Screening Program for Cervical Cancer | Sask cancer AGENCY

Cervical Cancer Screening Clinical Practice Guideline 2023

Joanne Sivertson MD FRCSC [1], Brent Jim MD FRCSC [1, 2, 3], Carla Holinaty MD CCFP [4], Mary Kinloch BSc MD CCFP [5, 6], Jessica Minion MD MSc FRCPC D(ABMM) [5, 7], Winston Lok MD [2, 8], Jennifer Brown Broderick MD MSc FRCSC DABOG [1, 2, 3]

[1] Department of Obstetrics and Gynecology, College of Medicine, University of Saskatchewan
[2] Saskatchewan Cancer Agency
[3] Division of Oncology, College of Medicine, University of Saskatchewan
[4] Department of Academic Family Medicine, College of Medicine, University of Saskatchewan
[5] Department of Pathology and Laboratory Medicine, College of Medicine, University of Saskatchewan
[6] Department of Pathology and Laboratory Medicine, Saskatchewan Health Authority
[7] Department of Laboratory Medicine, Roy Romanow Provincial Laboratory, Saskatchewan Health Authority
[8] Family Medicine

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*Cervical Cancer Task Force Members	Role
Mary Kinloch BSc MD CCFP [1, 2]	Chair
Joanne Sivertson MD FRCSC [3]	Chair of Clinical Guidelines Working Group
Brent Jim MD FRCSC [3, 4, 5]	Member of Clinical Guidelines Working Group
Carla Holinaty MD CCFP [6]	Member of Clinical Guidelines Working Group
Jennifer Brown Broderick MD MSc FRCSC DABOG [3, 4, 5]	Member of Clinical Guidelines Working Group
Winston Lok MD [4, 7]	Member of Clinical Guidelines Working Group
Carrie Gardipy RN APP BSN CCHN(C) [8]	Member of Knowledge Translation Sub-Committee
Cheryl Kisters NP [9]	Member of Knowledge Translation Sub-Committee
Cheryl Whiting RN BSc MN CON(C) [4]	Member
Christine McDougall MPH [4]	Member, Project Lead
Cory Kolt [4]	Member
Fergall Magee MD FRCPC MHSc [1, 2, 10]	Member

Francoise Verville NP MN AGD:ANP DNP [11]	Member of Knowledge Translation Sub-Committee
Heather Keith [8]	Member of Knowledge Translation Sub-Committee
Jessica Bailey BA BHSc MA RM [12]	Member of Knowledge Translation Sub-Committee
Jessica Minion MD MSc FRCPC D(ABMM) [1, 13]	Member
Jill Wooff MD [1, 2]	Member of Knowledge Translation Sub-Committee
Joelynne Radbourne RN BSCN MN NP [4, 9, 14]	Member of Knowledge Translation Sub-Committee
Keri Crawford [15]	Member
Maggie Sawatsky	Member
Margarita Bykova MN NP CON(C) [4]	Member of Knowledge Translation Sub-Committee
Margot Gough BA MPH [4]	Member
Mary Ellen Labreque NP PhD [16]	Member of Knowledge Translation Sub-Committee
Michelle Verwey RN BSc MSc(PHDC) [4]	Member, Project Lead
Prabhjot Sidhu CHIM [4]	Member
Rhonda Hartz [15]	Member
Ronald Angeles MD [1, 2]	Member
Sandra Lesko MLT [10]	Member
Shardelle Brown MPH [4]	Member, Project Lead
Shelley Polos BA (Hons.) BSW RSW [4]	Member
Tara Schmalenberg MN NP [17]	Member of Knowledge Translation Sub-Committee
Terri Hansen-Gardiner	Member, Knowledge Keeper

Affiliations

[1] Department of Pathology and Laboratory Medicine, College of Medicine, University of Saskatchewan
[2] Department of Pathology and Laboratory Medicine, Saskatchewan Health Authority
[3] Department of Obstetrics and Gynecology, College of Medicine, University of Saskatchewan
[4] Saskatchewan Cancer Agency
[5] Division of Oncology, College of Medicine, University of Saskatchewan
[6] Department of Academic Family Medicine, College of Medicine, University of Saskatchewan
[7] Family Medicine
[8] Northern Intertribal Health Authority
[9] Saskatchewan Health Authority
[10] Anatomical Pathology, Pathology and Laboratory Medicine, Saskatchewan Health Authority
[11] School of Nursing, Saskatchewan Polytechnic

[12] Provincial Midwifery, Saskatchewan Health Authority
[13] Department of Laboratory Medicine, Roy Romanow Provincial Laboratory, Saskatchewan Health Authority
[14] University of Regina
[15] Pathology and Laboratory Services, Saskatchewan Health Authority
[16] College of Nursing, University of Saskatchewan
[17] Touchwood Qu'Appelle Primary Health Care Network, Saskatchewan Health Authority

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Cervical Cancer Screening
Clinical Practice Guideline 2023

OBJECTIVE
Saskatchewan clinicians will understand the recent evidence, offer age and risk-appropriate cervical cancer screening, and follow up on abnormal screen results.

TARGET POPULATION
Consider all people with a cervix 25 - 69 years of age who are or have ever been sexually active*, including transgender people with a cervix.

EXCLUSIONS
People who have never been sexually active*.
People with symptoms, such as vaginal bleeding/spotting, require investigation. A Pap test is a screening test and SHOULD NOT BE USED to investigate medical complaints.

Recommendations

Screen:

- ✓ Asymptomatic average-risk people who are or have ever been sexually active* (see table 1).
- ✓ Start three years after the onset of sexual activity* or age 25, whichever is later.

AGE RANGE	21 - 24	25 - 29	30 - 69	≥ 70
SCREEN	Testing can be offered with proper counselling	Initiate routine screening	Routine screening	Screen if unscreened / under-screened (i.e., not screened regularly at three (3) year intervals)
INTERVAL	Every three (3) years	Every three (3) years	Every three (3) years	Until three (3) consecutive negative Pap tests (collected at least one year apart) within ten (10) years
EVIDENCE	Harm is likely greater than benefit (moderate evidence)	Benefit is likely greater than harm (moderate evidence)	Benefit is likely greater than harm (strong evidence)	Less evidence, but biologically plausible that the risk of disease is high / continues Screening may reduce morbidity and mortality

Table 1: Cervical Cancer Screening Algorithm

PRACTICE POINTS	
	• Regular screening should be emphasized for people 25 - 69 (and older if under/unscreened). People 21 and older should be counselled and allowed to access screening if they choose. • The decision to start or stop screening should be an individual one. People who place a higher value on the potential benefits than the potential harms may choose to begin screening between the ages of 21 - 24. Some people may choose to continue with screening beyond the age of 69. • To assist with the discussion and patient decision-making, see the FAQ resource.

* Sexual activity includes use of shared sex toys, vaginal or anal penetrative intercourse, as well as digital or oral sexual activity, involving the genital area with a partner of any gender.

Do Not Screen Persons

- **X** **Less than 21 years of age**
- **X** 70 years of age or older who have been adequately screened and choose to stop screening
- **X** With a limited life expectancy and no benefit from screening
- **X** With a total hysterectomy for benign disease with no history of high-grade cervical dysplasia
- **X** Who have never been sexually active[†]
- **X** With an undiagnosed cervical lesion

PRACTICE POINTS	
	• A Papanicolaou (Pap) test is a screening test for use in an **asymptomatic population** with no apparent symptoms and signs of neoplasia. • Symptomatic patients should be investigated, regardless of age. See the *reaffirmed SOGC Clinical Practice Guideline No. 292- Abnormal Uterine Bleeding in Pre-Menopausal Women*[1] • **Do NOT perform a Pap test in an attempt to diagnose a cervical lesion**. A biopsy is the correct test to diagnose visible lesions. A Pap test is ONLY appropriate for screening purposes and is NOT a diagnostic test.

Increased Risk Surveillance

Note: It is extremely important to include the clinical history on the laboratory requisition.

For patients who have ever had:	**Surveillance Recommendations:**
• Total hysterectomy with previous CIN II or III, AIS, or invasive cervical cancer ***without*** radiation [a]	Suggest annual vault smears for 25 years after the last treatment for high-grade dysplasia [a, b]
For patients who have been sexually active with immunosuppression from:	**Surveillance Recommendations:**
• Human immunodeficiency virus (HIV/AIDS) • Lymphoproliferative disorders • Organ transplantation • Use of long-term oral corticosteroids • Common / long-term use of immunosuppressants, tumor necrosis factor inhibitors	Evidence is limited/non-existent regarding the need for increased frequency (i.e., annual) screening in this cohort. Some patients may benefit from annual surveillance. Use clinical judgement and engage in informed, joint decision-making with the patient.
[a] For patients who have had a total hysterectomy to treat invasive cervical cancer ***without*** radiation, vault smears are recommended to screen for the development of VAIN. See Considerations After Hysterectomy. [b] To screen for vaginal dysplasia. Based on expert opinion/consensus. Consider patient choice.	

Table 2: Increased Risk Surveillance

PRACTICE POINTS	
	• Pap tests are NOT recommended for patients who have had a total hysterectomy for a benign indication without a history of high-grade cervical dysplasia. • Pap tests are a SCREENING tool and should not be used for surveillance of recurrence in patients after treatment for invasive cervical cancer.

[†] Sexual activity includes use of shared sex toys, vaginal or anal penetrative intercourse, as well as digital or oral sexual activity, involving the genital area with a partner of any gender.

Considerations for Screening Perinatal Patients

- ✓ Screen perinatal patients according to the recommendations for screening non-pregnant persons.
- ✓ Spotting is common after cervical sampling in pregnancy. Therefore, it is advisable to counsel women to expect it and to reassure them that they are not at increased risk of pregnancy loss (+/- anti-D immunoglobulin is not necessary for spotting secondary to Pap test screening).
- X **DO NOT over-screen. There is no need to perform a Pap test during prenatal and postpartum visits unless the patient is otherwise due for screening.**
- X DO NOT repeat the Pap test until six months postpartum if ASC-US or LSIL is detected during pregnancy. All other findings, especially more advanced lesions, should be managed according to the Management of Abnormal Pap Test Result.

General Checklist for Providing Optimal Pap Testing

- ✓ Discuss HPV vaccination and sexually transmitted infection (STI) prevention and testing with the person.
    - Testing for STIs does not require a pelvic exam or Pap test. Instead, a urine sample or vaginal swab is used for nucleic acid amplification tests (NAATs) to detect STIs.
- ✓ Screen people who have received the HPV vaccine.
- ✓ Screen people who have undergone subtotal hysterectomy and have retained their cervix.
- ✓ Encourage patients currently being monitored by colposcopy to attend their follow-up appointments as scheduled/recommended.
- ✓ Once a patient is discharged from colposcopy, continue screening with Pap tests at intervals appropriate for their risk (see table 2 on increased risk surveillance).
- Atrophic cells and cervical stenosis are common in older, postmenopausal people. This can result in difficulty obtaining satisfactory samples and test interpretation. This can also be seen in trans men secondary to their hormonal therapies. Therefore, topical estrogen supplementation may be necessary before Pap testing.
- X **It is *NOT* necessary to perform a Pap test or pelvic exam before prescribing contraception**.
- X DO NOT routinely perform pelvic exams on asymptomatic people with or without Pap testing.

Key Messages to Guide Personal Decision-Making

See appendix A.

Implementation Approaches

- Initiate opportunistic discussions about cervical cancer screening with patients when they present for other health concerns. Outreach and preventive health screening checklists increase the likelihood of engaging people to make informed decisions about cervical cancer screening.
- Use electronic medical records (EMRs) to identify patients who are due/overdue for screening and recall them for testing.
- Utilize the services offered by the Screening Program for Cervical Cancer (SPCC). The SPCC promotes and supports participation in regular cervical cancer screening through an initial invitation to screening, a reminder and recall system for Pap testing, and reminders for abnormal results follow-up. The SPCC also provides cervical cancer screening education and resources - see appendix B for more information.

Management of Abnormal Pap Test Result

As per laboratory and colposcopy guidelines (see table 3 below).

The lab will automatically perform HPV reflex testing on the original sample when the Pap result is ASC-US on patients ≥ 30 years and for LSIL on patients ≥ 50 years. **A repeat swab is not required for HPV testing.**

When the HPV reflex test reports the result as "no result," the lab will recommend an immediate vaginal swab be submitted for repeat HPV testing.

PRACTICE POINTS	• A repeat swab is NOT required for HPV testing. • The lab will automatically perform HPV reflex testing on the original sample when the Pap result is ASC-US on patients ≥ 30 years and for LSIL on patients ≥ 50 years.

Management of Abnormal Pap Test Result

Return to routine screening: Patient returns to three-year interval Pap testing from the date of the last NILM [negative for intraepithelial lesion or malignancy] specimen regardless of age and/or any previous testing interval.

Unsatisfactory: Repeat Pap in three months.

Transformational zone absent (SNTZ) is a lab code (now modified): Absence of endocervical glandular cells/transformation zone component. *The specimen is still considered satisfactory for evaluation and does not require a repeat.*

Atypical squamous cells of undetermined significance (ASC-US)

Patients ≤ 24 years: If screened, with ASC-US result, repeat Pap test every 12 months for two years (two tests):

- At 12 months: ONLY high-grade lesions refer for colposcopy.
- At 24 months: Negative → return to routine screening.
  ASC-US or greater → refer for colposcopy.

Patients 25 - 29 years: Repeat Pap test every 12 months for two years (two tests):

- If both repeat results are negative → follow-up is routine screening (every three years).
- If either repeat result is ASC-US or greater → refer for colposcopy.

Patients ≥ 30 years: (*The lab will automatically perform HPV reflex testing*)

- HPV Negative* → risk level equivalent to NILM. Follow-up is routine screening.
- HPV Positive → refer for colposcopy.
- HPV No Result → submit vaginal swab for repeat HPV testing.

Low-grade squamous intraepithelial lesion (LSIL)

Patients ≤ 24 years: If screened, with LSIL result, repeat Pap test every 12 months for two years (two tests):

- At 12 months: ONLY high-grade lesions refer for colposcopy.
- At 24 months: Negative → return to routine screening.
  ASC-US or greater → refer for colposcopy.

Patients 25 - 49 years: Repeat Pap test every 12 months for two years (two tests):

- If both repeat results are negative → follow-up is routine screening (every three years).
- If either repeat result is ASC-US or greater → refer for colposcopy.

Patients ≥ 50 years: *(The lab will automatically perform HPV reflex testing)*

- HPV Negative* → risk level is equivalent to NILM. Follow-up is routine screening.
- HPV Positive → refer for colposcopy.
- HPV No Result → submit vaginal swab for repeat HPV testing.

**The risk of CIN3+ over three years is virtually the same for HPV-negative patients as for patients with negative cytology without HPV testing.*

High-grade squamous intraepithelial lesion (HSIL)	ASC-H	Atypical glandular cells (AGC), adenocarcinoma in situ (AIS)	Squamous carcinoma, adenocarcinoma, other malignancy
Refer all ages for colposcopy.			Refer all ages to a specialist.

Patients with cytologically benign endometrial cells

- Endometrial sampling is required if:
  - there is abnormal bleeding
  - the patient is postmenopausal (even if asymptomatic)
- Also consider endometrial sampling if the patient is asymptomatic, pre-menopausal, and at increased risk for endometrial cancer due to chronic unopposed estrogen stimulation.

PRACTICE POINT	
	• In patients 30 - 49, HPV reflex testing is done for ASC-US but not LSIL. *Rationale: the differential diagnosis for an ASC-US Pap includes benign cytology, low-grade dysplasia, or high-grade dysplasia. LSIL is reported when the diagnosis is confidently low-grade dysplasia, eliminating the need to stratify the patient's risk with HPV testing.*

Table 3: Management of Abnormal Pap Test Result

Background

Introduction

These revised cervical cancer screening recommendations have been adapted from the Alberta clinical practice guidelines.[2] They have been reviewed by an expert review panel with consideration of new risk-based recommendations from the American Society for Colposcopy and Cervical Pathology, the Canadian Task Force on Preventive Health Care guidelines published in 2013, and cervical cancer screening approaches in other jurisdictions across Canada and elsewhere.[3] This background section provides a summary of evidence for cervical cancer screening recommendations, and provides an update on the status of HPV reflex testing and HPV vaccinations in Saskatchewan as they affect cervical cancer screening.

Natural History

Squamous cell carcinoma accounts for 80 - 90% of cervical malignancies. The remainder are predominantly adenocarcinomas. Persistent infection with one of the carcinogenic types of human papillomavirus (HPV) is a necessary but not sufficient cause of both squamous and glandular malignancy.[4] Both types arise from a four-step progression as depicted in figure 1:[5]

1. HPV infection of metaplastic epithelium at the cervical transformation zone
2. HPV persistence
3. Development of pre-cancer in persistently infected cells
4. Invasive cervical cancer

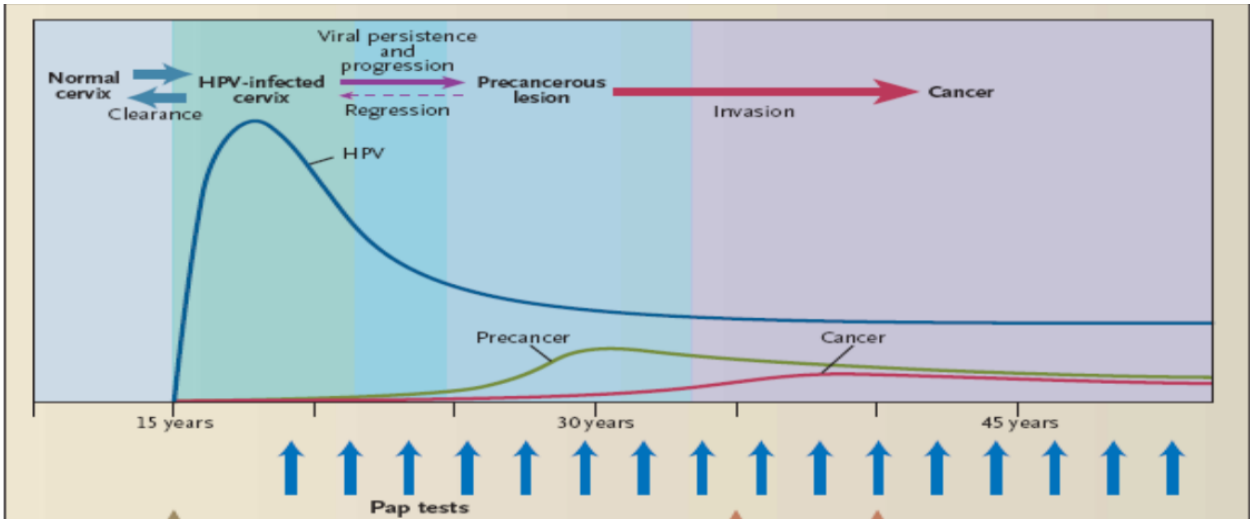

Figure 1: Image modified from Schiffman et al. 2007.[5] Reproduced with permission

HPV infection is very common in young people in their first decade of sexual activity. The lifetime cumulative prevalence of high-risk infection approaches 80%.[6] More than 90% of these infections are cleared spontaneously through cell-mediated immunity within two years of infection.[7]

Persistent infection and development to pre-cancer occur in less than 10% of these infections within five to ten years.[8] Regression from persistent HPV infection and from pre-cancer is also common.[7]

In the minority of persons with pre-cancerous changes, invasive cancer can arise. This process usually takes many years or even decades. Early detection and treatment during this lengthy pre-cancerous stage can prevent the vast majority of invasive cervical cancers.

Premalignant squamous lesions are classified as either low-grade squamous intraepithelial lesions (LSIL) or high-grade squamous intraepithelial lesions (HSIL). The majority of LSIL clear spontaneously and only infrequently progress to invasive carcinoma; however, approximately 13% of untreated HSIL will progress over time to invasive carcinoma.[9]

Very infrequently, cancers develop rapidly, progress to invasion, or metastasize before detection. The screening process is not effective for improving clinical outcomes when these rare cases occur.

PRACTICE POINT	• Family history does not change screening recommendations. Cervical cancer is not a genetic disease; only personal history affects one's risk of developing dysplasia.

Epidemiology

Prior to screening, the incidence of cervical cancer in Canada was more than 1 in 70 persons with a cervix, and mortality about 1 in 100 persons with a cervix.[10] Cervical cancer incidence and mortality have decreased substantially in the past 50 years.[10] It is now the 13th most commonly diagnosed cancer among Canadian persons with a cervix.[11] In comparison, cervical cancer is the second most commonly diagnosed cancer among persons with a cervix in less developed countries, where screening is not established.[12] Because of the lower screening rates, many immigrants are at higher risk of cervical cancer.

It is estimated that 1,450 people will be diagnosed with cervical cancer, and 380 people will die from it in Canada in 2022.[13] The lifetime probability of a person developing cervical cancer in Canada is estimated to be 1 in 161, and 1 in 486 will die from it.[14] Most advanced cervical cancer (with consequent mortality) occurs among people who have not undergone screening or have had a long interval between Pap tests.[15] Consequently, the greatest value comes from helping these people to participate.

Invasive cervical cancer is rare among persons younger than 21 because progression from HPV infection to pre-cancer typically takes five to ten years, and the development of invasive cancer mostly takes several additional years. Since the initiation of widespread cervical screening throughout Canada, the incidence of invasive cervical cancer in Canada declined from 15.4 per 100,000 in 1977 to an estimated 7.5 per 100,000 in 2015. Invasive cervical cancer mortality decreased from 4.8 per 100,000 in 1977 to an estimated 1.6 per 100,000 in 2015.[16] Age-specific incidences of invasive cervical cancer have reduced in all age groups during this time. The highest incidence of cervical cancer continues to occur between the ages of 35 to 44 (see figure 2).[17]

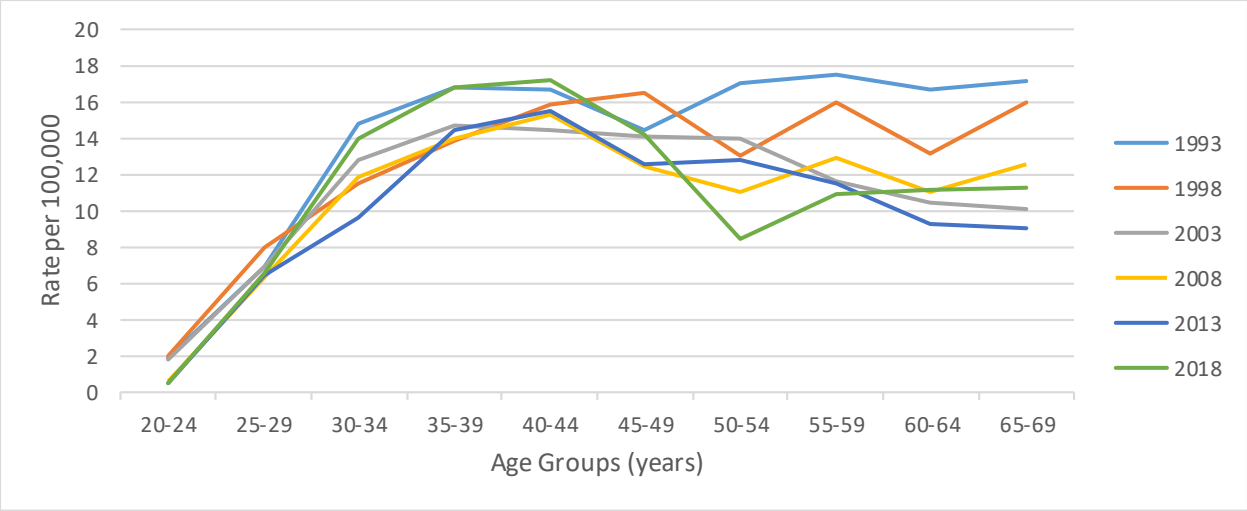

Figure 2: Age-specific Incidence of Cervical Cancer in Canada, 1993-2018[17]

The following data is provided by the Saskatchewan Cancer Agency using cancer registry data and information available through the SPCC. In 2019, there were 64 new cases of cervical cancer in Saskatchewan, 14 deaths attributable to the disease, and 263 potential years of life were lost due to cervical cancer. In 2021, approximately 50 cases of cervical cancer were expected to be diagnosed in Saskatchewan, with 15 deaths attributable to the disease.[14]

Balancing Risks and Benefits

The benefits of screening to reduce the incidence of invasive disease and death due to cervical cancer have been consistently shown in cohort and case-control studies. Most advanced cervical cancer (with consequent mortality) occurs among people who have not undergone screening or who have had a long interval between Pap tests.[15] Conversely, initiating screening when the risk is very low and/or screening too frequently can produce more harm than benefit.[18]

Younger persons are at increased risk of over-diagnosis and over-treatment. This is because they have more abnormal results, but these results are much less likely to represent a serious abnormality. We now understand there are several potential harms to over-diagnosis, including:

1. Inconvenience, discomfort, and embarrassment that people feel from attending Pap tests and having uncomfortable bimanual examinations;
2. Physical and psychological impacts from being informed about an abnormal test, being asked to undergo repeat testing, being referred for colposcopy, or undergoing biopsies, a loop electrosurgical excision procedure (LEEP), or other procedures; and
3. The risk for pregnancy loss for those who had a LEEP or cone biopsy rises from 0.6% to 1.8% (an increase of 1.2%), primarily in the second trimester.[19][20]

This latter risk is more serious in younger persons who are less likely to have started or completed their families. At the time of the procedure, it is impossible to differentiate which lesions will progress from those that are indolent. Colposcopists have become more cautious about the extent of excisions in

recent years, so there are fewer large excisions. Nevertheless, many LEEPS in young patients can be considered "over-treatment" since few of these lesions would progress to cancer.[21–23]

Informed Decision-Making

When presenting the information about possible benefits and harms of the screening process, each person's values, preferences, and beliefs about cervical screening must be considered. Screening should always be a choice and an informed decision made by the person. The above evidence and the subsequent recommendations are here to help you guide your patient in making that choice.

Screening Initiation

Persons Younger Than 21 Years

The 2012 Saskatchewan Cervical Cancer Screening clinical practice guideline recommended the initiation of screening at age 21. This was based on the evidence that cancer is extremely rare under that age. According to Saskatchewan SPCC data, persons under the age of 21 continue to be screened – including 629 people in 2020. This is inappropriate since the benefit is almost non-existent.[15]

If Pap tests are performed in this age group and LSIL is identified, there is a very high probability these changes will resolve spontaneously.[24] For this reason, recommended follow-up of persons younger than 21 with ASC-US or LSIL is more conservative than for older people. See Management of Abnormal Pap Test Result. HPV DNA testing results can also be misleading for people with ASC-US or LSIL under age 30. Because HPV is so frequent in this age group, HPV testing would result in high rates of colposcopy referrals with a very low probability of cervical carcinoma or progressive disease yet a tendency for over-treatment. Therefore, HPV testing in this age group is strongly discouraged.

Persons Aged 21-24 and 25-29

For people over 21, analysis of national mortality and incidence data show that mortality has dropped substantially in older age groups, but it was always low below the age of 30.[25] Current incidences and mortality in these screened people are similar to data from 1972 to 1976 before widespread screening.[25] In Saskatchewan, from 1992 - 2018, the annual incidence rate for cervical cancer was extremely low at age 20 or younger and remained low to age 25 (see figure 3).[17] There is a clear increase in incidence after 25 years of age.

There is also uncertainty about the effectiveness of screening for these rare cervical cancers in persons under 30. The National Health Services cervical cancer screening program in the United Kingdom (UK) investigated this concern and found that the effectiveness of screening improved with age, with odds ratios around 1 (no effect) in those under 25, around 0.5 by age 30, and 0.2 around age 50.[26] Further, they also showed that there was no protective effect against developing cervical cancer in the future from screening below the age of 25.[26] This was supported by data from elsewhere.[27] The UK modified its cervical screening policy to initiate screening at age 25 in 2003, while programs in the Netherlands and Finland start at age 30. The World Health Organization recommends "women under 30 should not be screened for cervical cancer".[28]

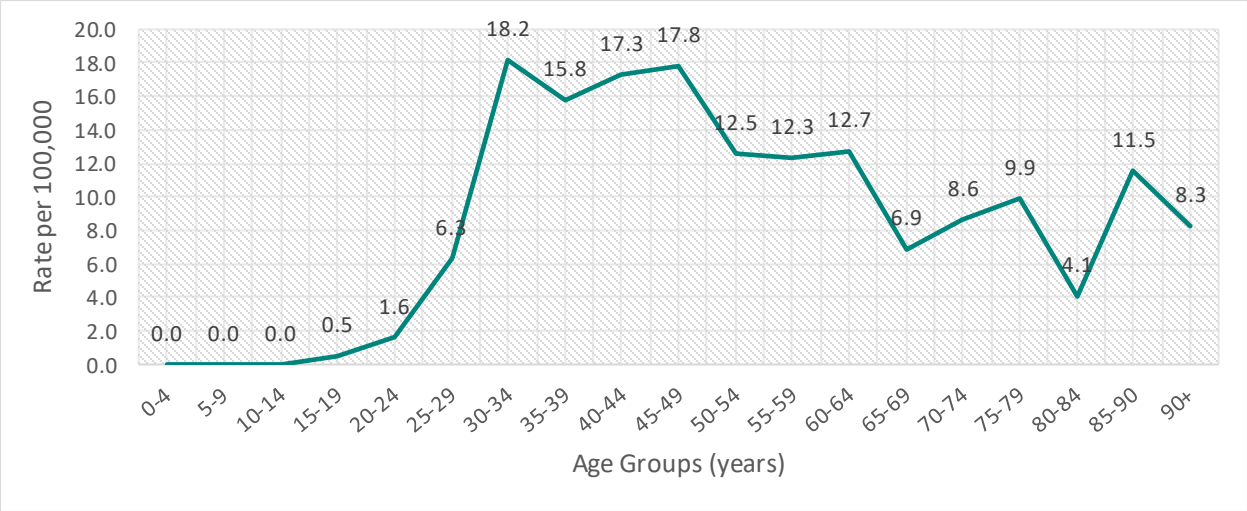

Figure 3: Age-specific Incidence of Cervical Cancer in Saskatchewan, 1992-2018[17]

Thus, current evidence regarding screening initiation for persons 21 to 29 years of age shows very low risk but not absence. Therefore, the small potential benefits of screening must be balanced against the substantial harms. The Canadian Task Force on Preventive Health Care concluded that the balance of benefit against harm changes in the middle of the decade. Screening may be initiated sometime in the years 25 - 29.[29] In Saskatchewan, women and people with a cervix are automatically enrolled in the SPCC at the age of 25 (see appendix B for more information about the SPCC). Clinicians can offer people a choice to be screened and/or may suggest screening to people who may be at a higher risk and more likely to benefit, e.g., early sexual debut, multiple partners (or whose partners have had multiple partners), or not HPV vaccinated. Smoking is also a risk factor, approximately doubling risk.[30]

Screening Interval

The evidence for screening intervals comes from case-control studies in several countries, showing a small increase in sensitivity between five and three-year intervals, but the gain from more frequent intervals was minimal.[31] When compared to the harms and costs to people of more frequent testing, many groups have recommended three years as a reasonable balance between benefits and harms.

Remembering a three-year interval for cervical cancer screening may be difficult for people and their health-care providers, therefore the SPCC (see appendix B) provides province-wide reminder notifications to people when they are due for their next cervical cancer screening.

When to Discontinue Screening

Countries have different approaches to when screening should be discontinued, ranging from 60 to 70 years of age. Cervical cancer occurs among older persons who have never been screened or have not been regularly screened. In addition, it can occur in patients who have had abnormalities treated earlier in life that recur in old age.

Based on life expectancy and provided persons 69 years of age and older have had three normal results from screening over the previous ten years, with no other related health problems, screening for cervical cancer can be discontinued. However, the decision to discontinue screening should be a personal one. People who have a long life expectancy, no other health issues, and are aware of the challenges associated with Pap testing at older ages (e.g., estrogen depletion/need for replacement, discomfort/pain, difficulty obtaining the sample, false-positive tests) may wish to continue with screening.

In Saskatchewan, women and persons with a cervix receive their last screening invitation from the SPCC at 69. However, consistent with personal health-care decision-making, participants are informed of the option to receive ongoing communication from SPCC should they choose. SPCC will align abnormal result follow-up communication to health-care providers and clients accordingly. See appendix B for more information on the SPCC.

Also, see the section below on Considerations After Hysterectomy.

Screening Test

Pap Test – Liquid-Based Cytology

Traditionally, the conventional Pap test sample was collected using a wooden spatula and brush, smeared onto a glass slide, and fixed. Saskatchewan now offers liquid-based cytology (LBC). The specimen is collected from the patient using a plastic spatula and brush, then placed into a jar containing a liquid preservative medium. This technology offers several advantages over conventional Pap testing:

1. Immediate preservation of collected cells;
2. Entire sample is recovered rather than lost with the discarded spatula/brush;
3. Preservative contains chemicals that lyse blood, mucus, and inflammatory cells allowing for a clean specimen and easier identification of abnormal cells;
4. Multiple slides can be prepared; and
5. Additional tests such as HPV reflex testing can be performed on the same sample.

Optimal Specimen Collection

Most cervical pre-cancer and cancer develop in the squamocolumnar junction, also called the transformation zone.[32] Because cells in this area of the cervixcervix area are always dividing, they are at risk for incorporation of high-risk HPV infection with subsequent transformation to abnormal cells. The transformation zone is characterized by columnar cells proximally, squamous metaplastic cells centrally, and mature squamous cells distally. Therefore, the ideal sample has both representations from ectocervical and columnar/metaplastic cells in adequate numbers.

The transformation zone can be identified by a change in colour and texture at visual examination. The squamous epithelium appears pale pink, shiny, and smooth. The columnar epithelium appears reddish

with a granular surface. The transformation zone typically recedes into the endocervical canal during menopause, reducing the chance of obtaining a squamocolumnar component in a Pap test specimen.

Obtaining an optimal specimen requires the clinician to clearly visualize the cervix where the collection device is sampling. The spatula must be swept around the full circumference of the cervix, even when the os is irregular in shape. The brush should be inserted most of its depth into the endocervical canal, though this is not always possible in older persons. Strict adherence to the sampling technique as recommended by the manufacturer, including minimal use of lubricant, can substantially improve the quality of the specimen.[32] In general, for reproductive age patients, sampling during the mid-cycle is optimal for collection.

During pregnancy, the cervix is more vascular and prone to easy bleeding. This may alarm people. It is advisable to counsel women to expect spotting and reassure them that they are not at increased risk of pregnancy loss (+/- anti-D immunoglobulin is not necessary for spotting secondary to Pap test screening). With longer intervals between Pap tests, it is better to time the test so it can be done postpartum to avoid changes related to delivery.

Pap tests in persons without a cervix but with a history of high-grade lesions or malignancy, require scraping of the vaginal vault. Cells from the apex of the vault should be collected using a spatula and transferred according to the liquid-based cytology manufacturer's recommendations.

HPV Reflex Testing

High-risk HPV (hr-HPV) types are potentially carcinogenic and may lead to the progression of cervical abnormality. There are many hr-HPV types, with types 16 and 18 being the most common.[33] The HPV reflex test can detect 14 carcinogenic HPV types.[33]

Reflex testing for hr-HPV will be automatically performed in Saskatchewan labs when a Pap test result is LSIL at age 50 and over, and for ASC-US at age 30 and over. The lab will use the original sample for HPV testing. **A repeat swab is not required for HPV testing**. This is a triage mechanism to determine if follow-up colposcopy is required for these results in these cohorts.[34] LSIL is less likely to resolve spontaneously in older patients. Therefore HPV testing is useful to stratify risk in patients 50 and over who are found to have low-grade dysplasia. In patients 30 - 49, reflex testing is done for ASC-US but not LSIL. The differential diagnosis for an ASC-US Pap includes benign cytology, low-grade dysplasia, or possibly high-grade dysplasia. In contrast, LSIL is reported when the diagnosis is confidently low-grade dysplasia. HPV testing in ASC-US helps stratify the patient's risk, which is not necessary for the setting of LSIL.

Treatment of high-grade abnormalities can eliminate a high-risk virus and, therefore, the risk of carcinoma. For people who test negative for a high-risk virus, there is a very low risk of developing cervical cancer, and more frequent screening is not required. However, people who have tested negative for high-risk HPV can subsequently acquire the high-risk virus types from new exposure and therefore require ongoing routine screening.

For persons 50 years of age and older, as estrogen levels begin to drop, atrophic cells may be detected on a Pap test. These atrophic cells may mimic intraepithelial abnormalities and may be reported as cytologic abnormalities.[34] Therefore, the lab will conduct routine HPV reflex testing for persons 50 years and older with ASC-US or LSIL Pap test results. If the HPV result is negative, the person can return to routine screening; if positive, referral to colposcopy is recommended.

When the HPV reflex test reports the result as "no result," the lab will recommend an immediate vaginal swab be submitted for repeat HPV testing.

Limitations of Screening

Like all screening tests, Pap tests are not 100% accurate. A false-negative result occurs when the Pap test fails to detect an abnormality on the cervix at the time of collection. In addition, false-negative results can occur from cervical sampling limitations. Therefore, providers performing Pap testing must use a thoughtful technique to sample the full cervix circumference and the endocervical canal. False-negative results can also occur from laboratory factors, so laboratories have quality assurance programs to minimize these errors.

False-positive screening test results are also of concern. Given the transient nature of many cervical abnormalities, screening detects many abnormalities destined to resolve independently. The current guidelines are intended to minimize the anxiety and potential harms associated with screening while helping reassure patients that clinically significant cervical changes are identified.

Despite its limitations, the Pap test is the best screening test to date.[35] This test is most effective at reducing squamous cell cancer, and less for adenocarcinoma.[35] To help overcome the false sense of security that can arise from a false-negative test result, it is important to advise people to report any symptomatic changes such as unusual vaginal bleeding or discharge, including bleeding after intercourse, after menopause, or between menstrual periods.

Other Considersations Regarding Cervical Cancer Screening

1. Persons Who are Pregnant

The first prenatal visit and the six-week postpartum check-up are often used by physicians as incidental opportunities for cervical screening. This is appropriate for those who otherwise do not attend screening, but if done as routine, it can produce over-screening. In addition, cervical changes associated with pregnancy and delivery produce Pap tests that are more difficult to interpret. There is no need to perform Pap tests during these visits unless the patient is due for a Pap test or is unlikely to return for screening at an appropriate time, e.g., non-participant in screening.

2. After Hysterectomy

Patients who have had a total hysterectomy for non-malignant pathology with no dysplasia in their cervix require no further Pap testing. However, patients who have undergone subtotal hysterectomy and retained their cervix should continue with routine screening according to the clinical practice guideline. Accordingly, the SPCC will continue to inform women and persons with a cervix post subtotal hysterectomy of Pap test due dates and communicate with health-care providers and clients for follow-up of abnormal results.

Patients with a history of proven biopsy-confirmed high-grade squamous intraepithelial lesion (HSIL), adenocarcinoma in situ (AIS), or early invasive cervical cancer are at higher risk for vaginal neoplasia.[36]

These patients, even if they have had hysterectomies for benign indications, should have vault smears annually for 25 years after their last treatment for dysplasia.

Patients who have had a hysterectomy to treat invasive cervical cancer, especially after subsequent radiation therapy, should NOT have Pap testing. Radiation results in cellular changes that limit the interpretation of Pap tests. Even in patients who have not received radiation, Pap testing has consistently low yield, with detection rates of recurrence ranging from 0 - 17%. Studies have shown that cytologic evidence was rarely the only abnormality in patients with recurrent cervical cancer, and therefore Pap testing is not beneficial in monitoring for recurrence. Vault smears should be collected annually for 25 years to screen for the development of vaginal intraepithelial neoplasia (VAIN), but only if the patient has not had radiation. If a Pap test is collected in this patient population, the Society of Gynecologic Oncology's Choosing Wisely campaign recommends no investigation of results showing less than high-grade changes.[37]

In Saskatchewan, the SPCC's invitation, recall, and reminder processes align with the target population of asymptomatic, average-risk persons with a cervix in the province. Accordingly, persons who have had total hysterectomies with previous CIN II or III, AIS, or invasive cervical cancer are not included in the invite, recall, or reminder systems through SPCC. Health-care providers are responsible for communication with their patients about their screening needs, due dates, results, follow-up, treatment, etc. See appendix B for more information about the SPCC.

3. Transgender Persons

The following recommendations are based on expert opinion, as the evidence on transgender cervical cancer screening is limited at this time.

Routine screening is recommended for trans men (female-to-male) if they have a cervix.[3839] A vault smear is also recommended for trans men whose cervix has been removed if they previously had a biopsy-proven high-grade cervical pathology result such as HSIL, AIS, CIN II or III, or invasive cervical cancer. However, no screening is recommended for trans men who have had their cervix removed and do not have a history of high-grade dysplasia or cervical cancer.

In addition, vault smears are recommended for trans women (male-to-female) who have had vaginoplasty with penile inversion or neo-cervix creation with the head of the penis.[38,39] No screening is recommended for trans women who have had vaginoplasty without the creation of a neo-cervix. Cervical cancer screening is not recommended for trans women who have not had vaginoplasty.

The SPCC is a cervical cancer screening program. Vault smear testing is outside the scope of the program. Health-care providers are responsible for communication with their patients about their screening needs, due dates, results, follow-up, treatment, etc. See appendix B for more information on the SPCC.

It is important for providers to recognize that traditional anatomic terms may feel uncomfortable to people who are not cis-gendered. In practice, it is a good idea to ask patients what words they use to describe their anatomy and then use these terms when in discussion with them.[39]

4. Contraception, STIs, and Pelvic Exams

In their policy statement on contraception in adolescents, the American Academy of Pediatrics no longer includes cervical cancer screening as a recommendation when prescribing contraceptives.[40]

There is no evidence supporting the use of a Pap test when testing for STIs or initiating a discussion with a person regarding STIs. A urine test or vaginal swab (per your laboratory requisition) for STIs is sufficient.

Pelvic examinations may cause pain, discomfort, fear, anxiety, or embarrassment in about 30% of people. Yet, no data was found to support the use of pelvic examination in asymptomatic, average-risk people who present for a Pap test and/or a wellness visit.[41,42] Therefore, this additional examination should not be undertaken routinely.

5. Immunosuppressed Patients

There is a scarcity of evidence to support increasing the frequency of cervical cancer screening for immunosuppressed patients and patients taking immunosuppressant medication. It does not appear that, in general, cervical cancer rates are higher or that cervical cancer progresses more rapidly in these patients.[43] Some studies, however, suggest that certain immunosuppressant medications such as azathioprine are associated with an increased risk of cervical cancer, and some highly immunosuppressed patients are at increased risk of HPV infection and cervical dysplasia when compared to the general population.[44] This may indicate a need for increased cervical screening in this cohort of patients.

In the absence of conclusive evidence, no recommendation can be made concerning shorter screening intervals, i.e., annual screening, for this cohort of patients. It is suggested that they be screened every three years until more conclusive evidence is forthcoming. However, depending on the degree of immunosuppression, i.e., severe immune deficiency, for whatever reason (e.g., AIDS, certain immunosuppressant medication), clinicians may choose to offer more frequent screening, perhaps every one or two years. If this is offered, the patient should be made aware that with more frequent HPV detection, the consequence may be over-diagnosis and over-treatment. As new evidence emerges on this topic, this guideline will be updated accordingly.

HPV Immunization

Persons who are HPV vaccinated are recommended to continue screening as per the guidelines.

The National Advisory Committee on Immunization (NACI) recommends HPV vaccination for all people between ages 9 and 26.[45,46] HPV vaccination is approved for women up to the age of 45.[46]

Saskatchewan's publicly funded, school-based immunization program vaccinates children in grade 6 (at age 11 - 12 years) with Gardasil®9.[47] This vaccine protects against infection from nine HPV types, including seven high-risk types which cause 90% of cervical cancers.[48] The school-based HPV immunization program started in 2008 for grade 6 girls. In 2017, it expanded to include all children in grade 6.

In the 2017 - 18 school-based program, 69.1% of girls were immunized with the complete two-dose series (76.5% had one dose).[49] Immunization rates for boys in the Saskatchewan school-based program were unavailable at the time of this guideline publication. Females born since January 1, 1996, and males born since January 1, 2006, are eligible to participate in Saskatchewan's HPV vaccination catch-up program until they reach 27 years of age.[47] Citizens may contact Public Health to participate in the catch-up program at no cost. Research has shown that the vaccination of young women in catch-up programs effectively improves herd immunity and reduces the risk of invasive cervical cancer.[45]

Immunocompromised persons between the ages of 9 and 26 are also eligible for publicly funded vaccination.[50] Immunocompromised patients include:

- HIV positive with a CD4 count under 500;
- Congenital immune deficiency;
- Acquired immune deficiency: disorders of B-lymphocyte (humoral) immunity, T-lymphocyte (cell) mediated immunity, complement component deficiency (C5-C9, properdin, factor H, factor D), or phagocytic functions. Acquired complement immunodeficiency includes treatment with the terminal complement inhibitor eculizumab Soliris™;
- Transplant candidate or recipient;
- Medical treatments:
    - Long-term/high-dose corticosteroids;
    - Cancer chemotherapies;
    - Radiation therapies;
    - Immunosuppressants: immunologic modulators, anti-rheumatic drugs including tumour necrosis factor blockers), monoclonal antibody medications; and,
    - Post-transplant – solid organ, islet cell, or hematopoietic stem cell.

HPV vaccination should also be offered to people who do not qualify for publicly funded programs. Many insurance plans will cover HPV vaccination, or the individual may decide to pay out of pocket.

The role of cytology and HPV testing continues to evolve as the cohort of HPV-vaccinated people approaches the age group recommended for screening. The first vaccinated cohort (grade 6 and 7 girls vaccinated in 2008) reached 21 in 2017/2018.[49] It is important for health-care providers to be aware that:

- HPV-vaccinated persons are also at risk, albeit lower, of developing cervical cancer if they do not receive regular screening. The current vaccines do not cover all carcinogenic HPV types, so people need to avoid a "false sense of security."
- Effectiveness of HPV vaccine for preventing cervical cancer over the long term is unknown.
- Not everyone in the cohort offered vaccination has been vaccinated – there is substantial variation throughout the province and country.

PRACTICE POINTS	• Continue screening according to the guidelines for people who have been HPV vaccinated. • HPV vaccination is an important tool for cervical cancer prevention. • The NACI recommends HPV vaccination for all people ages 9 to 26.[46,49] Saskatchewan has a variety of publicly funded vaccination programs for this age group. Contact Public Health for information on HPV vaccination.

Links to HPV Immunization Resources

Health-Care Provider Resources:

- To learn more about HPV immunization services in Saskatchewan, visit: https://www.saskatchewan.ca/residents/health/accessing-health-care-services/immunization-services
- To learn more about the Saskatchewan Immunization Manual, visit: https://www.ehealthsask.ca/services/Manuals/pages/sim.aspx
- To learn more about HPV immunization programs across Canada, visit: https://www.partnershipagainstcancer.ca/topics/hpv-immunization-policies/
- To learn more about the NACI's recommendations, visit: https://www.canada.ca/en/public-health/services/publications/healthy-living/update-recommended-human-papillomavirus-vaccine-immunization-schedule.html#a6

Patient Resources:

- For additional HPV information, visit: https://www.hpvinfo.ca/
- Direct patients to a decision-making tool "HPV: Should I get the vaccine?" https://www.saskhealthauthority.ca/your-health/conditions-diseases-services/healthline-online/abo9722

Future Direction

The Canadian Partnership Against Cancer (CPAC) has set the goal of eliminating cervical cancer by 2040 in Canada.[51] To achieve this goal, priorities are to improve HPV immunization rates, improve follow-up of abnormal screening results, and implement primary HPV screening. In addition, specific strategies are being developed to improve cancer prevention through peoples-specific actions amongst First Nations, Inuit, and Métis populations.[52–57] These specific priorities include culturally appropriate care closer to home, First Nations-governed research and data systems, and peoples-specific, self-determined cancer care.

Emerging evidence suggests HPV testing is superior to cytology as a primary screening tool.[51,58–61] Transitioning to primary HPV testing for screening has been shown to be cost-neutral or even cost savings over time, as screening intervals can be extended.[51,60] Studies have also shown that HPV testing can be successfully collected by individual themselves, which holds the promise of increased patient comfort and participation.[51,62–64] This may be particularly beneficial to Indigenous and remote communities. The Canadian colposcopy guideline has been updated in 2023 to provide evidence-based guidance on the risk-based management of cervical dysplasia in the colposcopy setting in the context of

primary HPV-based screening and HPV testing in colposcopy.[65] Therefore, we recommend a move to primary HPV screening within the next five years.

Appendix A

Key Messages to Guide Personal Decision-Making

✓ Information to ensure persons are fully informed as to the risks and benefits of screening at different ages:

Age below 21

- Cervical cancer incidence and mortality are extremely low.
- High rates of transient HPV infections with associated Pap test abnormalities. At this age, most HPV infections are cleared by the immune system, and the dysplasia resolves spontaneously, so no treatment is required.
- The discovery of abnormality may lead to harms through unnecessary treatments.

Age 21 - 24

- There is a low incidence of cervical cancer, and mortality from cervical cancer is very low.
- Cancers that develop in this age group are more aggressive and not typically detected early enough with Pap screening to impact survival.
- Abnormal results are common and often transient, leading to unnecessary treatments and potential harms.
- Screening benefit is unclear, but the harms likely outweigh the benefits.

Age 25 - 29

- Screening is potentially beneficial as the incidence and mortality of cervical cancer rise in this age group.
- There are still more false-positive tests in this age group compared to older age groups.
- The balance of benefits and harms is more in favour of screening.

Age 30 - 69

- Cervical cancer incidence and mortality are high in unscreened persons.
- Evidence is strong for screening effectiveness.
- The benefit is likely to be greater than the harms.

Age ≥ 70

- Cervical cancer incidence is similar to those 60 - 69 years and begins to rise again with age. However, the risk of death from other causes increases disproportionately, and therefore the evidence is limited for screening effectiveness for those having had regular screening.
- It is important to screen for cervical cancer in those who are unscreened or inadequately screened.
- The decision to stop screening should be a personal one based on the person's life expectancy, quality of life, personal values, and understanding of the challenges of screening beyond this age, e.g., estrogen depletion, pain, difficulty obtaining samples, false-positive results.

See FAQ resource for additional considerations regarding different age groups.

Appendix B

Screening Program for Cervical Cancer

The Screening Program for Cervical Cancer (SPCC) is a program of the Saskatchewan Cancer Agency dedicated to preventing cervical cancer. Like other organized population-based screening programs, SPCC provides an administrative structure responsible for service delivery, follow-up of abnormal results, quality assurance, and ongoing evaluation. The SPCC informs participants when they are due for a Pap test, notifies clients of their results, and communicates with health-care providers and participants to ensure appropriate follow-up of abnormal results.

SPCC Eligibility

The SPCC automatically enrolls women and persons with a sex marker of "F", with a valid Saskatchewan health card, into the program at the age of 25. The SPCC sends communication inviting eligible people to participate in screening, explains the program, and provides information about cervical screening. SPCC will communicate with transgender men and transgender women individually to discuss their screening needs.

The SPCC's invitation, recall, and reminder processes align with the target population of asymptomatic, average-risk persons in the province. For example, persons requiring cervical screening following abnormal results are not reminded of routine Pap tests until abnormal result follow-up is resolved.

Persons who have had total hysterectomies with previous CIN II or III, AIS, or invasive cancer without radiation who require vault smears, are not included in the invite, recall, or reminder system. Health-care providers are responsible for communication with their patients about their screening needs, due dates, results, follow-up, treatment, etc.

Informing Participants of Results/Follow-Up

Participants are informed about their Pap test results. If the result is normal, the participant continues with routine screening. If the result is abnormal/unsatisfactory, the participant is advised to contact their health-care provider for further follow-up or treatment, and the participant's screening schedule is changed accordingly.

If no follow-up information is received from the health-care provider within the recommended timeframe, SPCC communicates to the health-care provider and participant recommending further follow-up according to screening guidelines.

Colposcopy

When a patient is referred to colposcopy by their health-care provider, the SPCC will track compliance to ensure participants receive appropriate and timely follow-up. If no follow-up information is received from the health-care provider within the recommended timeframe, SPCC communicates to the health-care provider and participant recommending further follow-up according to screening guidelines.

Health-care providers performing colposcopies are strongly encouraged to utilize the SPCC Colposcopy Form for colposcopy reporting and billing. This form allows the SPCC to track patient follow-up and

provincial colposcopy data and adjust program communication appropriately. If it is not used, the SPCC may not be aware a colposcopy has been done and be unaware of the recommended patient follow-up. This makes facilitating patient care impossible.

SPCC Resources

Health-Care Provider Screening Resources

✓ Refer to the following resources available on the SPCC health-care provider resources website:

- o Checklist for 2023 Revised Cervical Screening Guidelines
- o Summary of the Cervical Cancer Screening Clinical Practice Guideline
- o FAQs and Decision Points for Initiating and Discontinuing Pap Testing
- o Follow-up for Abnormal Pap Test Algorithm
- o HPV Reflex Information for Health-Care Providers
- o Cervical Cancer Screening Quick Reference
- o Screening After Hysterectomy
- o Colposcopy Referral List
- o SPCC Colposcopy Form (for colposcopy reporting and billing purposes)*
- o Cervical Cancer Screening Clinical Practice Guidelines – An Interdisciplicary Practitioner Review video
- o Liquid-Based Cytology Resources
- o Cervical Health Resources for HCPs and Patients
- o Cervical Health Resources Tool

**Paper copies of the SPCC Colposcopy Form can be requested free of charge by contacting the SPCC by email at ED.Coordinator@saskcancer.ca or by phone at 1-800-667-0017.*

Participant Screening Resources

✓ Refer people to the following resources available from the SPCC Client Cervical Screening Resources webpage:

- o A Pap Test Can Save Your Life pamphlet
- o Understanding Your Cervical Screening Test Results pamphlet (Pap)
- o Understanding Your Cervical Screening Results: Pap and HPV Test Results pamphlet
- o I'm HPV Positive handout
- o Cervical Screening is Improving poster
- o What Do These Changes Mean to Me poster
- o How Is My Pap Test Changing booklet

Phone:
1-800-667-0017

Email:
ED.Coordinator@saskcancer.ca

Online:
www.saskcancer.ca/spcc

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Cervical screening is improving.

Saskatchewan has introduced HPV reflex testing for objective risk stratification of ASC-US and LSIL cytology.

Based on age and cytology results, an HPV reflex test is automatically run from the same sample to detect the presence of 14 carcinogenic HPV sub-types.

Combined Pap and HPV reflex testing is an even better and safer screening approach for your patients. It supports people to get the right follow-up care, reduces colposcopic overtreatment and safely extends the routine screening interval.

Screening Program for Cervical Cancer

Sask cancer AGENCY

Phone:
1-800-667-0017

Email:
ED.Coorindator@saskcancer.ca

Online:
www.saskcancer.ca/spcc

Address:
200-4545 Parliament Avenue
Regina, SK S4W 0G3

Phone:
639-625-2010

Email:
info@saskcancer.ca

Online:
www.saskcancer.ca