cases 17,916 controls		OR 0.3490 (0.2953 to 0.4124)	-	⊕OOO VERY LOW	CRITICAL
Incidence of Invasive Cervical Cancer (cytology versus no screening) Cohort Study (follow-up 3 years; assessed with: local cancer registry, histology records at hospitals/clinics)												
1[15]	observational studies	no serious risk of bias[16]	no serious inconsistency[3]	no serious indirectness	no serious imprecision[8]	none[5]	63/103,491 (0.0609%)[17]	20/12,531 (0.1596%)[18]	RR 0.3814 (0.2307 to 0.6305)	987 fewer (from 590 fewer to 1,228 fewer)	⊕⊕OO LOW	CRITICAL

[1] Sankaranarayanan[72]
[2] Random sequence generation unclear and allocation concealment not described, however study limitations were not downgraded for these risks/uncertainties.
[3] Single study, therefore inconsistency not applicable.
[4] Directness downgraded due to concerns regarding population characteristics (rural women living in a low income country) and intervention characteristics [one-time opportunistic screening; short duration (3 months) of training received by lab technicians responsible for processing and reading the samples].
[5] Insufficient number of studies to assess publication bias.
[6] Rates were adjusted for age by study authors.
[7] Study authors do not provide a Hazard Ratio for the HPV testing and cytology groups combined versus the control group. Using sample and event data we computed a Relative Risk.

[8] The number of events is small (<300, a threshold rule of thumb value for dichotomous outcomes), however considering the specific outcome the evidence is not downgraded.
[9] There are 12 included case-control studies: Andrae,[80] Aristizabal,[104] Berrino,[105] Clarke,[106] Decker[81] Hernández-Avila[82] Herrero[107] Hoffman[83] Jiménez-Pérez[84] Makino[85] Nieminen[73] Talbott[86]. The number of studies appears as 13 because two different data sets from one study[73] were used as separate entries in the meta-analysis.
[10] Case-control
[11] Newcastle-Ottawa Scale completed to assess the quality of each of the studies. None of the studies satisfied all of the rating criteria. Despite some uncertainties (e.g., lack of information on non-response rates in some studies) and limitations (e.g., one-third of the studies used hospital controls rather than community controls) the evidence was not downgraded.
[12] Heterogeneity statistics were significant: $Chi^2 = 50.98$, $df = 12$ ($P < 0.00001$); $I^2 = 76\%$. Sensitivity analyses were conducted but heterogeneity could not be explained by differences in study design, populations, interventions, or length of exposure. All studies favour screening; only two of the 13 studies marginally intersect the line of no difference.
[13] Directness was downgraded due to concerns regarding: the inclusion of both organized and opportunistic screening approaches; the diversity of study locations which included both developed and developing countries (Canada, US, Finland, Sweden, Japan, Italy, South Africa, Columbia, Costa Rica, Panama, Mexico); and the related potential for important differences in participants and screening procedures, particularly given that half of the studies looked at screening that occurred more than 20 years ago and all of the studies looked at screening that occurred more than 10 years ago.
[14] Publication bias was "strongly suspected" due to asymmetry in the funnel plot and the recognition that the risk of publication bias may be substantial for observational studies, particularly small studies that utilize data from electronic medical records or disease registries.[199]
[15] Herbert[94] (cohort study)
[16] Newcastle-Ottawa Scale for cohort studies was completed; 8 out of a possible 9 stars were awarded.
[17] 63 cases of cervical cancer diagnosed in women who had been screened in the 0.5 to 5.5 year interval; 37 of these cases were screen detected cancers while 26 cases were symptomatic cancers.
[18] 20 cases of cervical cancer diagnosed in women who had been screened in the 0.5 to 5.5 year interval; 6 of these cases were screen detected cancers while 14 cases were symptomatic cancers.

Table 16: GRADE Summary of Findings Table for Effect of Screening on Incidence of Invasive Cervical Cancer

Outcomes	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)	Comments
	Assumed Risk Number per Million **Control**	Corresponding Risk Number per Million **Screening**				
Incidence of Invasive Cervical Cancer (invited to screening with HVP testing or cytology versus no screening) Assessed with: cancer registry data; Follow-up: 8 years	**3,747**[1]	**4,216** (3,401 to 5,226)[1]	**RR 1.1249** (0.9075 to 1.3945)[2]	97,672 (1 study[3])	⊕⊕⊕⊖ **moderate**[4,5,6,7,8]	
Incidence of Invasive Cervical Cancer (invited to screening with HPV testing versus no screening) Assessed with: cancer registry data; Follow-up: 8 years	**3,747**[1]	**3,934** (2,889 to 5,358)[1]	**HR 1.0500** (0.7705 to 1.4309)	65,614 (1 study[3])	⊕⊕⊕⊖ **moderate**[4,5,6,7,8]	
Incidence of Invasive Cervical Cancer (invited to screening with cytology versus no screening) Assessed with: cancer registry data; Follow-up: 8 years	**3,747**[1]	**5,018** (3,710 to 6,788)[1]	**HR 1.3400** (0.9899 to 1.814)	63,546 (1 study[3])	⊕⊕⊕⊖ **moderate**[4,5,6,7,8]	
Exposure to Cytology Screening (cases: women diagnosed with invasive cervical cancer; controls: women with no cervical cancer) Assessed with: self-reports, hospital, clinic and registry records; Exposure ranged from within previous 3 years to lifetime history	See comment	See comment	**OR 0.3490** (0.2953 to 0.4124)	0 (13 studies[9,10])	⊕⊖⊖⊖ **very low**[11,12,13,14]	4,781 cases and 17,916 controls
Incidence of Invasive Cervical Cancer (cytology versus no screening) Cohort Study Assessed with: local cancer registry, histology records at hospitals/clinics; Follow-up: 3 years	**1,596**[15]	**609** (368 to 1,006)[16]	**RR 0.3814** (0.2307 to 0.6305)	116,022 (1 study[17])	⊕⊕⊖⊖ **low**[5,7,8,18]	

*****The **assumed risk** is the median control group risk. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence Interval; **RR:** Risk Ratio; **OR:** Odds Ratio; **HR:** Hazard Ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

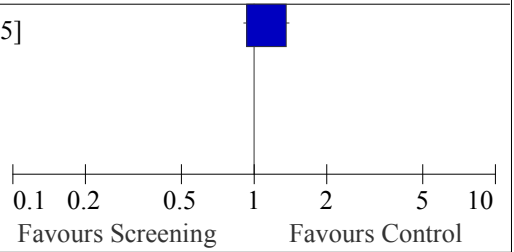
[1] Rates were adjusted for age by study authors.
[2] Study authors do not provide a Hazard Ratio for the HPV testing and cytology groups combined versus the control group. Using sample and event data we computed a Relative Risk.
[3] Sankaranarayanan[72]
[4] Random sequence generation unclear and allocation concealment not described, however study limitations were not downgraded for these risks/uncertainties.
[5] Single study, therefore inconsistency not applicable.
[6] Directness downgraded due to concerns regarding population characteristics (rural women living in a low income country) and intervention characteristics [one-time opportunistic screening; short duration (3 months) of training received by lab technicians responsible for processing and reading the samples].
[7] Insufficient number of studies to assess publication bias.

[8] The number of events is small (<300, a threshold rule of thumb value for dichotomous outcomes), however considering the specific outcome the evidence is not downgraded.
[9] There are 12 included case-control studies: Andrae,[80] Aristizabal,[104] Berrino,[105] Clarke,[106] Decker[81] Hernández-Avila[82] Herrero[107] Hoffman[83] Jiménez-Pérez[84] Makino[85] Nieminen[73] Talbott[86]. The number of studies appears as 13 because two different data sets from one study[73] were used as separate entries in the meta-analysis
[10] Case-control
[11] Newcastle-Ottawa Scale completed to assess the quality of each of the studies. None of the studies satisfied all of the rating criteria. Despite some uncertainties (e.g., lack of information on non-response rates in some studies) and limitations (e.g., one-third of the studies used hospital controls rather than community controls) the evidence was not downgraded.
[12] Heterogeneity statistics were significant: $Chi^2 = 50.98$, df = 12 ($P < 0.00001$); $I^2 = 76\%$. Sensitivity analyses were conducted but heterogeneity could not be explained by differences in study design, populations, interventions, or length of exposure. All studies favour screening; only two of the 13 studies marginally intersect the line of no difference.
[13] Directness was downgraded due to concerns regarding: the inclusion of both organized and opportunistic screening approaches; the diversity of study locations which included both developed and developing countries (Canada, US, Finland, Sweden, Japan, Italy, South Africa, Columbia, Costa Rica, Panama, Mexico); and the related potential for important differences in participants and screening procedures, particularly given that half of the studies looked at screening that occurred more than 20 years ago and all of the studies looked at screening that occurred more than 10 years ago.
[14] Publication bias was "strongly suspected" due to asymmetry in the funnel plot and the recognition that the risk of publication bias may be substantial for observational studies, particularly small studies that utilize data from electronic medical records or disease registries.[199]
[15] 20 cases of cervical cancer diagnosed in women who had been screened in the 0.5 to 5.5 year interval; 6 of these cases were screen detected cancers while 14 cases were symptomatic cancers.
[16] 63 cases of cervical cancer diagnosed in women who had been screened in the 0.5 to 5.5 year interval; 37 of these cases were screen detected cancers while 26 cases were symptomatic cancers.
[17]Herbert[94] (cohort study)
[18] Newcastle-Ottawa Scale for cohort studies was completed; 8 out of a possible 9 stars were awarded.

Forest Plot 4: Effect of Screening on Incidence of Invasive Cervical Cancer - Invited to Screening with HPV Testing or Cytology versus No Screening (RCT)

Study	Screening Events	Screening Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sankaranarayanan et al. 2009	279	66,184	118	31,488	100.0%	1.1249 [0.9075, 1.3945]

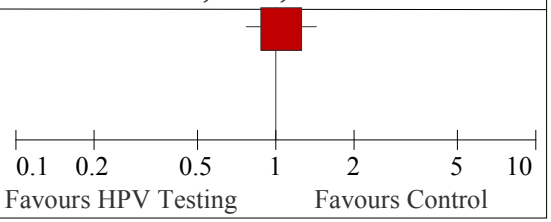
Test for overall effect: Z = 1.07 (P = 0.28)
M-H: Mantel-Haenszel)



Forest Plot 5: Effect of Screening on Incidence of Invasive Cervical Cancer - Invited to Screening with HPV Testing versus No Screening (RCT)

Study	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Sankaranarayanan et al. 2009	0.0488	0.1579	100.0%	1.0500 [0.7705, 1.4309]

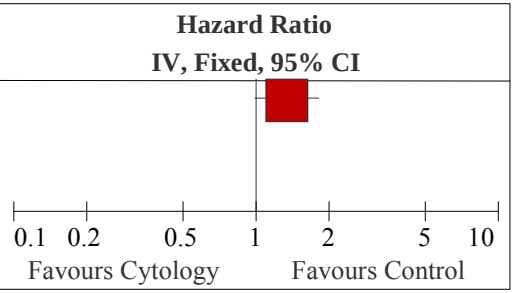
Test for overall effect: Z = 0.31 (P = 0.76)
(IV: Inverse Variance)



Forest Plot 6: Effect of Screening on Incidence of Invasive Cervical Cancer - Invited to Screening with Cytology versus No Screening (RCT)

Study	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Sankaranarayanan et al. 2009	0.2927	0.1545	100.0%	1.3400 [0.9899, 1.8140]

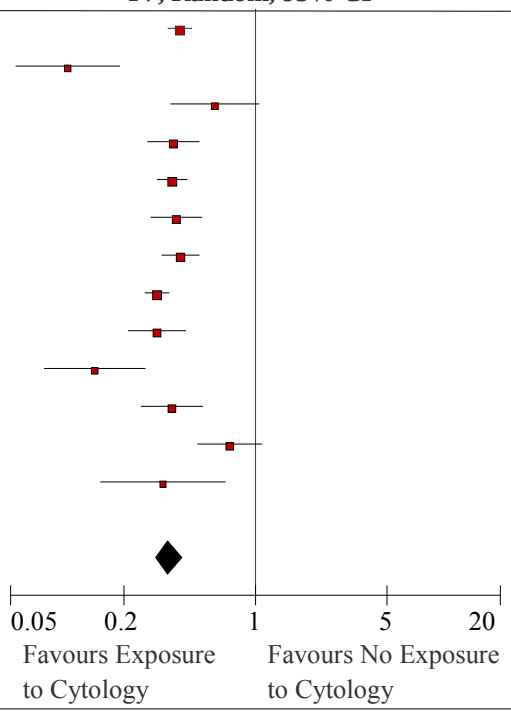
Test for overall effect: Z = 1.89 (P = 0.06)
(IV: Inverse Variance)



Forest Plot 7: Effect of Screening on Incidence of Invasive Cervical Cancer - Exposure to Cytology Screening (Case-Control Studies)

Study	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Andrae et al. 2008	-0.9243	0.0726	11.1%	0.3968 [0.3442, 0.4575]
Aristizabal et al. 1984	-2.2966	0.3222	4.4%	0.1006 [0.0535, 0.1892]
Berrino et al. 1986	-0.4977	0.2744	5.4%	0.6079 [0.3550, 1.0409]
Clarke et al. 1979	-1.0032	0.1601	8.4%	0.3667 [0.2679, 0.5019]
Decker et al. 2009	-1.0189	0.0921	10.6%	0.3610 [0.3014, 0.4324]
Hernández-Avila et al. 1998	-0.9676	0.1579	8.5%	0.3800 [0.2789, 0.5178]
Herrero et al. 1992	-0.9163	0.1153	9.9%	0.4000 [0.3191, 0.5014]
Hoffman et al. 2003	-1.204	0.0734	11.1%	0.3000 [0.2598, 0.3464]
Jiménez-Pérez et al. 1999	-1.204	0.1768	7.9%	0.3000 [0.2121, 0.4242]
Makino et al. 1995	-1.9661	0.3133	4.6%	0.1400 [0.0758, 0.2587]
Nieminen et al. 1999 (Organized)	-1.0217	0.1917	7.5%	0.3600 [0.2472, 0.5242]
Nieminen et al. 1999 (Opportunistic)	-0.3147	0.1992	7.3%	0.7300 [0.4940, 1.0787]
Talbott et al. 1995	-1.1313	0.3882	3.4%	0.3226 [0.1507, 0.6904]
Total (95% CI)			**100.0%**	**0.3490 [0.2953, 0.4124]**

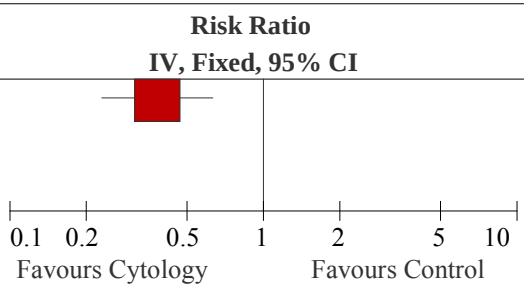
Heterogeneity: Tau² = 0.06; Chi² = 50.98, df = 12 (P < 0.00001); I² = 76%
Test for overall effect: Z = 12.36 (P < 0.00001)



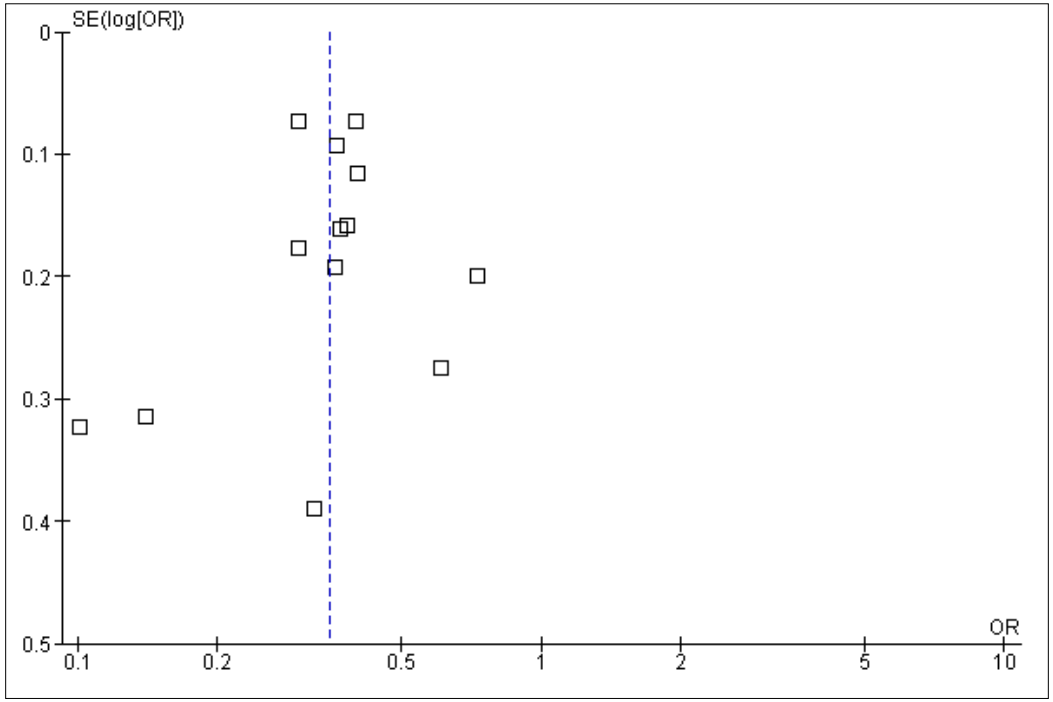
Forest Plot 8: Effect of Screening on Incidence of Invasive Cervical Cancer - Screening with Cytology versus No Screening (Cohort Study)

Study	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Herbert et al. 1996	-0.9639	0.2565	100.0%	0.3814 [0.2307, 0.6305]

Test for overall effect: Z = 3.76 (P = 0.0002)
(IV: Inverse Variance)



Funnel Plot 1: Effect of Screening on Incidence of Invasive Cervical Cancer - Exposure to Cytology Screening (Case-Control Studies)



Evidence Set 3: KQ1 – What is the effect of cervical cancer screening on incidence of stage II or higher cervical cancer?

Table 17: GRADE Evidence Profile Table for Effect of Screening on Incidence of Stage II or Higher Cervical Cancer
- Invited to Screening with HPV Testing or Cytology versus No Screening
- Invited to Screening with HPV Testing versus No Screening
- Invited to Screening with Cytology versus No Screening

Table 18: GRADE Summary of Findings Table for Effect of Screening on Incidence of Stage II or Higher Cervical Cancer
- Invited to Screening with HPV Testing or Cytology versus No Screening
- Invited to Screening with HPV Testing versus No Screening
- Invited to Screening with Cytology versus No Screening

Forest Plots
- Forest Plot 9: Effect of Screening on Incidence of Stage II or Higher Cervical Cancer - Invited to Screening with HPV Testing or Cytology versus No Screening
- Forest Plot 10: Effect of Screening on Incidence of Stage II or Higher Cervical Cancer - Invited to Screening with HPV Testing versus No Screening
- Forest Plot 11: Effect of Screening on Incidence of Stage II or Higher Cervical Cancer - Invited to Screening with Cytology versus No Screening

Table 17: GRADE Evidence Profile Table for Effect of Screening on Incidence of Stage II or Higher Cervical Cancer

Quality Assessment							No. of Participants		Effect		Quality	Importance
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Screening	Control	Relative (95% CI)	Absolute per Million (Range)		
Incidence of Stage II or Higher Cervical Cancer (invited to screening with HPV testing or cytology versus no screening; Follow-up: 8 years; Assessed with: cancer registry data)												
1[1]	randomized trials	no serious risk of bias[2]	no serious inconsistency[3]	serious[4]	no serious imprecision[5]	none[6]	97/66,184 (0.1466%)[7]	82/31,488 (0.2604%)[7]	RR 0.5628 (0.4196 to 0.7549)[8]	1,139 fewer (from 638 fewer to 1,511 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of Stage II or Higher Cervical Cancer (invited to screening with HPV testing versus no screening; Follow-up: 8 years; Assessed with: cancer registry data)												
1[1]	randomized trials	no serious risk of bias[2]	no serious inconsistency[3]	serious[4]	no serious imprecision[5]	none[6]	39/34,126 (0.1143%)[7]	82/31,488 (0.2604%)[7]	HR 0.4677 (0.3160 to 0.6922)	1,385 fewer (from 801 fewer to 1,781 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of Stage II or Higher Cervical Cancer (invited to screening with cytology versus no screening; Follow-up: 8 years; Assessed with: cancer registry data)												
1[1]	randomized trials	no serious risk of bias[2]	no serious inconsistency[3]	serious[4]	no serious imprecision[5]	none[6]	58/32,058 (0.1809%)[7]	82/31,488 (0.2604%)[7]	HR 0.7500 (0.5100 to 1.1030)	650 fewer (from 1,275 fewer to 268 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] Sankaranarayanan[72]
[2] Random sequence generation unclear and allocation concealment not described, however study limitations were not downgraded for these risks/uncertainties.
[3] Single study, therefore inconsistency not applicable.
[4] Directness downgraded due to concerns regarding population characteristics (rural women living in a low income country) and intervention characteristics [one-time opportunistic screening; short duration (3 months) of training received by lab technicians responsible for processing and reading the samples].
[5] The number of events is small (<300, a threshold rule of thumb value for dichotomous outcomes), however considering the specific outcome the evidence is not downgraded.
[6] Insufficient number of studies to assess publication bias.
[7] Rates were adjusted for age by study authors.
[8] Study authors do not provide a Hazard Ratio for the HPV testing and cytology groups combined versus the control group. Using sample and event data we computed a Relative Risk.

Table 18: GRADE Summary of Findings Table for KQ1 – Effect of Screening on Incidence of Stage II or Higher Cervical Cancer

Outcomes	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk Number per Million **Control**	Corresponding Risk Number per Million **Screening**			
Incidence of Stage II or Higher Cervical Cancer (invited to screening with HPV testing or cytology versus no screening) Assessed with: cancer registry data; Follow-up: 8 years	**2,604**[1]	**1,466** (1,093 to 1,966)[1]	**RR 0.5628** (0.4196 to 0.7549)[2]	97,672 (1 study[3])	⊕⊕⊕⊖ **moderate**[4,5,6,7,8]
Incidence of Stage II or Higher Cervical Cancer (invited to screening with HPV testing versus no screening) Assessed with: cancer registry data; Follow-up: 8 years	**2,604**[1]	**1,219** (824 to 1,803)[1]	**HR 0.4677** (0.3160 to 0.6922)	65,614 (1 study[3])	⊕⊕⊕⊖ **moderate**[4,5,6,7,8]
Incidence of Stage II or Higher Cervical Cancer (invited to screening with cytology versus no screening) Assessed with: cancer registry data; Follow-up: 8 years	**2,604**[1]	**1,954** (1,329 to 2,872)[1]	**HR 0.7500** (0.5100 to 1.1030)	63,546 (1 study[3])	⊕⊕⊕⊖ **moderate**[4,5,6,7,8]

*The **assumed risk** is the median control group risk. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence Interval; **RR:** Risk Ratio; **HR:** Hazard Ratio

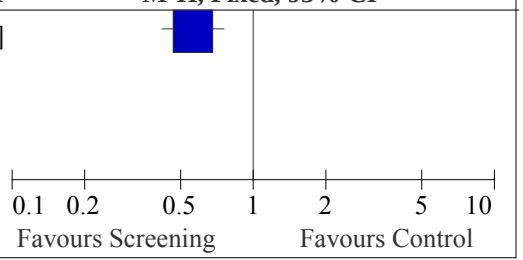
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Rates were adjusted for age by study authors.
[2] Study authors do not provide a Hazard Ratio for the HPV testing and cytology groups combined versus the control group. Using sample and event data we computed a Relative Risk.
[3] Sankaranarayanan[72]
[4] Random sequence generation unclear and allocation concealment not described, however study limitations were not downgraded for these risks/uncertainties.
[5] Single study, therefore inconsistency not applicable.
[6] Directness downgraded due to concerns regarding population characteristics (rural women living in a low income country) and intervention characteristics [one-time opportunistic screening; short duration (3 months) of training received by lab technicians responsible for processing and reading the samples].
[7] The number of events is small (<300, a threshold rule of thumb value for dichotomous outcomes), however considering the specific outcome the evidence is not downgraded.
[8] Insufficient number of studies to assess publication bias.

Forest Plot 9: Effect of Screening on Incidence of Stage II or Higher Cervical Cancer - Invited to Screening with HPV Testing or Cytology versus No Screening

Study	Screening Events	Screening Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sankaranarayanan et al. 2009	97	66,184	82	31,488	100.0%	0.5628 [0.4196, 0.7549]

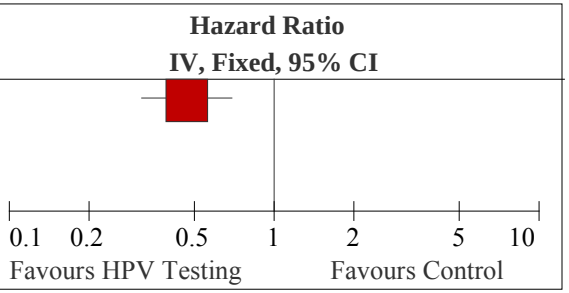
Test for overall effect: Z = 3.84 (P = 0.0001)
(M-H: Mantel-Haenszel)



Forest Plot 10: Effect of Screening on Incidence of Stage II or Higher Cervical Cancer - Invited to Screening with HPV Testing versus No Screening

Study	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Sankaranarayanan et al. 2009	-0.7599	0.2	100.0%	0.4677 [0.3160, 0.6922]

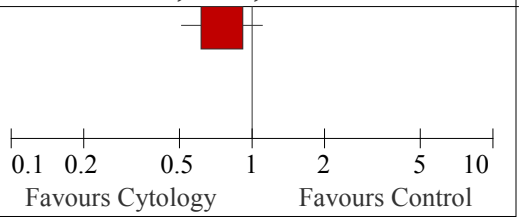
Test for overall effect: Z = 3.80 (P = 0.0001)
(IV: Inverse Variance)



Forest Plot 11: Effect of Screening on Incidence of Stage II or Higher Cervical Cancer - Invited to Screening with Cytology versus No Screening

Study	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Sankaranarayanan et al. 2009	-0.2877	0.1968	100.0%	0.7500 [0.5100, 1.1030]

Test for overall effect: Z = 1.46 (P = 0.14)
(IV: Inverse Variance)



Evidence Set 4: KQ1b – What is the effect of cervical cancer screening with HPV testing compared to conventional cytology on mortality from and incidence of invasive cervical cancer?

Table 19: GRADE Evidence Profile Table for Effect of Screening with HPV Testing Compared to Screening with Cytology
- Cervical Cancer Mortality
- Incidence of Invasive Cervical Cancer
- Incidence of Stage II or Higher Cervical Cancer

Table 20: GRADE Summary of Findings Table for Effect of Screening with HPV Testing Compared to Screening with Cytology
- Cervical Cancer Mortality
- Incidence of Invasive Cervical Cancer
- Incidence of Stage II or Higher Cervical Cancer

Forest Plots
- Forest Plot 12: Effect of Screening with HPV Testing Compared to Screening with Cytology on Cervical Cancer Mortality
- Forest Plot 13: Effect of Screening with HPV Testing Compared to Screening with Cytology on Incidence of Invasive Cervical Cancer
- Forest Plot 14: Effect of Screening with HPV Testing Compared to Screening with Cytology on Incidence of Stage II or Higher Cervical Cancer

Table 19: GRADE Evidence Profile Table for Effect of Screening with HPV Testing Compared to Screening with Cytology

Quality Assessment							No. of Participants		Effect		Quality	Importance
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Screening with HPV Testing	Screening with Cytology	Relative (95% CI)	Absolute per Million (Range)		
Cervical Cancer Mortality (invited to screening with HPV testing versus invited to screening with cytology; Follow-up 8 years; Assessed with: district death registrations, hospital records, annual house visits)												
1[1]	randomized trials	no serious risk of bias[2]	no serious inconsistency[3]	serious[4]	no serious imprecision[5]	none[6]	34/34,126 (0.0996%)[7]	54/32,058 (0.1684%)[7]	RR 0.5915 (0.3852 to 0.9082)[8]	688 fewer (from 155 fewer to 1,036 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of Invasive Cervical Cancer (invited to HPV testing versus invited to screening with cytology; Follow-up 3 to 8 years; Assessed with: cancer registry data)												
2[9]	randomized trials	no serious risk of bias[2]	no serious inconsistency	serious[4]	no serious imprecision[5]	none[6]	133/63,163 (0.2106%)[7]	160/61,097 (0.2619%)[7]	RR 0.7832 (0.6226 to 0.9853)[8]	568 fewer (from 38 fewer to 988 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of Stage II or Higher Cervical Cancer (invited to HPV testing versus invited to screening with cytology; Follow-up 8 years; Assessed with: cancer registry data)												
1[1]	randomized trials	no serious risk of bias[2]	no serious inconsistency[3]	serious[4]	no serious imprecision[5]	none[6]	39/34,126 (0.1143%)[7]	58/32,058 (0.1809%)[7]	RR 0.6317 (0.4211 to 0.9476)[8]	666 fewer (from 95 fewer to 1,047 fewer)	⊕⊕⊕O MODERATE	CRITICAL

[1] Sankaranarayanan[72]
[2] Random sequence generation unclear and allocation concealment not described, however study limitations were not downgraded for these risks/uncertainties.
[3] Single study, therefore inconsistency not applicable.
[4] Directness downgraded due to concerns in the Sankaranarayanan[72] study regarding population characteristics (rural women living in a low income country) and intervention characteristics [one-time opportunistic screening; short duration (3 months) of training received by lab technicians responsible for processing and reading the samples].
[5] The number of events is small (<300, a threshold rule of thumb value for dichotomous outcomes), however considering the specific outcome the evidence is not downgraded.
[6] Insufficient number of studies to assess publication bias.
[7] Rates were adjusted for age by Sankaranarayanan[72]
[8] Study authors do not provide a Hazard Ratio for the HPV testing group versus the cytology group. Using sample and event data we computed a Relative Risk.
[9] Sankaranarayanan[72]; Anttila[78]

Table 20: GRADE Summary of Findings Table for Effect of Screening with HPV Testing Compared to Screening with Cytology

Outcomes	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk Number per Million **Screening with Cytology**	Corresponding Risk Number per Million **Screening with HPV Testing**			
Cervical Cancer Mortality (invited to screening with HPV testing versus invited to screening with cytology) Assessed with: district death registrations, hospital records, annual house visits; Follow-up: 8 years	**1,684**[1]	**996** (649 to 1,530)[1]	**RR 0.5915** (0.3852 to 0.9082)[2]	66,184 (1 study[3])	⊕⊕⊕⊖ **moderate**[4,5,6,7,8]
Incidence of Invasive Cervical Cancer (invited to HPV testing versus invited to screening with cytology) Assessed with: cancer registry data; Follow-up: 3 to 8 years	**2,619**[1]	**2,051** (1,630 to 2,580)[1]	**RR 0.7832** (0.6226 to 0.9853)[2]	124,260 (2 studies[9])	⊕⊕⊕⊖ **moderate**[4,6,7,8]
Incidence of Stage II or Higher Cervical Cancer (invited to HPV testing versus invited to screening with cytology) Assessed with: cancer registry data; Follow-up: 8 years	**1,809**[1]	**1,143** (762 to 1,714)[1]	**RR 0.6317** (0.4211 to 0.9476)[2]	66,184 (1 study[3])	⊕⊕⊕⊖ **moderate**[4,5,6,7,8]

*The **assumed risk** is the median control group risk. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence Interval; **RR:** Risk Ratio

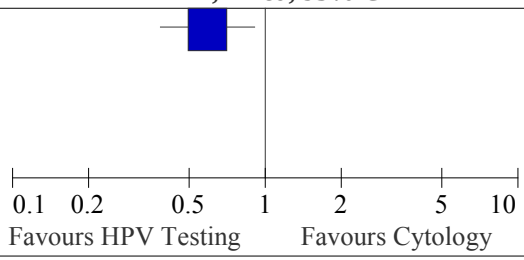
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Rates were adjusted for age by Sankaranarayanan[72]
[2] Study authors do not provide a Hazard Ratio for the HPV testing group versus the cytology group. Using sample and event data we computed a Relative Risk.
[3] Sankaranarayanan[72]
[4] Random sequence generation unclear and allocation concealment not described, however study limitations were not downgraded for these risks/uncertainties.
[5] Single study, therefore inconsistency not applicable.
[6] Directness downgraded due to concerns in the Sankaranarayanan[72] study regarding population characteristics (rural women living in a low income country) and intervention characteristics [one-time opportunistic screening; short duration (3 months) of training received by lab technicians responsible for processing and reading the samples].
[7] The number of events is small (<300, a threshold rule of thumb value for dichotomous outcomes), however considering the specific outcome the evidence is not downgraded.
[8] Insufficient number of studies to assess publication bias.
[9] Sankaranarayanan[72]; Anttila[78]

Forest Plot 12: Effect of Screening with HPV Testing Compared to Screening with Cytology on Cervical Cancer Mortality

Study	HPV Testing Events	HPV Testing Total	Cytology Events	Cytology Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sankaranarayanan et al. 2009	34	34,126	54	32,058	100.0%	0.5915 [0.3852, 0.9082]

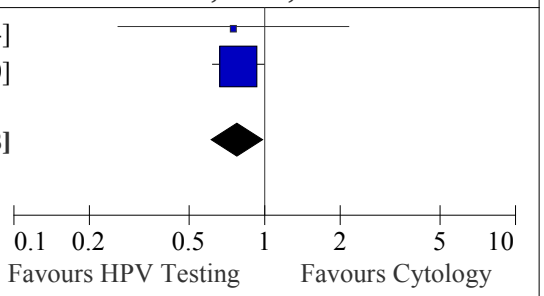
Test for overall effect: Z = 2.40 (P = 0.02)
(M-H: Mantel-Haenszel)



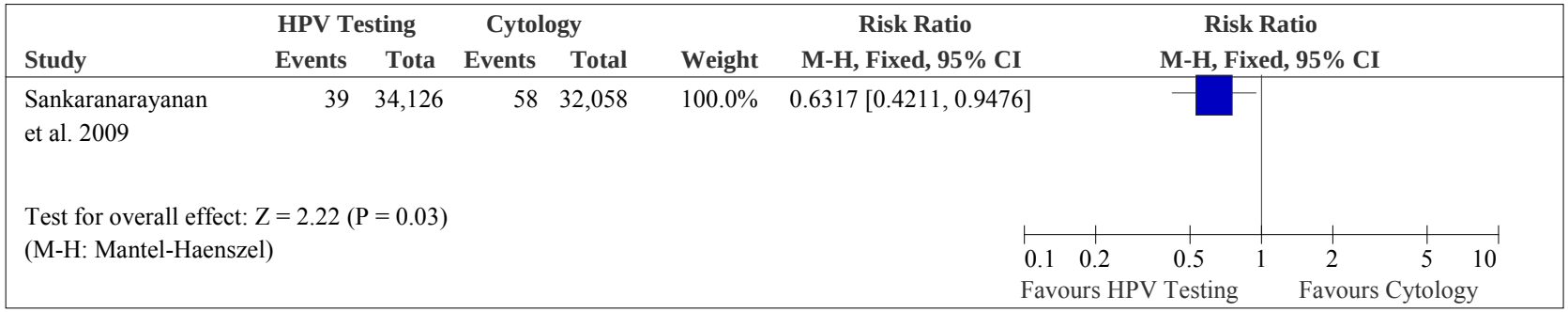
Forest Plot 13: Effect of Screening with HPV Testing Compared to Screening with Cytology on Incidence of Invasive Cervical Cancer

Study	HPV Testing Events	HPV Testing Total	Cytology Events	Cytology Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anttila et al. 2010	6	29,037	8	29,039	4.9%	0.7501 [0.2603, 2.1614]
Sankaranarayanan et al. 2009	127	34,126	152	32,058	95.1%	0.7849 [0.6204, 0.9930]
Total (95% CI)		**63,163**		**61,097**	**100.0%**	**0.7832 [0.6226, 0.9853]**
Total events	133		160			

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 2.09 (P = 0.04)
(M-H: Mantel-Haenszel)



Forest Plot 14: Effect of Screening with HPV Testing Compared to Screening with Cytology on Incidence of Stage II or Higher Cervical Cancer



Evidence Set 5: KQ1c – What is the effect of computer-assisted screening compared to conventional cytology screening on mortality from and incidence of invasive cervical cancer?

Table 21: GRADE Evidence Profile Table for Effect of Computer- Assisted Screening Compared to Conventional Cytology Screening

- Cervical Cancer Mortality
- Incidence of Invasive Cervical Cancer

Table 22: GRADE Summary of Findings Table for Effect of Computer-Assisted Screening Compared to Conventional Cytology Screening

- Cervical Cancer Mortality
- Incidence of Invasive Cervical Cancer

Forest Plots

- Forest Plot 15: Effect of Computer-Assisted Screening Compared to Conventional Cytology Screening on Cervical Cancer Mortality
- Forest Plot 16: Effect of Computer-Assisted Screening Compared to Conventional Cytology Screening on Incidence of Invasive Cervical Cancer

Table 21: GRADE Evidence Profile Table for Effect of Computer-Assisted Screening Compared to Conventional Cytology Screening

Quality Assessment							No. of Participants		Effect		Quality	Importance
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Computer-Assisted Screening	Conventional Cytology Screening	Relative (95% CI)	Absolute per Million (Range)		
Mortality from Cervical Cancer (Follow-up 4 to 8 years; Assessed with: cancer and population registries)												
1[1]	randomized trials	no serious risk of bias[2]	no serious inconsistency[3]	no serious indirectness[4]	no serious imprecision[5]	none[6]	19/169,159 (0.0112%)	34/334,232 (0.0102%)	RR 1.1041 (0.6298 to 1.9356)	11 more (from 38 fewer to 95 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Incidence of Invasive Cervical Cancer (Follow-up 4 to 8 years; Assessed with: cancer and population registries)												
1[1]	randomized trials	no serious risk of bias[2]	no serious inconsistency[3]	no serious indirectness[4]	no serious imprecision[5]	none[6]	83/169,159 (0.0491%)	165/334,232 (0.0494%)	RR 0.9939 (0.7635 to 1.2938)	3 fewer (from 117 fewer to 145 more)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] Anttila[79]
[2] Random sequence generation was not done and allocation concealment is unclear. However the evidence was not downgraded for these risks/uncertainties.
[3] Single study, therefore inconsistency not applicable.
[4] Organized population-based screening program in Finland.
[5] The number of events is small (<300, a threshold rule of thumb value for dichotomous outcomes), however considering the specific outcome the evidence is not downgraded.
[6] Insufficient number of studies to assess publication bias.

Table 22: GRADE Summary of Findings Table for Effect of Computer-Assisted Screening Compared to Conventional Cytology Screening

Outcomes	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk Number per Million **Conventional Cytology Screening**	Corresponding Risk Number per Million **Computer-Assisted Screening**			
Mortality from Cervical Cancer Assessed with: cancer and population registries; Follow-up: 4 to 8 years	**102**	**112** (64 to 197)	**RR 1.1041** (0.6298 to 1.9356)	503,391 (1 study[1])	⊕⊕⊕⊕ **high**[2,3,4,5,6]
Incidence of Invasive Cervical Cancer Assessed with: cancer and population registries; Follow-up: 4 to 8 years	**494**	**491** (377 to 639)	**RR 0.9939** (0.7635 to 1.2938)	503,391 (1 study[1])	⊕⊕⊕⊕ **high**[2,3,4,5,6]

***The **assumed risk** is the median control group risk. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence Interval; **RR:** Risk Ratio

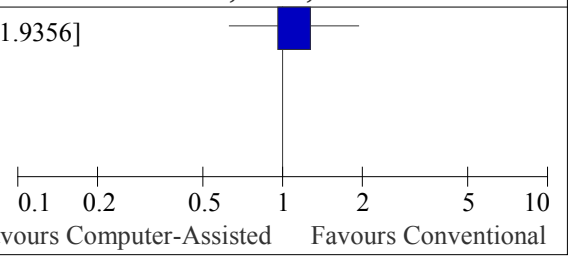
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Anttila[79]
[2] Random sequence generation was not done and allocation concealment is unclear. However the evidence was not downgraded for these risks/uncertainties.
[3] Single study, therefore inconsistency not applicable.
[4] Organized population-based screening program in Finland.
[5] The number of events is small (<300, a threshold rule of thumb value for dichotomous outcomes), however considering the specific outcome the evidence is not downgraded.
[6] Insufficient number of studies to assess publication bias.

Forest Plot 15: Effect of Computer-Assisted Screening Compared to Conventional Cytology Screening - Cervical Cancer Mortality

Study	Computer-Assisted Events	Computer-Assisted Total	Conventional Cytology Events	Conventional Cytology Total	Weight	Risk Ratio IV, Fixed, 95% CI
Anttila et al. 2011	19	169,159	34	334,232	100.0%	1.1041 [0.6298, 1.9356]

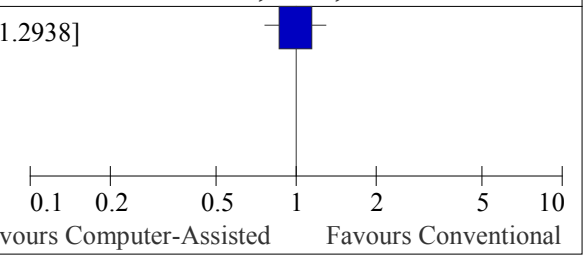
Test for overall effect: Z = 0.35 (P = 0.73)
(M-H: Mantel-Haenszel)



Forest Plot 16: Effect of Computer-Assisted Screening Compared to Conventional Cytology Screening - Incidence of Invasive Cervical Cancer

Study	Computer-Assisted Events	Computer-Assisted Total	Conventional Cytology Events	Conventional Cytology Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anttila et al. 2011	83	169,159	165	334,232	100.0%	0.9939 [0.7635, 1.2938]

Test for overall effect: Z = 0.05 (P = 0.96)
(M-H: Mantel-Haenszel)



Evidence Set 6: KQ1d – What is the effect of varying the screening interval on incidence of invasive cervical cancer?

Table 23: Summary of Studies Examining the Effect of Varying the Screening Interval on Incidence of Invasive Cervical Cancer

Table 23: Summary of Studies Examining the Effect of Varying the Screening Interval on Incidence of Invasive Cervical Cancer

Study	Study Design	Location	No. Cases	No. Controls	Intervals (Months)	OR (95% CI) of Screening for Cervical Cancer
Andrae[80]	Case-Control	Sweden	1,230	6,124	6 to 42 (ages <53) 6 to 66 (ages 54-65) 6 to 78 (ages ≥66)	0.3968 (0.3442-0.4575)
					no screening	1.00
Berrino[105]	Case-Control	Italy	121	350	0 to 11	0.14 (no CI given)
					12 to 23	0.16 (no CI given)
					24 to 35	1.16 (no CI given)
					36 to 47	0.75 (no CI given)
					>48	1.01 (no CI given)
					no previous negative	1.00
Herrero[107]	Case-Control	Latin America	759	1,430	12 to 23	1.00
					24 to 47	1.0 (0.7-1.3)
					48 to 71	1.7 (1.0-2.5)
					72 to 119	1.4 (0.8-2.3)
					≥120	1.8 (1.0-2.5)
					never	3.0 (2.3-4.0)
Hoffman[83]	Case-Control	South Africa	524	1,540	<60	0.3 (0.2-0.4)
					60 to 119	0.3 (0.2-0.4)
					120 to 179	0.4 (0.3-0.5)
					≥180	0.5 (0.4-0.7)
					never	1.00
Jiménez-Pérez[84]	Case-Control	Mexico	143	311	1 to 12	0.2 (0.1-0.4)
					13 to 60	0.2 (0.1-0.5)
					>60	0.5 (0.3-0.9)
					never	1.00
Kasinpila[102]	Case-Control	Thailand	89	223	6 to 11	1.38 (0.56-3.40)
					12 to 35	0.27 (0.13-0.56)
					≥36	0.42 (0.20-0.88)
					Never	1.00

Study	Study Design	Location	No. Cases	No. Controls	Intervals (Months)		OR (95% CI) of Screening for Cervical Cancer		
La Vecchia[108]	Case-Control	Italy	191	191	<36		0.12 (0.07-0.20)		
					36 to 60		0.33 (0.14-0.80)		
					>60		0.34 (0.16-0.42)		
					never		1.00		
Makino[85]	Case-Control	Japan	198	396	12		0.09 (0.055-0.163)		
					24		0.17 (0.083-0.335)		
					36		0.67 (0.259-1.727)		
					48		0.45 (0.125-1.593)		
					≥60		1.00		
Miller[87]	Case-Control	US	482	934	12		1.00		
					24		1.72 (1.12-2.64)		
					36		2.06 (1.21-3.50)		
					37 to 60		3.16 (1.93-5.18)		
					61 to 120		4.73 (3.03-7.38)		
					>120		8.86 (5.29-14.82)		
Sasieni[88]	Case-Control	UK	348	677	0 to 11		0.18 (0.09-0.35)		
					12 to 23		0.33 (0.18-0.61)		
					24 to 35		0.26 (0.14-0.47)		
					36 to 47		0.32 (0.17-0.56)		
					48 to 65		0.64 (0.36-1.14)		
					>66 or no testing		1.00		
Sasieni[89]	Case-Control	UK	1,305	2,532			**Ages 20-39**	**Ages 40-54**	**Ages 55-69**
					no previous negative		1.00	1.00	1.00
					Model A	0 to 18	0.24 (0.16-0.37)	0.12 (0.08-0.18)	0.13 (0.08-0.22)
						18 to 30	0.33 (0.21-0.51)	0.14 (0.08-0.22)	0.13 (0.07-0.23)
						30 to 42	0.67 (0.43-1.04)	0.25 (0.16-0.40)	0.15 (0.08-0.26)
						42 to 54	1.06 (0.65-1.72)	0.30 (0.18-0.50)	0.18 (0.09-0.34)
						54 to 66	1.40 (0.75-2.62)	0.61 (0.34-1.09)	0.28 (0.14-0.57)
						66 to 78	1.86 (0.88-3.93)	0.72 (0.36-1.43)	0.33 (0.14-0.79)
						>78	2.37 (1.16-4.85)	0.69 (0.36-1.34)	0.55 (0.27-1.10)

Study	Study Design	Location	No. Cases	No. Controls	Intervals (Months)		OR (95% CI) of Screening for Cervical Cancer		
					Model B	0 to 35	0.28 (0.20-0.41)	0.12 (0.08-0.17)	0.13 (0.08-0.19)
						36 to 59	1.03 (0.68-1.56)	0.39 (0.26-0.58)	0.20 (0.12-0.33)
						≥60	2.05 (1.20-3.49)	0.72 (0.43-1.18)	0.45 (0.25-0.81)
Sasieni[91]	Case-Control	UK	3,305	6,516			**Adenocarcinoma**	**Squamous**	**Adenosquamous**
					0 to 42		0.57 (0.42-0.76)	0.25 (0.21-0.29)	0.17 (0.09-0.32)
					42 to 66		0.63 (0.46-0.85)	0.39 (0.33-0.45)	0.24 (0.12-0.48)
					>66		1.00	1.00	1.00
Yang[92]	Case-Control	Australia	877	2,614	no test in 48 months		1.00		
					irregular (1 test)		0.152 (0.119, 0.194)		
					regular (2+ tests)		0.043 (0.033, 0.057)		
Zappa[93]	Case-Control	Italy	208	832	<36		0.25 (0.15, 0.42)		
					36 to 71		0.34 (0.21, 0.56)		
					≥72		0.56 (0.38, 0.82)		
					never		1.00		
Herbert[94]	Cohort	UK	116,022				**Referent**	**Relative Risk (95% CI)**	
					short (6 to 42)		43 to 66	0.4498 (0.2627-0.7704)	
					long (43 to 66)				
					total interval (6 to 66)		no screening during interval	0.3814 (0.2307-0.6305)	
					overdue (>66)		no history	0.3367 (0.1377-0.8230)	
					no history				
Rebolj[95]	Cohort	Netherlands	218,847 women aged 45 to 54 445,382 women aged 30 to 44				**Cumulative Incidence Rate (95% CI)**		
							Ages 30-44	Ages 45-54	P value
					0 to 12		1 (0-3)	2 (1-5)	0.66
					13 to 36		6 (4-0)	11 (7-17)	0.09
					37 to 60		16 (12-21)	14 (10-21)	0.65
					61 to 120		41 (33-51)	36 (24-52)	0.48
					121 to 180		70 (51-95)	73 (39-135)	0.85
					181 to 240		128 (79-207)	105 (50-219)	0.27

Evidence Set 7: KQ1e – What is the effect of varying ages to start and stop screening on incidence of invasive cervical cancer?

Table 24: Summary of Studies Examining the Effect of Varying Ages to Start and Stop Screening on Incidence of Invasive Cervical Cancer

Table 24: Summary of Studies Examining the Effect of Varying Ages to Start and Stop Screening on Incidence of Invasive Cervical Cancer

Study	Study Design	Location	No. Cases	No. Controls	Ages	Results
Andrae[80]	Case-Control	Sweden	1,230	6,124	21 to 29 30 to 65 >65	Age at diagnosis / No. cases / No. control / OR (95% CI) 21-29 years Not screened: 37 / 120 / 1.00 Screened: 26 / 189 / 0.4219 (0.2421-0.7353) 30-65 years Not Screened: 394 / 1,142 / 1.00 Screened: 383 / 2,733 / 0.3984 (0.3401-0.4673) ≥66 years Not Screened: 358 / 1,574 / 1.00 Screened: 32 / 366 / 0.3584 (0.2433-0.5291)
Hoffman[83]	Case-Control	South Africa	524	1,540	<30 30 to 39 40 to 49 50 to 59	For ages 30 years and older there was a significant protective effect of any history of Pap testing: • Ages <30 years adjusted OR 0.7 (95% CI 0.3-2.1) • Ages 30-39 years adjusted OR 0.3 (95% CI 0.2-0.6) • Ages 40-49 years adjusted OR 0.3 (95% CI 0.2-0.4) • Ages 50-59 years adjusted OR 0.3 (95% CI 0.2-0.4)
Sasieni[88]	Case-Control	UK	348	677	20 to 34 35 to 49 50 to 64 65 to 74 ≥75	• 55% of fully invasive cases had at least one smears other than within 6 months of diagnosis vs. 71% Controls (p=0.002); cases more likely to have no screening history than in all but the oldest age group (75+) **Ages / % of Cases Screened / % Controls Screened** 20 to 34: 86 / 91 35 to 49: 71 / 87 50 to 64: 57 / 74 65 to 74: 32 / 40 ≥75: 10 / 9

<table>
<tr><th>Study</th><th>Study Design</th><th>Location</th><th>No. Cases</th><th>No. Controls</th><th>Ages</th><th>Results</th></tr>
<tr><td>Sasieni[89]</td><td>Case-Control</td><td>UK</td><td>1,305</td><td>2,532</td><td>20 to 39
40 to 54
55 to 69</td><td>• Across age groups, participation in screening consistently declined with increasing age in cases (80% of cases aged 20-39; 68% of cases aged 40-54; 48% of cases aged 55-69)
• In the control group, participation rates remained constant for women aged 20-54 years (around 83-84%) and then declined in the 55-69 year old group (70.7%)
• In all three age categories more women with invasive cancer had no history of screening up to six months prior to diagnosis compared with women who did not have cervical cancer</td></tr>
<tr><td>Sasieni[90]</td><td>Case-Control</td><td>UK</td><td>4,012</td><td>7,889</td><td>20 to 29
30 to 39
40 to 49
50 to 59</td><td>ORs for effect of screening at particular ages versus no screening:
For diagnosis between ages 25-29
• Screened at age 20-21 (not 22-24) OR 1.51 (95% CI 0.95-2.38)
• Screened at age 22-24 OR 1.11 (95% CI 0.83-1.50)
For diagnosis between ages 35-39
• Screened at age 30-31 (not 32-34) OR 0.79 (95% CI 0.57-1.1)
• Screened at age 32-34 OR 0.55 (95% CI 0.44-0.69)
For diagnosis between ages 45-49
• Screened at age 40-41 (not 42-44) OR 0.40 (95% CI 0.27-0.58)
• Screened at age 42-44 OR 0.37 (95% CI 0.29-0.48)
For diagnosis between ages 55-59
• Screened at age 50-51 (not 52-54) OR 0.27 (95% CI 0.17-0.43)
• Screened at age 52-54 OR 0.26 (95% CI 0.19-0.36)</td></tr>
<tr><td>Rebolj[95]</td><td>Cohort</td><td>Netherlands</td><td colspan="2">218,847 women aged 45 to 54

445,382 women aged 30-44</td><td>30-44
45-54</td><td>
<table>
<tr><th>Time (years) since third negative smear</th><th>30-44 years Cumulative Incidence Rate (CIR) (95% CI)</th><th>45-54 years CIR (95% CI)</th><th>P value</th></tr>
<tr><td>1</td><td>1 (0-3)</td><td>2 (1-5)</td><td>0.66</td></tr>
<tr><td>>1 to ≤3</td><td>6 (4-10)</td><td>11 (7-17)</td><td>0.09</td></tr>
<tr><td>>3 to ≤5</td><td>16 (12-21)</td><td>14 (10-21)</td><td>0.65</td></tr>
<tr><td>>5 to ≤10</td><td>41 (33-51)</td><td>36 (24-52)</td><td>0.48</td></tr>
<tr><td>>10 to ≤15</td><td>70 (51-95)</td><td>73 (39-135)</td><td>0.85</td></tr>
<tr><td>>15 to ≤20</td><td>128 (79-207)</td><td>105 (50-219)</td><td>0.27</td></tr>
</table>
• Overall hazard ratio was 0.84 (95% CI 0.59-1.21) for the older compared to the younger group</td></tr>
</table>

Evidence Set 8: KQ2 – What are the harms of cervical cancer screening?

Table 25: Summary of Studies Examining False-Positive Rates for Cervical Cancer Screening

Table 25: Summary of Studies Examining False-Positive Rates for Cervical Cancer Screening

Study	Screening Test	False-positive For	Sample*	# False-positives	False-positive Rate %	Formula
Doornewaard[96]	conventional PAPNET	LSIL, HSIL/carcinoma	5,217 women with negative follow-up 7 years later	210 conventional (LSIL 204, HSIL/carcinoma 6) 207 PAPNET (LSIL 195, HSIL/carcinoma 12)	4.0253 conventional 3.9678 PAPNET	FP=FP/(FP+TN)
Slagel[97]	conventional PAPNET	all diagnoses (same rates when only dysplasia and carcinoma considered)	500 smears from consecutive unselected patients	3 conventional 82 PAPNET	0.7092 conventional 19.3853 PAPNET	FP=FP/(FP+TN)
Lorenzin[100]	cytology	LSIL HSIL carcinoma	1,099 cases reported pathology 648 LSIL 374 HSIL 77 carcinoma	110 LSIL 65 HSIL 1 carcinoma	19.6078 LSIL 18.0055 HSIL 1.3158 carcinoma	FP=FP/(FP+TP)
Levine[99]	cytology	squamous-cell carcinoma	128 cases reported malignancy	19	14.8438	FP=FP/(FP+TP)
Mount[98]	conventional liquid-based	squamous-cell carcinoma, adenocarcinoma	68 cases reported malignancy 32 conventional 36 liquid-based	7 overall 4 conventional 3 liquid	10.2941 overall 12.005 conventional 8.3333 liquid	FP=FP/(FP+TP)
Abali[101]	cytology	LSIL HSIL carcinoma	97 women with squamous cell abnormalities (LSIL+) in smear results	16 LSIL 6 HSIL 0 carcinoma	22.6804 LSIL+	FP=FP/(FP+TP)

*includes inadequate or unverified samples not included in false-positive calculations

Evidence Set 9: CQ1 - What are the harms of cervical cancer screening for pre-cancer?

Table 26: Summary of Studies Examining False-Positive Rates and Specificity of Screening Tests for Pre-cancer

First Author, Year	Study Design and Location	Sample	Cytology/HPV Cut Point(s)	Histology Cut Point(s)	Screening Test(s)	Age Groups, Cut Points, and/or Test Types Considered in Analysis	False-positive Rate % (95% CI)	Specificity % (95% CI)
Cuzick[200]	Systematic review and meta-analysis Europe (UK, France, Germany, the Netherlands) and North America (US, Canada)	8 studies >600,000 women mostly aged 30-60 years; age range 15-87	ASC-US, borderline changes, Pap IIw or equivalent	CIN2+	Cytology	All ages	-	96.3 (96.1-96.5)
						<35 years	-	94.9 (NR)
						35-49 years	-	96.8 (NR)
						50+ years	-	97.6 (NR)
					HPV (HC-II, PCR)	All ages	-	90.7 (90.4-91.1)
						<35 years	-	85.8 (NR)
						35-49 years	-	92.8 (NR)
						50+ years	-	94.2 (NR)
Koliopoulos[201]	Systematic review and meta-analysis Europe, Asia, Africa, Central and South America, North America	25 studies (number of studies pooled varied by test; range 2-18) >220,000 women age range 15-94 primary screening populations	ASC-US+ LSIL+ HCII: >1 pg/ml PCR: positive result	CIN2+	Cytology (conventional, liquid-based)	ASC-US+ all ages	-	91.9 (90.2-93.6)
						ASC-US+ >30 years	-	95.8 (94.2-97.3)
						LSIL+ all ages	-	96.0 (94.8-97.2)
						LSIL+ >30 years	-	95.6 (91.7-99.4)
					HPV (HC-II, PCR	HC-II all ages	-	86.5 (83.1-89.8)
						HC-II >30 years	-	86.0 (81.9-90.0)
						PCR all ages	-	94.7 (92.5-96.9)
				CIN3+	Cytology (conventional, liquid-based)	ASC-US all ages	-	89.8 (87.1-92.5)
						LSIL+ all ages	-	92.9 (90.1-95.8)
					HPV (HC-II, PCR	HC-II all ages	-	90.4 (87.1-93.6)
						PCR all ages	-	88.8 (69.7-108.0)
Arbyn[51]	Systematic review and meta-analysis Europe (France, Italy, Spain, UK), North America (US, Canada), Brazil, South-Africa	8 studies >11,000 women	ASC-US+ LSIL+ HSIL+	CIN2+	Cytology (conventional)	ASC-US+ all ages	-	71.3 (58.3-81.6)
						LSIL+ all ages	-	81.2 (71.9-88.0)
						HSIL+ all ages	-	96.7 (95.6-97.5)
					Cytology (liquid-based)	ASC-US+ all ages	-	64.6 (50.1-76.8)
						LSIL+ all ages	-	78.8 (69.8-85.7)
						HSIL+ all ages	-	97.0 (93.8-98.6)

First Author, Year	Study Design and Location	Sample	Cytology/HPV Cut Point(s)	Histology Cut Point(s)	Screening Test(s)	Age Groups, Cut Points, and/or Test Types Considered in Analysis	False-positive Rate % (95% CI)	Specificity % (95% CI)
Dillner[202]	Pooled analysis of data from studies involved in multinational cohort study Europe (Germany, Sweden, Denmark, UK, France, Spain)	7 studies (only 5 studies included in analysis; only 2 studies included for 30-34 and <30) >24,000 women Varied ages; 4 studies restricted to women 30+	ASC-US+	CIN3+	Cytology	All ages	-	95.4 (93.0-97.7)
						>49 years	-	96.4 (96.0-97.0)
						35-49 years	-	95.9 (94.0-97.9)
						<35 years	-	93.7 (89.1-97.4)
						30-34 years	-	92.4 (91.5-93.4)
						<30 years	-	87.5 (86.4-88.4)
					HPV	All ages	-	89.3 (92.9-94.2)
						>49 years	-	91.2 (87.2-95.7)
						35-49 years	-	91.4 (86.1-94.4)
						<35 years	-	84.7 (74.7-92.6)
						30-34 years	-	92.1 (91.4-92.9)
						<30 years	-	87.3 (86.1-88.2)
					Cytology & HPV	All ages	-	87.2 (81.0-92.5)
						>49 years	-	88.7 (85.0-93.4)
						35-49 years	-	89.2 (83.7-93.1)
						<35 years	-	82.9 (72.9-91.4)
						30-34 years	-	81.3 (80.0-83.0)
						<30 years	-	69.4 (66.6-71.4)
Cuzick[203]	Summary and update of meta-analyses and systematic reviews Various locations; no list provided	7 studies No sample details	HPV positive	CIN2+	HPV (PCR)	All ages	-	95.1 (93.4-96.8)
		8 studies No sample details	ASC-US+ HPV: 1pg/ml		Cytology & HPV (HC-II)	All ages	-	88.2 (85.8-90.5)
Nanda[204]	Systematic review; no pooled analysis US, UK, France, Italy, Zimbabwe, Yugoslavia, India	12 studies >24,000 low-risk women Varied ages	LSIL	CIN 2-3	Cytology	All ages	-	Range: 91 to 98

First Author, Year	Study Design and Location	Sample	Cytology/HPV Cut Point(s)	Histology Cut Point(s)	Screening Test(s)	Age Groups, Cut Points, and/or Test Types Considered in Analysis	False-positive Rate % (95% CI)	Specificity % (95% CI)
Lörincz[205]	Review; no pooled analysis Europe, North America, Asia, Africa (11 countries total)	9 studies >77,000 women Varied ages; range across studies 16-80 years	ASC-US+	CIN2-3	Cytology	Conven all ages	-	Range: 88 to 99
						Liquid all ages	-	Range: 78 to 95
					HPV	HC-II all ages	-	Range: 83 to 95
					Cytol & HPV	All ages	-	Range: 86 to 94
				CIN3	Cytology	Conven all ages	-	Range: 94 to 99
						Liquid all ages	-	Range: 82 to 86
					HPV	HC-II all ages	-	Range: 73 to 95
					Cytol & HPV	All ages	-	Range: 68 to 95
Lynge[206]	Review of screening RCTs; no pooled analysis Europe (Sweden, the Netherlands, UK, Italy, Finland)	6 studies (false-positive data only reported for 5) >188,000 women across all studies Age ranges varied; overall range 29-64	ASC-US+ HPV positive	CIN2+	Cytology	All ages	Range: 1.2 to 6.6	-
					HPV	All ages	Range: 4.9 to 11.9	-
Clavel[207]	Cross-sectional France	7,932 women undergoing routine screening Median age 34 years; range 15-76	ASC-US to HSIL HPV: 1pg/ml	CIN2+	Cytology (conventional, liquid-based)	Conven all ages	-	95.3 (94.5-96.2)
						Conven >30 years	-	95.6 (94.6-96.6)
						Liquid all ages	-	93.1 (92.4-93.8)
						Liquid >30 years	-	94.8 (94.1-95.5)
					HPV (in same order, same samples as cytology)	HC-II all ages	-	87.3 (85.9-88.7)
						HC-II >30 years	-	90.1 (88.6-91.6)
						HC-II all ages	-	85.6 (84.7-86.5)
						HC-II >30 years	-	88.4 (87.4-89.4)

First Author, Year	Study Design and Location	Sample	Cytology/HPV Cut Point(s)	Histology Cut Point(s)	Screening Test(s)	Age Groups, Cut Points, and/or Test Types Considered in Analysis	False-positive Rate % (95% CI)	Specificity % (95% CI)
Agorastos[208]	Cross-sectional Northern Greece	1,296 women attending routine, spontaneous screening Mean age 43 years; range 17-67	ASC-US+ HPV positive	CIN1+	Cytology (conventional)	All ages	-	98.9 (98.2-99.4)
						<30 years	-	98.9 (94.3-100)
						>30 years	-	98.9 (98.1-99.4)
					HPV (PCR)	All ages	-	98.1 (97.2-98.8)
						<30 years	-	92.6 (85.4-97.0)
						>30 years	-	98.5 (97.7-99.2)
					Cytology & HPV	All ages	-	97.2 (96.1-98.0)
						<30 years	-	91.5 (84.1-96.3)
						>30years	-	97.6 (96.6-98.4)
				CIN2+	Cytology (con)	All ages	-	98.4 (97.6-99.1)
					HPV (PCR)	All ages	-	97.4 (96.3-98.2)
					Cytology+HPV	All ages	-	96.2 (95.1-97.2)
Beerman[209]	Population-based, parallel cohort The Netherlands	86,469 women attending routine screening (51,154 conventional; 35,315 liquid) Mean age 43.8 years; range 30-60	ASC-US+	CIN1+	Cytology (conventional)	All ages (30-60)	1.83	98.2 (98.1-98.3)
					Cytology (liquid-based)	All ages (30-60)	2.25	97.8 (97.6-97.9)
Bigras[210]	Cross-sectional Switzerland	13,842 women at low risk for cervical cancer Mean age 44.4; range 17-93; 96.4% ≥30 years	ASC-US+ HPV positive	CIN2+	Cytology (liquid-based)	All ages	3.1 (2.8-3.4)*	96.9 (96.6-97.2)
					HPV (HC-II)	All ages	7.6 (7.1-8.1)*	92.4 (91.9-92.9)
Bulk[211]	RCT (POBASCAM trial) The Netherlands	2,193 women who were advised to repeat cytology or have colposcopy Age range 29-60	BMD+ (borderline or mild dyskaryosis or worse) HPV positive	CIN2+	Cytology	All ages (29-60)	-	97.7 (97.4-98.1)
					HPV	All ages (29-60)	-	96.1 (96.0-96.1)
					Cytol & HPV	All ages (29-60)	-	99.3 (99.0-99.5)
				CIN3+	Cytology	All ages (29-60)	-	97.4 (97.2-97.9)
					HPV	All ages (29-60)	-	95.6 (95.5-95.8)
					Cytol & HPV	All ages (29-60)	-	99.0 (98.8-99.3)

First Author, Year	Study Design and Location	Sample	Cytology/HPV Cut Point(s)	Histology Cut Point(s)	Screening Test(s)	Age Groups, Cut Points, and/or Test Types Considered in Analysis	False-positive Rate % (95% CI)	Specificity % (95% CI)
Cárdenas-Turanzas[212]	Cross-sectional United States, Canada	835 women in screening group Ages ≥30 years; Mean age 46.7 years	ASC-US+ HPV positive	CIN2-3	Cytology	All ages ≥30	6*	93 (91-95)
					HPV	All ages ≥30	7*	94 (92-95)
Coste[213] De Cremoux[214] Cochand-Priollet[215]	Cross-sectional France	1,757 women attending routine screening Mean age 33.3 years;	HSIL+ HPV: 1pg/ml	CIN2+	Cytol (conven)	All ages	1.0 (0.6-1.6)*	99 (99-99)
					Cytol (liquid)	All ages	1.6 (1.0-2.3)*	98 (98-99)
					HPV (HC-II)	All ages	-	85 (83-87)
					Cytol & HPV	All ages	-	97 (97-98)
Dalla Palma[216]	Cross-sectional (NTCC study) Italy	Analysis included only women >35 years	ASC-US+ LSIL+ HPV positive	CIN2+	Cytology	ASC-US >35 years	26.7 (12-45)	97.0 (94-99)
						LSIL+ >35 years	8.6 (4-16)	97.2 (95-99)
					Cytology & HPV	ASC-US >35 years	4.8 (0-24)	99.0 (94-100)
						LSIL+ >35 years	12.1 (5-22)	95.7 (92-98)
Insinga[217]	Cohort United States	150,052 women attending routine screening Age range 15-80+	ASC-US+	CIN1-3	Cytology	All ages	2.4	-
						15-19 years	3.1	-
						20-24 years	3.5	-
						25-29 years	2.1	-
						30-39years	2.6	-
						40-49 years	2.4	-
						50-59 years	2.3	-
						60-69 years	1.6	-
						70-79 years	1.8	-
						≥80 years	2.1	-

First Author, Year	Study Design and Location	Sample	Cytology/HPV Cut Point(s)	Histology Cut Point(s)	Screening Test(s)	Age Groups, Cut Points, and/or Test Types Considered in Analysis	False-positive Rate % (95% CI)	Specificity % (95% CI)
Kulasingam[218]	Cross-sectional United States	4,075 women attending clinics for routine exams Mean age 25 years; range 18-50	ASC-US+ HPV positive	CIN2-3	Cytology (liquid-based)	<30 years	17.9*	82.1 (81.3-83.0)
						≥30 years	13.6*	86.4 (84.7-88.3)
					HPV (PCR, HC-II)	<30 years PCR	22.2*	77.8 (76.7-78.9)
						<30 years HC-II	28.9*	71.1 (67.3-74.0)
						≥30 years PCR	12.7*	87.3 (85.5-89.5)
						≥30 years HC-II	17.0*	83.0 (76.6-87.2)
					Cytol & HPV	<30 years PCR	-	89.3 (88.4-90.2)
						<30 years HC-II	-	88.3 (87.4-89.2)
						≥30 years PCR	-	95.7 (94.1-97.0)
						≥30 years HC-II	-	95.0 (93.0-96.4)
				CIN3+	Cytology (liquid-based)	All ages	17.6*	82.4 (81.8-83.1)
						<30 years	18.5*	81.5 (80.7-82.3)
						≥30 years	13.6*	86.4 (84.8-88.1)
					HPV (PCR, HC-II)	All ages PCR	21.2*	78.8 (77.9-79.7)
						All ages HC-II	27.4*	72.6 (69.4-75.0)
						<30 years PCR	23.2*	76.8 (75.7-77.8)
						<30 years HC-II	29.9*	70.1 (66.5-73.1)
						≥30 years PCR	12.6*	87.4 (85.7-89.6)
						≥30 years HC-II	17.0*	83.0 (76.8-87.1)
					Cytol & HPV	All ages PCR	-	89.8 (89.2-90.5)
						All ages HC-II	-	88.9 (88.1-89.6)
						<30 years PCR	-	88.5 (87.7-89.3)
						<30 years HC-II	-	87.6 (86.7-88.4)
						≥30 years PCR	-	95.4 (93.9-96.7)
						≥30 years HC-II	-	94.7 (92.8-96.1)
Mayrand[50,219]	RCT Canada	10,154 women attending routine cervical screening Ages 30-69	ASC-US+ HPV: 1pg/ml	CIN2-3	Cytology (conventional)	All ages (30-69)		96.8 (96.3-97.3)
					HPV (HC-II)	All ages (30-69)		94.1 (93.4-94.8)

First Author, Year	Study Design and Location	Sample	Cytology/HPV Cut Point(s)	Histology Cut Point(s)	Screening Test(s)	Age Groups, Cut Points, and/or Test Types Considered in Analysis	False-positive Rate % (95% CI)	Specificity % (95% CI)
Petry[220]	Cross-sectional Germany	7,908 women attending routine screening Mean age 42.7 years; 94.6% in 30-60 year range	Any degree of abnormality (≥PapIIw, ≈borderline ASC-US) HPV positive	CIN2+	Cytology	All ages (30-60)	2.0 (1.2-3.3)*	98.0 (96.7-98.8)
					HPV (HC-II)	All ages (30-60)	4.7 (3.4-6.5)*	95.3 (93.5-96.6)
					Cytol & HPV	All ages (30-60)	6.2 (4.7-9.2)*	93.8 (91.8-95.3)
				CIN3+	Cytology	All ages (30-60)	2.0 (1.2-3.3)*	98.0 (96.7-98.8)
					HPV (HC-II)	All ages (30-60)	4.8 (3.5-6.6)*	95.2 (93.4-96.5)
					Cytol & HPV	All ages (30-60)	5.1 (3.8-6.9)*	94.9 (93.1-96.2)
Ronco[221]	RCT (NTCC trial) Italy	16,658 women attending routine screening Age range 35-60	ASC-US+ HPV: 1pg/ml	CIN2+	Cytol (liquid)	All ages (35-60)	-	94.8 (94.5-95.2)
					HPV (HC-II)	All ages (35-60)	-	93.2 (92.8-93.6)
				CIN3+	Cytol (liquid)	All ages (35-60)	-	94.7 (94.4-95.0)
					HPV (HC-II)	All ages (35-60)	-	93.0 (92.6-93.4)
Szarewski[222]	Cross-sectional London, UK	953 women Referred for colposcopy after abnormal smear Median age 29.9 (51% <30; 34% 30-39; 15% 40+)	Any degree of abnormality	CIN2+	HPV: HC-II	All ages	-	28.4 (25.0-32.0)
						≥30 years		33.5 (28.4-38.9)
						<30 years	-	23.4 (19.0-28.3)
					HPV: Amplicor	All ages	-	21.7 (18.6-25.0)
						≥30 years		26.9 (22.2-32.0)
						<30 years	-	16.6 (12.8-21.0)
					HPV: CINtec p16 ^{INK4a} Cyt	All ages	-	68.7 (63.7-73.4)
						≥30 years		72.5 (65.3-78.9)
						<30 years	-	65.3 (58.1-72.0)
					HPV: Linear Array	All ages	-	32.8 (29.2-36.5)
						≥30 years		39.1 (33.7-44.6)
						<30 years	-	26.6 (22.0-31.7)
					HPV: Clinical-Arrays	All ages	-	37.1 (33.0-41.4)
						≥30 years		40.2 (34.3-46.4)
						<30 years	-	34.1 (28.4-40.1)

*value not reported in paper; calculation provided in USPSTF 2011 report[62]

Table 27: Specificity of Screening Tests for Pre-cancer - All Ages

Study ID	Cytology Cutoff	Specificity % (95% CI) Cytology	CC	LBC	HPV	HC-II	PCR	Cyt & HPV
Detection of CIN1+								
Agorastos[208]	ASC-US+	-	98.9 (98.2-99.4)	-	-	-	98.1 (97.2-98.8)	97.2 (96.1-98.0)
Detection of CIN2+								
Cuzick[200]	ASC-US+	96.3 (96.1-96.5)	-	-	90.7 (90.4-91.1)	-	-	-
Koliopoulos[201]	ASC-US+	91.9 (90.2-93.6)	-	-	-	86.5 (83.1-89.8)	94.7 (92.5-96.9)	-
	LSIL+	96.0 (94.8-97.2)	-	-				
Arbyn[51]	ASC-US+	-	71.3 (58.3-81.6)	64.6 (50.1-76.8)	-	-	-	-
	LSIL+	-	81.2 (71.9-88.0)	78.8 (69.8-85.7)				
	HSIL+	-	96.7 (95.6-97.5)	97.0 (93.8-98.6)				
Cuzick[203]	ASC-US+	-	-	-	-	-	95.1 (93.4-96.8)	88.2 (85.8-90.5)
Clavel[207]	ASC-US+	-	95.3 (94.5-96.2)	93.1 (92.4-93.8)	-	87.3 (85.9-88.7)	-	-
						85.6 (84.7-86.5)		
Agorastos[208]	ASC-US+	-	98.4 (97.6-99.1)	-	-	-	97.4 (96.3-98.2)	96.2 (95.1-97.2)
Bigras[210]	ASC-US+	-	-	96.9 (96.6-97.2)	-	92.4 (91.9-92.9)	-	-
Coste[213]	HSIL+	-	99 (99-99)	98 (98-99)	-	85 (83-87)	-	97 (97-98)
Detection of CIN2-3								
Nanda[204]	LSIL	91 to 98 (R)	-	-	-	-	-	-
Lörincz[205]	ASC-US+	-	88 to 89 (R)	78 to 95 (R)	-	83 to 95 (R)	-	86 to 94 (R)
Detection of CIN3+								
Koliopoulos[201]	ASC-US+	89.8 (87.1-92.5)	-	-	-	90.4 (87.1-93.6)	88.8 (69.7-108.0)	-
	LSIL+	92.9 (90.1-95.8)	-	-				
Dillner[202]	ASC-US+	95.4 (93.0-97.7)	-	-	89.3 (92.9-94.2)	-	-	87.2 (81.0-92.5)
Lörincz[205]	ASC-US+	-	94 to 99 (R)	82 to 86 (R)	-	73 to 95 (R)	-	68 to 95 (R)
Kulasingam[218]	ASC-US+	-	-	82.4 (81.8-83.1)	-	72.6 (69.4-75.0)	78.8 (77.9-79.7)	88.9 (88.1-89.6)
								89.8 (89.2-90.5)

(R): range for un-pooled studies

Table 28: Specificity of Screening Tests for Pre-cancer - Ages 30 and Above

Study ID	Cytology Cutoff	Specificity % (95% CI)						
		Cytology	CC	LBC	HPV	HC-II	PCR	Cyt & HPV
Detection of CIN1+								
Agorastos[208]	ASC-US+	-	98.9 (98.1-99.4)	-	-	-	98.5 (97.7-99.2)	97.6 (96.6-98.4)
Beerman[209]	ASC-US+	-	98.2 (98.1-98.3)	97.8 (97.6-97.9)	-	-	-	-
Detection of CIN2+								
Koliopoulos[201]	ASC-US+	95.8 (94.2-97.3)	-	-	-	86.0 (81.9-90.0)	-	-
	LSIL+	95.6 (91.7-99.4)	-	-				
Clavel[207]	ASC-US+	-	95.6 (94.6-96.6)	94.8 (94.1-95.5)	-	90.1 (88.6-91.6)	-	-
						88.4 (87.4-89.4)		
Bulk[211]***	BMD+	97.7 (97.4-98.1)	-	-	96.1 (96.0-96.1)	-	-	99.3 (99.0-99.5)
Dalla Palma[216]**	ASC-US+	97.0 (94-99)	-	-	-	-	-	99.0 (94-100)
	LSIL+	97.2 (95-99)	-	-	-	-	-	95.7 (92-98)
Petry[220]	ASC-US+	98.0 (96.7-98.8)	-	-	-	95.3 (93.5-96.6)	-	93.8 (91.8-95.3)
Ronco[221]	ASC-US+	-	-	94.8 (94.5-95.2)	-	93.2 (92.8-93.6)	-	-
Detection of CIN2-3								
Cárdenas-Turanzas[212]	ASC-US+	93 (91-95)	-	-	94 (92-95)	-	-	-
Kulasingam[218]	ASC-US+	-	-	86.4 (84.7-88.3)	-	83.0 (76.6-87.2)	87.3 (85.5-89.5)	95.0 (93.0-96.4)
								95.7 (94.1-97.0)
Mayrand[50]	ASC-US+	-	96.8 (96.3-97.3)	-	-	94.1 (93.4-94.8)	-	-
Detection of CIN3+								
Bulk [211]***	BMD+	97.4 (97.2-97.9)	-	-	95.6 (95.5-95.8)	-	-	99.0 (98.8-99.3)
Kulasingam[218]	ASC-US+	-	-	86.4 (84.8-88.1)	-	83.0 (76.8-87.1)	87.4 (85.7-89.6)	94.7 (92.8-96.1)
								95.4 (93.9-96.7)
Petry[220]	ASC-US+	98.0 (96.7-98.8)	-	-	-	95.2 (93.4-96.5)	-	94.9 (93.1-96.2)
Ronco[221]	ASC-US+	-	-	94.7 (94.4-95.0)	-	93.0 (92.6-93.4)	-	-

** Ages 35 and above
***Ages 29 and above

Table 29: Specificity of Screening Tests for Pre-cancer - Ages 30 and Below

Study ID	Cytology Cutoff	Specificity % (95% CI) Cytology	CC	LBC	HPV	HC-II	PCR	Cyt & HPV
Detection of CIN1+								
Agorastos[208]	ASC-US+	98.9 (94.3-100)	-	-	-	92.6 (85.4-97.0)	91.5 (84.1-96.3)	98.9 (94.3-100)
Detection of CIN2+								
Cuzick[200]**	ASC-US+	94.9	-	-	85.8	-	-	-
Detection of CIN2-3								
Kulasingam[218]	ASC-US+	-	-	82.1 (81.3-83.0)	-	71.1 (67.3-74.0)	77.8 (76.7-78.9)	88.3 (87.4-89.2) 89.3 (88.4-90.2)
Detection of CIN3+								
Dillner[202]	ASC-US+	87.5 (86.4-88.4)	-	-	87.3 (86.1-88.2)	-	-	69.4 (66.6-71.4)
Kulasingam[218]	ASC-US+	-	-	81.5 (80.7-82.3)	-	70.1 (66.5-73.1)	76.8 (75.7-77.8)	87.6 (86.7-88.4) 88.5 (87.7-89.3)

**Ages 35 and below

Table 30: False-Positive Rates of Screening Tests for Pre-cancer - All Ages

Study ID	Cytology Cutoff	Ages (years)	False-Positive Rate % (95% CI)						
			Cytology	CC	LBC	HPV	HC-II	PCR	Cyt & HPV
	Detection of CIN1+								
Beerman[209]	ASC-US+	30-60	-	1.83	2.25	-	-		-
Insinga[217]	ASC-US+	All ages	2.4	-	-	-	-	-	-
		15-19	3.1						
		20-24	3.5						
		25-29	2.1						
		30-39	2.6						
		40-49	2.4						
		50-59	2.3						
		60-69	1.6						
		70-79	1.8						
		≥80	2.1						
	Detection of CIN2+								
Lynge[206]	ASC-US+	All ages	1.2 to 6.6 (R)	-	-	4.9 to 11.9 (R)	-	-	-
Bigras[210]	ASC-US+	All ages	-	-	3.1 (2.8-3.4)^	-	7.6 (7.1-8.1)^	-	-
Coste[213]	HSIL+	All ages	-	1.0 (0.6-1.6)^	1.6 (1.0-2.3)^	-	-	-	-
Dalla Palma[216]	ASC-US	>35	26.7 (12-45)	-	-	-	-	-	4.8 (0-24)
	LSIL+	>35	8.6 (4-16)					-	12.1 (5-22)
Petry[220]	ASC-US+	30-60	2.0 (1.2-3.3)^	-	-	-	4.7 (3.4-6.5)^	-	6.2 (4.7-9.2)^
	Detection of CIN2-3								
Cárdenas-Turanzas[212]	ASC-US+	≥30	6^	-	-	7^	-	-	-
Kulasingam[218]	ASC-US+	<30	-	-	17.9^	-	28.9^	22.2^	-
		≥30	-	-	13.6^	-	17.0^	12.7^	-
	Detection of CIN3+								
Kulasingam[218]	ASC-US+	All ages	-	-	17.6^	-	27.4^	21.2^	-
		<30	-	-	18.5^	-	29.9^	23.2^	-
		≥30	-	-	13.6^	-	17.0^	12.6^	-
Petry[220]	ASC-US+	30-60	2.0 (1.2-3.3)^	-	-	-	4.8 (3.5-6.6)^	-	5.1 (3.8-6.9)^

(R): range for un-pooled studies

^ value not reported in paper; calculation provided in USPSTF 2011 report[62]

Appendix 1: Search Strategies for Cervical Cancer Screening

Medline-OVID (Q1)

April 18, 2012

1. exp randomized controlled trials as topic/
2. randomized controlled trial.pt.
3. controlled clinical trial.pt.
4. (random* or sham or placebo*).tw.
5. placebos/
6. random allocation/
7. single blind method/
8. double blind method/
9. ((singl* or doubl* or trebl* or tripl*) adj25 (blind* or dumm* or mask*)).ti,ab.
10. (rct or rcts).tw.
11. (control* adj2 (study or studies or trial*)).tw.
12. or/1-11
13. Epidemiologic studies/
14. exp case-control studies/
15. exp cohort studies/
16. Case-control.tw.
17. (cohort adj (study or studies)).tw.
18. Cohort analy$.tw.
19. (Follow up adj (study or studies)).tw.
20. (observational adj (study or studies)).tw.
21. Longitudinal.tw.
22. Retrospective.tw.
23. Cross sectional.tw.
24. Cross-sectional studies/
25. or/13-24
26. (animals not humans).sh.
27. 25 not 26
28. Cervix Uteri/
29. Uterine Cervical Neoplasms/
30. ((cervix or cervical) adj2 (cancer$ or neoplasm$ or carcinom$ or tumo?r$)).ti,ab.
31. Cervical Intraepithelial Neoplasia/
32. Uterine Cervical Dysplasia/
33. Papillomavirus Infections/ or Papillomaviridae/
34. or/28-33
35. cervix uteri/cy
36. (hpv adj3 (screen* or test*)).tw.
37. ((Pap or Papanicolaou) adj (smear or test* or screening*)).tw.
38. 35 or 36 or 37
39. 37 not 34
40. mass screening/ or screen*.ti.
41. "Cytodiagnosis"/
42. "Early Detection of Cancer"/
43. vaginal smears/
44. (early adj (detection or diagnosis)).ti,ab.
45. DNA Probes, HPV/du, ge [Diagnostic Use, Genetics]
46. cytology.ti,ab.

47. or/40-46
48. 34 and 47
49. 38 or 48
50. limit 49 to yr="1995 -Current"
51. animals/ not (animals/ and humans/)
52. 50 not 51
53. limit 52 to (english or french)
54. 12 and 53
55. 27 and 53
56. 55 not 54

EMBASE-OVID (Q1)

April 25, 2012
1. uterine cervix/
2. uterine cervix cancer/
3. ((cervix or cervical) adj2 (cancer* or neoplasm* or carcinom* or tumo?r*)).ti,ab.
4. uterine cervix carcinoma in situ/
5. uterine cervix dysplasia/
6. papillomavirus infection/
7. wart virus/
8. or/1-7
9. early diagnosis/
10. vagina smear/
11. (early adj (detection or diagnosis)).ti,ab.
12. mass screening/
13. screen*.ti,ab.
14. DNA probe/
15. cytodiagnosis/
16. exp female genital tract cytology/
17. or/9-16
18. 8 and 17
19. (hpv adj3 (screen* or test*)).tw.
20. ((pap or papanicolaou) adj (smear or test* or screening*)).tw.
21. or/18-20
22. (performance measures or performance indicators).tw.
23. 18 and 21 and 22
24. 21 or 23
25. limit 24 to yr="1995 -Current"
26. limit 25 to (english or french)
27. randomized controlled trial/
28. controlled clinical trial/
29. (random* or sham or placebo*).tw.
30. placebo/
31. randomization/
32. single blind procedure/
33. double blind procedure/
34. ((singl* or doubl* or trebl* or tripl*) adj5 (blind* or dumm*or mask*)).ti,ab.
35. (rct or rcts).tw.
36. (control* adj2 (study or studies or trial*)).tw.
37. or/27-36

38. human/
39. nonhuman/
40. animal/
41. animal experiment/
42. or/39-41
43. 42 not (42 and 38)
44. 37 not 43
45. 26 and 44
46. 26 not 45
47. limit 46 to (conference abstract or conference paper or editorial or letter or note)
48. 46 not 47

Cochrane Central-OVID (Q1)

April 25, 2012
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 cervix uteri/cy
9 (hpv adj3 (screen* or test*)).tw.
10 ((Pap or Papanicolaou) adj (smear or test* or screening*)).tw.
11 8 or 9 or 10
12 10 not 7
13 mass screening/ or screen*.ti.
14 "Cytodiagnosis"/
15 "Early Detection of Cancer"/
16 vaginal smears/
17 (early adj (detection or diagnosis)).ti,ab.
18 DNA Probes, HPV/du, ge [Diagnostic Use, Genetics]
19 cytology.ti,ab.
20 or/13-19
21 7 and 20
22 11 or 21
23 limit 22 to yr="1995 -Current"

Medline-OVID (Q2)

April 25, 2012
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="1995 -Current"

EMBASE-OVID (Q2)

April 25, 2012
1. exp diagnostic error/
2. (adverse adj2 (effect? or event?)).tw.
3. (overtest$ or overdiagnos$ or over-test$ or over-diagnos$).mp.
4. misdiagnos$.mp.
5. (false$ adj (positiv$ or negativ$)).mp.
6. ((incorrect$ or false$ or wrong$ or bias$ or mistake$ or error$ or erroneous$) adj3 (result$ or finding$ or test$ or diagnos$)).mp.
7. ((inappropriat$ or unnecess$ or unneed$) adj3 (treat$ or Surg$ or therap$ or regimen$)).mp.
8. exp spontaneous abortion/
9. exp premature labor/
10. anxiety/

11. psychosexual disorder/ or sexual dysfunction/
12. depression/
13. or/1-12
14. LEEP.tw.
15. 13 and 14
16. COLPOSCOPY/ae [Adverse Drug Reaction]
17. vagina smear/ae [Adverse Drug Reaction]
18. mass screening/ae [Adverse Drug Reaction]
19. low level laser therapy/ae [Adverse Drug Reaction]
20. ELECTROSURGERY/ae [Adverse Drug Reaction]
21. CRYOSURGERY/ae [Adverse Drug Reaction]
22. or/15-21
23. uterine cervix/
24. uterine cervix cancer/
25. ((cervix or cervical) adj2 (cancer* or neoplasm* or carcinom* or tumo?r*)).ti,ab.
26. uterine cervix carcinoma in situ/
27. uterine cervix dysplasia/
28. papillomavirus infection/
29. wart virus/
30. or/23-29
31. early diagnosis/
32. vagina smear/
33. (early adj (detection or diagnosis)).ti,ab.
34. mass screening/
35. screen*.ti,ab.
36. DNA probe/
37. cytodiagnosis/
38. exp female genital tract cytology/
39. or/31-38
40. 30 and 39
41. (hpv adj3 (screen* or test*)).tw.
42. ((pap or papanicolaou) adj (smear or test* or screening*)).tw.
43. or/40-42
44. 13 and 43
45. 22 and 30
46. 44 or 45
47. limit 46 to yr="1995 -Current"
48. limit 47 to english
49. limit 47 to french
50. 48 or 49

Cochrane Central-OVID (Q2)

April 25, 2012
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 yr="1995 -Current"

Medline-OVID (CQs)
February 3, 2011
1. meta analysis/
2. systematic review/
3. (meta analy* or metaanaly* or met analy* or metanaly*).tw.
4. (collaborative research or collaborative review* or collaborative overview*).tw.
5. (integrative research or integrative review* or intergrative overview*).tw.
6. (quantitative adj3 (research or review* or overview*)).tw.
7. (research integration or research overview*).tw.
8. (systematic* adj3 (review* or overview*)).tw.

9. (methodologic* adj3 (review* or overview*)).tw.
10. biomedical technology assessment/
11. (hta or thas or technology assessment*).tw.
12. ((hand adj2 search*) or (manual* adj search*)).tw.
13. ((electronic adj database*) or (bibliographic* adj database*)).tw.
14. ((data adj2 abstract*) or (data adj2 extract*)).tw.
15. (data adj3 (pooled or pool or pooling)).tw.
16. (analys* adj3 (pool or pooled or pooling)).tw.
17. mantel haenszel.tw.
18. (cochrane or Pubmed or pub med or medline or embase or psycinfo or psyclit or psychinfo or psychlit or cinahl or science citation index).ab.
19. or/1-18
20. Cervix Uteri/
21. Uterine Cervical Neoplasms/
22. ((cervix or cervical) adj2 (cancer$ or neoplasm$ or carcinom$ or tumo?r$)).ti,ab.
23. Cervical Intraepithelial Neoplasia/
24. Uterine Cervical Dysplasia/
25. Papillomavirus Infections/ or Papillomaviridae/
26. or/20-25
27. "Early Detection of Cancer"/
28. ((Pap or Papanicolaou) adj (smear or test* or screening*)).tw.
29. vaginal smears/
30. (early adj (detection or diagnosis)).ti,ab.
31. mass screening/ or screen*.ti,ab.
32. DNA Probes, HPV/du, ge [Diagnostic Use, Genetics]
33. or/27-32
34. 26 and 33
35. (hpv adj3 (screen* or test*)).tw.
36. 34 or 35
37. Radiotherapy/ae, co, ct, mo [Adverse Effects, Complications, Contraindications, Mortality]
38. Hysterectomy/ae, ct, co, mo [Adverse Effects, Contraindications, Mortality]
39. Colposcopy/ae, ct [Adverse Effects, Contraindications]
40. Conization/ae, ct [Adverse Effects, Contraindications]
41. Electrosurgery/ae, ct, mo [Adverse Effects, Contraindications, Mortality]
42. (Loop electrosurg* or LEEP).ti.
43. infection/ or pelvic infection/ or surgical wound infection/
44. exp Urinary Incontinence/
45. (adverse adj2 (effect? or event?)).tw.
46. ((inappropriat$ or unnecess$ or unneed$) adj3 (treat$ or Surg$ or therap$ or regimen$)).mp.
47. exp Abortion, Spontaneous/
48. exp Obstetric Labor, Premature/
49. anxiety/
50. depression/
51. Sexual Dysfunctions, Psychological/ or Sexual Dysfunction, Physiological/
52. or/37-51
53. 26 and 52

54. limit 53 to yr="2005 -Current"
55. limit 54 to (english or french)
56. 19 and 55
57. 55 not 56
58. exp Ethnic Groups/
59. first nations.tw.
60. (aboriginal? and canada).tw.
61. native canadians.tw.
62. (immigran* or new canadians).tw.
63. ((African or Asian or Indo or Columbian or Spanish or Chinese) adj2 Canadian?).mp.
64. Pregnant Women/
65. Homosexuality, Female/
66. lesbian?.tw.
67. Immunocompromised Host/
68. (immunocompromised adj3 women).tw.
69. (HIV adj3 women).tw.
70. Hysterectomy/
71. Papillomavirus Vaccines/
72. hpv vacc*.tw.
73. multiple partners.tw.
74. Rural Population/
75. (rural adj (population? or area? or region?)).tw.
76. or/58-75
77. 36 and 76
78. limit 77 to yr="2005 -Current"
79. limit 78 to (english or french)
80. 19 and 79
81. 79 not 80
82. exp "Costs and Cost Analysis"/
83. cost.tw.
84. or/82-83
85. 36 and 84
86. limit 85 to yr="2005 -Current"
87. limit 86 to (english or french)
88. 19 and 87
89. 87 not 88
90. *"patient acceptance of health care"/ or *patient compliance/ or *patient participation/ or patient satisfaction/ or patient preference/ or *treatment refusal/
91. (women? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
92. (consumer? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
93. (patient? adj3 (acceptance or perference? or satisfaction or experience?)).tw.
94. willingness to pay.tw.
95. ((conjoint or contingent) adj3 (valuation or analysis)).tw.
96. or/90-95
97. 36 and 96
98. limit 97 to yr="2005 -Current"

99. limit 98 to (english or french)
100. 99 and 19
101. 99 not 100
102. ((process or performance or outcome) adj2 (measure? or indicator?)).tw.
103. 102 and 36
104. limit 103 to yr="2005 -Current"
105. limit 104 to (english or french)
106. Self-Examination/
107. self sampling.tw.
108. self collection.tw.
109. or/106-108
110. 36 and 109
111. limit 110 to yr="2005 -Current"
112. limit 111 to (english or french)
113. vaginal smears/
114. ((Pap or Papanicolaou) adj (smear or test* or screening*)).tw.
115. 113 or 114
116. exp Health Personnel/
117. 115 and 116
118. limit 117 to yr="2005 -Current"
119. limit 118 to (english or french)
120. exp Canada/
121. 36 and 120
122. limit 121 to yr="2005 -Current"
123. limit 122 to (english or french)
124. 56 or 80 or 88 or 100 or 105 or 112 or 119 or 123
125. 57 or 81 or 89 or 101
126. 125 not 124

EMBASE-OVID (CQs)
February 7, 2011
1. meta analysis/
2. systematic review/
3. (meta analy* or metaanaly* or met analy* or metanaly*).tw.
4. (collaborative research or collaborative review* or collaborative overview*).tw.
5. (integrative research or integrative review* or intergrative overview*).tw.
6. (quantitative adj3 (research or review* or overview*)).tw.
7. (research integration or research overview*).tw.
8. (systematic* adj3 (review* or overview*)).tw.
9. (methodologic* adj3 (review* or overview*)).tw.
10. biomedical technology assessment/
11. (hta or thas or technology assessment*).tw.
12. ((hand adj2 search*) or (manual* adj search*)).tw.
13. ((electronic adj database*) or (bibliographic* adj database*)).tw.
14. ((data adj2 abstract*) or (data adj2 extract*)).tw.
15. (data adj3 (pooled or pool or pooling)).tw.

16. (analys* adj3 (pool or pooled or pooling)).tw.
17. mantel haenszel.tw.
18. (cochrane or Pubmed or pub med or medline or embase or psycinfo or psyclit or psychinfo or psychlit or cinahl or science citation index).ab.
19. or/1-18
20. uterine cervix/
21. uterine cervix cancer/
22. ((cervix or cervical) adj2 (cancer* or neoplasm* or carcinom* or tumo?r*)).ti,ab.
23. uterine cervix carcinoma in situ/
24. uterine cervix dysplasia/
25. papillomavirus infection/
26. wart virus/
27. or/20-26
28. early diagnosis/
29. vagina smear/
30. (early adj (detection or diagnosis)).ti,ab.
31. mass screening/
32. screen*.ti,ab.
33. DNA probe/
34. cytodiagnosis/
35. exp female genital tract cytology/
36. or/28-35
37. 27 and 36
38. (hpv adj3 (screen* or test*)).tw.
39. ((pap or papanicolaou) adj (smear or test* or screening*)).tw.
40. or/37-39
41. radiotherapy/ae [Adverse Drug Reaction]
42. exp hysterectomy/ae [Adverse Drug Reaction]
43. colposcopy/ae [Adverse Drug Reaction]
44. uterine cervix conization/ae [Adverse Drug Reaction]
45. electrosurgery/ae [Adverse Drug Reaction]
46. FEMALE GENITAL TRACT INFECTION/ or GYNECOLOGIC INFECTION/ or POSTOPERATIVE INFECTION/ or INFECTION/
47. (adverse adj2 (effect? or event?)).tw.
48. ((inappropriat* or unnecess* or unneed*) adj3 (treat* or Surg* or therap* or regimen*)).mp.
49. spontaneous abortion/
50. exp "immature and premature labor"/
51. anxiety/
52. exp depression/
53. exp female sexual dysfunction/
54. or/41-53
55. 27 and 54
56. limit 55 to yr="2005 -Current"
57. limit 56 to (english or french)
58. 19 and 57
59. 57 not 58

60. exp "ethnic and racial groups"/
61. first nations.tw.
62. (aboriginal? and canada).tw.
63. native canadians.tw.
64. (immigran* or new canadians).tw.
65. ((African or Asian or Indo or Columbian or Spanish or Chinese) adj2 Canadian).mp.
66. pregnant woman/
67. lesbian/
68. lesbian?.tw.
69. immunocompromised patient/
70. (immunocompromised adj3 women).tw.
71. (HIV adj3 women).tw.
72. human immunodeficiency virus infected patient/
73. exp hysterectomy/
74. hpv vacc*.tw.
75. Wart virus vaccine/
76. multiple partners.tw.
77. rural health care/
78. rural population/
79. (rural adj (population? or area? or region?)).tw.
80. or/60-79
81. 40 and 80
82. limit 81 to yr="2005 -Current"
83. limit 82 to (english or french)
84. 19 and 83
85. 83 not 84
86. exp economic evaluation/
87. cost.tw.
88. or/86-87
89. 40 and 88
90. 19 and 89
91. exp patient attitude/
92. (women? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
93. (consumer? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
94. (patient? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
95. willingness to pay.tw.
96. ((conjoint or contingent) adj3 (valuation or analysis)).tw.
97. or/91-96
98. 40 and 97
99. limit 98 to yr="2005 -Current"
100. limit 99 to (english or french)
101. 19 and 100
102. ((process or performance or outcome) adj2 (measure? or indicator?)).tw.
103. performance measurement system/
104. or/102-103
105. 40 and 104

106. limit 105 to yr="2005 -Current"
107. limit 106 to (english or french)
108. self examination/
109. self sampling.tw.
110. self collection.tw.
111. or/108-110
112. 40 and 111
113. limit 112 to (english or french)
114. papanicolaou test/ or vagina smear/
115. ((Pap or Papanicolaou) adj (smear or test* or screening*)).tw.
116. 114 or 115
117. exp health care personnel/
118. 116 and 117
119. 40 and 118
120. limit 119 to yr="2005 -Current"
121. limit 120 to (english or french)
122. 58 or 84 or 90 or 101 or 105 or 113 or 121
123. 59 or 85 or 100 or 107 or 113
124. exp Canada/
125. 40 and 124
126. limit 125 to yr="2005 -Current"
127. limit 126 to (english or french)
128. 127 not 122

Cochrane Central-OVID (CQs)
February 7, 2011
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. Radiotherapy/ae, co, ct, mo [Adverse Effects, Complications, Contraindications, Mortality]
19. Hysterectomy/ae, ct, co, mo [Adverse Effects, Contraindications, Mortality]
20. Colposcopy/ae, ct [Adverse Effects, Contraindications]

21. Conization/ae, ct [Adverse Effects, Contraindications]
22. Electrosurgery/ae, ct, mo [Adverse Effects, Contraindications, Mortality]
23. (Loop electrosurg* or LEEP).ti.
24. infection/ or pelvic infection/ or surgical wound infection/
25. exp Urinary Incontinence/
26. (adverse adj2 (effect? or event?)).tw.
27. ((inappropriat$ or unnecess$ or unneed$) adj3 (treat$ or Surg$ or therap$ or regimen$)).mp.
28. exp Abortion, Spontaneous/
29. exp Obstetric Labor, Premature/
30. anxiety/
31. depression/
32. Sexual Dysfunctions, Psychological/ or Sexual Dysfunction, Physiological/
33. or/18-32
34. 7 and 33
35. limit 34 to yr="2005 -Current"
36. exp Ethnic Groups/
37. first nations.tw.
38. (aboriginal? and canada).tw.
39. native canadians.tw.
40. (immigran* or new canadians).tw.
41. ((African or Asian or Indo or Columbian or Spanish or Chinese) adj2 Canadian?).mp.
42. Pregnant Women/
43. Homosexuality, Female/
44. lesbian?.tw.
45. Immunocompromised Host/
46. (immunocompromised adj3 women).tw.
47. (HIV adj3 women).tw.
48. Hysterectomy/
49. Papillomavirus Vaccines/
50. hpv vacc*.tw.
51. multiple partners.tw.
52. Rural Population/
53. (rural adj (population? or area? or region?)).tw.
54. or/36-53
55. 17 and 54
56. exp "Costs and Cost Analysis"/
57. cost.tw.
58. or/56-57
59. 17 and 58
60. *"patient acceptance of health care"/ or *patient compliance/ or *patient participation/ or patient satisfaction/ or patient preference/ or *treatment refusal/
61. (women? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
62. (consumer? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
63. (patient? adj3 (acceptance or perference? or satisfaction or experience?)).tw.
64. willingness to pay.tw.
65. ((conjoint or contingent) adj3 (valuation or analysis)).tw.

66. or/60-65
67. 17 and 66
68. ((process or performance or outcome) adj2 (measure? or indicator?)).tw.
69. 68 and 17
70. Self-Examination/
71. self sampling.tw.
72. self collection.tw.
73. or/70-72
74. 17 and 73
75. vaginal smears/
76. ((Pap or Papanicolaou) adj (smear or test* or screening*)).tw.
77. 75 or 76
78. exp Health Personnel/
79. 77 and 78
80. exp Canada/
81. 17 and 80
82. 34 or 55 or 59 or 67 or 69 or 74 or 79 or 81
83. limit 82 to yr="2005 –Current"

Appendix 2: Grey Literature Search Strategy

Google search limited to Canada. Search run on February 23, 2011.

- "cervical cancer screening AND harms"
- "cervical cancer screening AND Canada"
- "cervical cancer screening AND costs"
- HPV vaccination
- Pap smear OR Pap test

Specific Sites Search: search terms included "cervical cancer screening" OR "cervical cancer AND screening" OR "cervical cancer" OR "HPV vaccination" OR "pap smear" OR "pap test"

Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS), Québec
http://www.aetmis.gouv.qc.ca/

Canadian Agency for Drugs and Technologies in Health (CADTH)
http://www.cadth.ca
http://www.cadth.ca/index.php/en/hta/reports-publications.

Centre for Evaluation of Medicines (Father Sean O'Sullivan Research Centre; St. Joseph's Health care Hamilton; and McMaster University, Faculty of Health Sciences, Hamilton, Ontario)
http://www.thecem.net/

Centre for Health Services and Policy Research, University of British Columbia
http://www.chspr.ubc.ca/cgi-bin/pub

Health Quality Council, Saskatchewan
http://www.hqc.sk.ca/

Institute for Clinical Evaluative Sciences (ICES), Ontario
http://www.ices.on.ca/

IHE Institute of Health Economics, HTA Unit, Alberta
http://www.ihe.ca/publications/library/

Manitoba Centre for Health Policy (MCHP)
http://umanitoba.ca/medicine/units/mchp/

Ontario Health Technology Advisory Committee (OHTAC): Analyses and Recommendations
http://www.health.gov.on.ca/english/providers/program/ohtac/tech/recommend/rec_mn.html

Technology Assessment Unit of the McGill University Health Centre
http://www.mcgill.ca/tau/publications/

Centre for Health Economics and Policy Analysis (CHEPA), McMaster University

http://www.chepa.org/

Institute of Health Economics (IHE)
http://www.ihe.ca

Canadian Institute for Health Information (CIHI)
http://www.cihi.ca/CIHI-ext-portal/internet/EN/Home/home/cihi000001

Health Canada
http://www.hc-sc.gc.ca/english/

Public Health Agency of Canada
http://www.phac-aspc.gc.ca/index-eng.php

Statistics Canada
http://www.statcan.gc.ca/start-debut-eng.html

Partnership Against Cancer
http://www.partnershipagainstcancer.ca

NHS Cancer Screening Programs
http://www.cancerscreening.nhs.uk/cervical/publications

European Community Health Indicators Monitoring
http://www.healthindicators.eu

Cancer Care Ontario
http://www.cancercare.on.ca

Association on Public Health Epidemiologists in Ontario
http://www.apheo.ca

OECD iLibrary
http://www.oecd-ilibrary.org

Journal of Aboriginal and Indigenous Community Health
http://www.pimatisiwin.com/online/

hpvinfo.ca
http://www.hpvinfo.ca/hpvinfo/professionals/guidelines.aspx

Appendix 3: List of External Reviewers – Protocol

Jim Bentley	Dalhousie University
Karen Canfell	Cancer Council New South Wales, Australia
Chris Del Mar	Bond University, Australia
Laura MacDougall	Alberta Health Services
Gina Ogilvie	BC Centre for Disease Control
Jay Onysko	Public Health Agency of Canada
Julietta Patnick	National Health Services Cancer Screening Programs, UK

We wish to acknowledge and thank these individuals for their input into the review protocol.

Appendix 4: List of External Reviewers – Evidence Synthesis

Jim Bentley	Dalhousie University
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Heather Bryant	Canadian Partnerships Against Cancer
Margaret Czesak	Health Canada
Chris Del Mar	Bond University, Australia
Barbara Foster	Health Canada
Patricia Goggin	Institut national de santé publique du Québec
Brian Hauck	Society of Canadian Colposcopists
Jon Kerner	Canadian Partnerships Against Cancer
Marie-Hélène Mayrand	Society of Canadian Colposcopists
Robert Nuttall	Canadian Cancer Society
Gina Ogilvie	BC Centre for Disease Control
Julietta Patnick	National Health Services Cancer Screening Programs, UK
Louise Pelletier	Public Health Agency of Canada
Gilles Plourde	Health Canada
Erica Weir	College of Family Physicians

We wish to acknowledge and thank these individuals for their input into this evidence review.

Appendix 5: Performance Indicators for Measuring the Impact of Cervical Cancer Screening

1. Program extension – number of women in target population of catchment area actively served by program divided by total women in region or country[177]
2. Coverage of the target population by invitation[177]
3. Percentage of the eligible women in the target population who receive at least one cervical cancer screen in the indexed time period – this can be divided based on screening type, invitation status and program design (organized versus opportunistic)[177,178]
4. Compliance to invitation[177]
5. Percentage of eligible women who are re-screened within 36-months of a negative index test[178]
6. Compliance with referral for repeat cytology (screening test)[177]
7. Referral rate for colposcopy[177]
8. Positive Predictive Value of referral for colposcopy[177]
9. Detection rate for histological diagnosis[177,178]
10. Cancer incidence after normal screening result[177]
11. Compliance with referral to colposcopy[177]
12. Number of pre-cancerous lesions detected per 1,000 women who had a cervical cancer screening test in a 12 month period[177,178]
13. Proportion treated for pre-cancerous lesions[177]
14. The average time from the date the specimen is taken to the date the finalized report is issued over a 12 month period[178]
15. Cancer incidence[178]
16. Disease extent at diagnosis: cancer stage[178]
17. Screening history in cases of invasive cancer[178]

Appendix 6: Acknowledgements

We would like to thank the following staff members and consultants for their work and/or advice on this review:

Pat Carson	Research Assistant
Mahbubul Haq	Research Assistant
Sohel Nazmul	Statistical Consultant
Mark Oremus	Statistical Consultant
Sharon Peck-Reid	Research Assistant
Maureen Rice	Librarian
Nancy Santesso	GRADE Consultant
Harry Shannon	Statistical Consultant

We gratefully acknowledge the support of Canadian Institute for Health Research for funds to support the McMaster Evidence Review and Synthesis Centre for this systematic review.

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