Cervical Cancer Screening

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Objective(s)

1. Describe HPV virology and its role in the natural history of cervical cancer.
2. Choose appropriate screening tests and intervals for patients at average risk for cervical cancer.
3. Identify high-risk populations and apply alternate screening guidelines
4. Apply risk-based guidelines to manage abnormal results in average and high-risk individuals.

Teaching Instructions

Plan to spend at least 30-60 minutes preparing for this talk. Read through the Facilitator Guide/Teaching instructions and familiarize yourself with the Interactive Board. All clickable elements are denoted with a shaded, rounded rectangle and/or mouse cursor icon.

The anticipated time to give this talk is 20 min without cases and 30 min with cases.

Print out copies of the Learner's Handout so they may follow along during the presentation and take notes as you expand on the charts and screening timelines and apply it through the practice cases. Begin with reviewing the objectives for the session.

Objective 1: Describe HPV virology and its role in the natural history of cervical cancer.
(Pathophysiology)

Ask your learners each of the prompt questions and click to reveal the answers.

What causes cervical cancer?

Persistent infection with high-risk human papillomavirus (hrHPV), chiefly types 16 and 18, cause almost all cases of cervical cancer.[1] There are more than 150 types of HPV, among which, about 40 can infect the cervix, and approximately 15 are known to be oncogenic or "high risk." HPV infection is very common among healthy adults[2] and there is a significant rate of transient HPV infection, particularly among young adults.[3] For example, about 70% of new HPV infections are undetectable within 12 months and 90% within 2 years.[4] However, a small percentage of infections persist, leading to precancerous changes, and ultimately progressing to cervical cancer over a period of many years or decades.

What risk factors increase risk for persistent HPV infection?

Factors that increase the risk of persistent HPV infection include older age, oncogenic subtypes, immunosuppression (e.g., HIV, medications), smoking (breakdown of products in cigarette smoke concentrate in cervical mucous and impair immunity), and infection with other STIs or combined oral contraceptive pill (cOCP) use (although it is unclear if this is correlation or causation).[1]

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Cervical Anatomy - What are the parts of the cervix and which cell type is found in each location? How do these varying cell types impact the kinds of cervical cancer?

- The ectocervix is lined with squamous epithelium, while the endocervix is lined by columnar epithelium. Where the ectocervix and endocervix meet is called the squamocolumnar junction.
- The **transformation zone** is a small region of squamous metaplasia (where columnar epithelium is replaced by squamous epithelium) located at the squamocolumnar junction. The HPV virus appears to preferentially infect squamous epithelial cells at the transformation zone beginning with basal layer cells then spreading vertically. HPV inserts its DNA into epithelial cells, leading to increased replication and production of oncoproteins that inhibit tumor suppressor genes leading to uncontrolled replication and resistance to apoptosis. Greater than 90% of cervical cancers develop at the transformation zone,[5] so it is vital to sample this region during screening.
- Given the distinct cellular linings of the cervix, malignancy arising from the ectocervix is squamous cell carcinoma, while malignancy arising from the endocervix is adenocarcinoma (much less common).

Objective 2: Choose appropriate screening tests and intervals for patients at average risk for cervical cancer using USPSTF 2018 or ACS 2020 cervical cancer screening guidelines (*Screening, Average Risk*)

Ask your learners about the role of screening for cervical cancer.
Cervical cancer screening seeks to detect treatable changes and precancers likely to progress to invasive cancer. Over the last century, screening has been highly effective in reducing the incidence, morbidity, and mortality from cervical cancer.[6]

Screening tests - What are the different available technologies or tests that can be used for cervical cancer screening? *Click on "screening tests" to reveal the answer.*
There are three available tests for cervical cancer screening:

- **Cytology**: also known as Pap test or Pap smear
- **Primary HPV test** (high-risk HPV testing only): HPV testing detects the DNA of high-risk types of HPV in a sample taken from the cervix. Most HPV tests genotype the sample to identify if HPV-16, -18, or other high-risk genotypes are present.
- **Co-test**: cytology and HPV test administered together

When a sample from a primary HPV test is positive for HPV, regardless of genotype, this sample should have additional reflex cytology testing performed.

Note that the term "HPV-based testing" is often used in guidelines and can represent Primary HPV testing **or** co-testing.

Who do we screen? - What cervical cancer screening guidelines are available for average risk individuals?
Screening recommendations have greatly evolved over time, largely due to our improved understanding of the natural history of cervical cancer, the causal role of hrHPV infection, and changing technologies. We are going to review two currently recommended guidelines, USPSTF 2018 and ACS 2020. Either is an acceptable method for screening average-risk individuals.

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- **US Preventive Services Task Force (USPSTF)**:[7]

Age range	Recommendation	Notes
21-29 years	Cytology (Pap smear) alone every 3 years	HPV-based testing in those <30 because of high prevalence of transient HPV in this age group.
30-65 years	Cytology (Pap smear) every 3 years - OR - HPV-based testing (primary HPV testing OR co-testing) every 5 years	Cytology (Pap smear) alone has lower sensitivity for precancer and cancer (especially adenocarcinoma) than HPV-based testing HPV-based testing every 5 years is an effective screening strategy due to higher sensitivity and the long preclinical phase from hrHPV infection to development of precancerous lesions and then cervical cancer.

- **2020 American Cancer Society (ACS)**:[6]

Age range	Recommendation	Notes
25-65 years	Primary HPV testing every 5 years is preferred Acceptable alternatives (given access to primary HPV testing may be limited as there are currently only two FDA approved primary HPV tests): - Co-testing every 5 years - Cytology (Pap smear) alone every 3 years	Start at age 25 because cervical cancer incidence and mortality is low in women <25. - In young women, there is high prevalence of HPV but most infections are easily cleared and do not cause persistent cytologic abnormalities. Screening this age group can lead to unnecessary treatment and associated harms, including potential adverse obstetric outcomes. - Primary HPV testing instead of cytology (Pap smear) in women 25–29 years old increases life-years saved, at the cost of additional colposcopies. Primary HPV testing is more sensitive than cytology (Pap smear) alone and is more efficient than co-testing. - Co-testing offers very little incremental benefit in detection as compared to primary HPV testing but increases the number of procedures and the risk for harms.

- Both groups agree on:[6, 7]
  - When to stop: *Click on "when do we stop?" to reveal the answer.*
    - Over age 65 if at average risk for cervical cancer with no history of CIN 2+ (CIN2 or worse) in the past 25 years and with adequate prior screening:
      - 3 consecutive negative cytologies in last 10 years (most recent within 3 years)
      - 2 consecutive negative HPV-based tests in last 10 years (most recent within 5 years)
  - History of hysterectomy: *Click on "what if they are post-hysterectomy?"*.

- Screening can stop if patients have a total hysterectomy (with removal of the cervix) for benign indications with no history of CIN 2+ in the past 25 years
- Follow age-specific screening recommendations regardless of HPV-vaccination status.

Objective 3: Identify high-risk populations and apply alternate screening guidelines *(Screening, High Risk)*

Ask learners to give examples of individuals who might be at higher risk for developing cervical cancer, then click on the "high-risk" tab in the left-hand navigation panel to reveal the answer.

Patients who are immunocompromised or on immunosuppression are at higher risk for cervical cancer and have distinct screening and management recommendations. This group includes patients with HIV, solid organ transplant, stem cell transplant, lupus, and inflammatory bowel disease and rheumatoid arthritis on active immunosuppression.

Patients with HIV: Cervical cancer screening guidelines for persons living with HIV have been well-supported by evidence from retrospective and prospective studies. Current CDC guidelines for patients infected with HIV [8]

Age range	Recommendation	Notes
<30 years	Cytology (Pap smear) at baseline, then annually for 3 years. - OR - If three consecutive Pap smears are normal, then Pap smears every 3 years (until age 30)	Screening should begin at time of diagnosis but not before the age of 21. Cytology (Pap smear) only is recommended. Co-testing is not recommended due to high HPV prevalence in this age group.
≥30 years	Cytology (Pap smear) only: - Cytology (Pap smear) only at baseline, then annually for 3 years (if not already completed <30 years) - If three consecutive Pap smears are normal, then Pap smears every 3 years - OR - Co-testing: every 3 years	Cytology or Co-testing is acceptable. Screening should continue throughout a patient's lifetime (and not, as in the general population, end at 65 years of age), considering the patient's life expectancy.

Post-hysterectomy: Unlike average risk patients, patients with HIV who have undergone total hysterectomy for benign causes still require annual screening with cytology and co-testing in the following situations:

- Progression of HIV disease
- Inadequate viral suppression with ART

Non-HIV immunosuppressed patients: Recommendations remain limited due to lack of quality evidence. A panel of health care professionals involved in cervical cancer research and care proposed that screening guidelines for patients who are immunocompromised but do not have HIV follow either: [9]

- Current Centers for Disease Control and Prevention (CDC) guidelines for patients infected with HIV – this can be followed by patients with solid organ transplant, hematopoietic stem cell transplant, systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) on immunosuppression, or rheumatoid arthritis (RA) on immunosuppression.
- Guidelines for the general population – this can be followed by patients with IBD or RA not on immunosuppressive therapy or patients with type 1 diabetes mellitus.

Objective 4: Apply risk-based guidelines to manage abnormal results in average risk individuals. *(Management)*

Management (Average Risk)

If your patient is at average risk for developing cervical cancer, use the **American Society of Colposcopy and Cervical Pathology (ASCCP) 2019 risk-based management guidelines**[10] to interpret HPV and/or cytology (Pap smear) results and colposcopic biopsy results and decide on appropriate next steps. These guidelines have been officially endorsed by the American College of Obstetricians and Gynecologists (ACOG). ASCCP has created a management guidelines application online (free, https://app.asccp.org) and for smartphones (for purchase).

These guidelines are based on the principal of "equal management for equal risk" and therefore follow a risk-based rather than a results-based approach to determine management. Specifically, management decisions are based on the clinical question: ***is the immediate risk of CIN3+ (CIN3, AIS, or cancer) greater than 4%?***

Based on data from a prospective longitudinal cohort of 1.5 million patients from Kaiser Permanente Northern California, the tool estimates a patient's risk using their current screening test results and prior screening test and biopsy results (if known), while considering personal factors such as age and immunosuppression. For example: the longer a hrHPV infection has been present, the higher the risk of CIN 3+. Additionally, HPV type (-16 or -18 versus other) impacts risk.

- If **immediate risk** is <4%, then the tool looks at the **5-year risk** of CIN3+ and finds the correct surveillance interval: *Click on "Determine surveillance interval" to reveal surveillance.*
  - >0.55% 5-yr risk → return in 1 year
  - 0.15–0.54% → return in 3 years
  - <0.15% → return in 5 years
- If the tool determines **immediate risk** of CIN3+ is >4%, then the level of risk determines the correct further management: *Click on "Further management" to reveal next steps.*
  - 4-24% → Colposcopy (e.g., to confirm if CIN3+ is present prior to treatment)
  - 25-59% → expedited treatment or colposcopy (e.g., depending on if a patient desires future pregnancy)
  - 60-100% → expedited treatment (60–100% immediate risk) such as excision or cervical ablation
- Treatment options include:
  - Excision - cold knife conization, loop electrosurgical excision procedure [LEEP], laser cone. Generally preferred to ablative treatment, particularly for histologic HSIL (CIN2 or CIN3) and AIS because tissue and pathology can be obtained.

- Cervical ablation - cryotherapy, CO_2 laser ablation, thermal ablation
- Hysterectomy

BONUS: Pap smear vs. Colposcopy

Click on "colposcopy" to further teach more about the differences between Pap smear and colposcopy. Ask your learners to explain the difference between a Pap smear and colposcopy? What results you might receive with each test?

- **Pap smear (Cytology)** - the sample collected during a Pap smear is reviewed by a pathologist and a cytology report is generated. Cytology refers to the examination of exfoliated cervical cells under a microscope to check for the presence of abnormal cells or changes suggestive of acute HPV infection, precancer or cancer.[6]
  - *Cytologic findings:* Possible cytology results include (roughly in order of increasing prevalence of abnormal cells):
    - Negative for intraepithelial lesion or malignancy (NILM)
    - Atypical squamous cells of undetermined significance (ASC-US)
    - Low-grade intraepithelial lesion (LSIL)
    - Atypical squamous cells, cannot rule out high-grade squamous intra-epithelial lesion (ASC-H)
    - Atypical glandular cells (AGC)
    - High-grade intraepithelial lesion (HSIL)
  - If a patient's cytology and/or HPV result and history suggest their risk of CIN3+ is elevated, the next step may be to undergo colposcopy.
- **Colposcopy** – colposcopy is an in-office procedure, during which the cervix is examined using a high-power microscope (colposcope) with the addition of acetic acid to help identify any abnormal appearing areas requiring biopsy to rule out precancerous or cancerous changes.[11] When a biopsy is performed, this sample is reviewed by a pathologist and a histology report is generated. Histology refers to the examination of tissue architecture under a microscope to assess the amount of vertical extension of abnormal cells into the cervical epithelium and staining for p16 (a tissue marker of HPV oncogene overexpression) to determine histologic grade. Histologic grade is often reported using a hybrid grading system.
  - *Histologic findings:* Possible results include (roughly in order of increasing prevalence of abnormal cells):
    - No carcinoma in-situ or no cervical intraepithelial neoplasia (CIN)
    - Histologic LSIL or CIN 1
    - Histologic HSIL or CIN 2-3 or unspecified
    - Adenocarcinoma in situ (AIS)

Management (High Risk)

Immunosuppressed patients: patients with HIV, prior transplant (stem cell or solid organ), IBD or RA on immunosuppression, chronic steroid use

- Refer to ASCCP web or mobile app "Special situation" → "Immunosuppressed" for quick reference[10]
- Colposcopy for:
  - ASC-US, HPV-positive
  - LSIL or more concerning cytology, regardless of HPV test results (if done)

Previous history of high-grade cervical dysplasia (CIN 2+):[10] patients with a history of high-grade dysplasia require increased short term and long-term surveillance.

- Short-term follow-up after treatment
    - If still has a cervix: HPV-based testing at 6 months (not necessary if treated with total hysterectomy), followed by
    - Three consecutive annual HPV-based tests (regardless of treatment)
- Long-term surveillance
    - HPV-based testing at 3-year intervals for a minimum of 25 years (even if >65 years old)
        - Use shared decision making to decide about continuing q3 year screening beyond 65 years if 25-year surveillance period is complete
            - Long-term population studies suggest persistent twofold increase in cervical cancer risk after treatment of histologic HSIL, which continues for at least 25 years and seems to be increased for patients older than 50
            - As cervical cancer risk seems to remain above general population levels, continued screening is acceptable, as long as the patient remains in good health
        - Discontinuation of screening is recommended if a patient has a limited life expectancy

Take Home Points:

1. Persistent infection with oncologic subtypes of HPV cause nearly all cases of cervical cancer.
2. Routine screening for average risk individuals can be done with cytology alone, HPV testing with reflex cytology, or co-testing (both). USPSTF and ACS slightly differ in their recommendations but agree that screening can stop at age 65.
3. Management of abnormal results and interval of routine screening is based on immediate risk of CIN3, as calculated by the ASCCP application.
4. Patients with immunocompromise or immunosuppression are at higher risk of HPV-related cervical cancer and have unique screening and management protocols.

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