ACOG
The American College of Obstetricians and Gynecologists

Gynecologic Cancer Screening for the Generalist

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President Elect

Disclosures

- I have no actual or potential conflict of interest in relation to this program/presentation.

Objectives

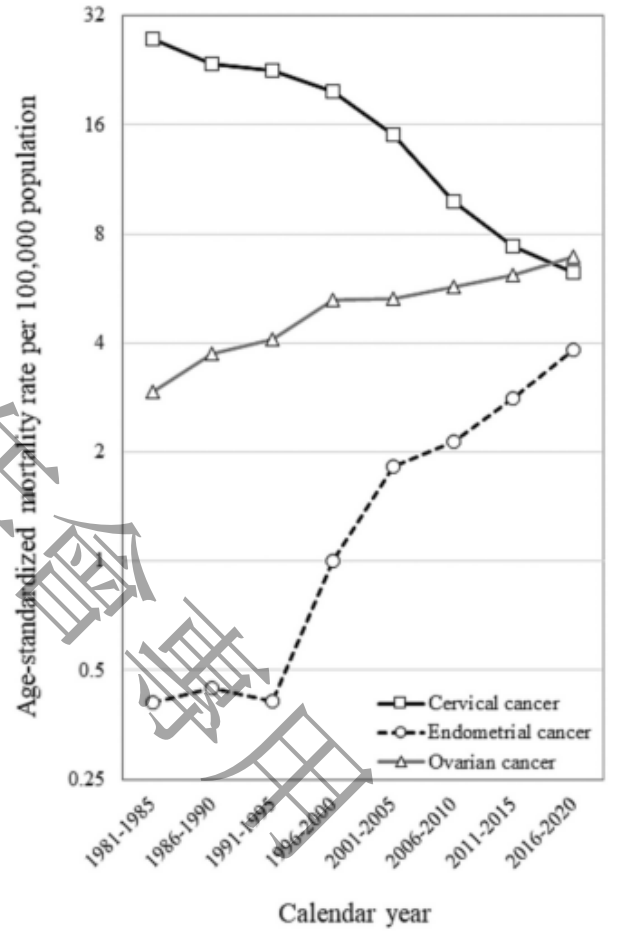
- To understand risk factors, risk reduction, and evaluation for cervical, endometrial, ovarian and vulvar and vaginal cancers

- To review recommendations for screening of cervical, endometrial, ovarian and vulvar and vaginal cancers in the United States

Gynecologic Cancers in Taiwan

2019-2020	Global Statistics	Taiwan
Most common cancers		
Cervical	4th	9th
Endometrial	6th	5th
Ovarian	8th	7th
Leading cause cancer mortality		
Cervical	4th	8th
Endometrial	14th	11th
Ovarian	8th	7th

- To reduce disease burden in Taiwan, health authorities:
  - Implemented a national cervical cancer screening program in 1995, providing free pap smear examination annually for women older than 30 years.
  - Provided free HPV vaccines for every girl in the first year of junior high school (i.e., girls aged 11 to 12 years) since December 2018
- Did not find and screening programs or relevant health policies for prevention of endometrial and ovarian cancers
  - Increasing mortality rate and threat to women's reproductive health within gynecologic cancers



By understanding risk factors, potential risk reductions, screening and evaluation, we can then educate clinicians and patients, create guidelines and eliminate barriers to access through infrastructure changes.

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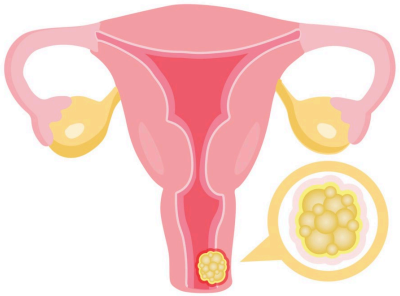
Su, Shih-Yung., 2023. Mortality trends and disease burdens of cervical, endometrial and ovarian cancers from 1981 to 2020 in Taiwan. Preventative Medicine. 172; 107551.

Cervical Cancer – Epidemiology



- Most common gynecologic malignancy in the world
  - In 2020, estimated 604,000 new cases and 342,000 deaths (90% of deaths in low- and middle-income countries)
  - In US, 11,500 cases diagnosed/year, 4,000 women die each year
  - Around 85% of the global burden occurs in undeveloped countries
  - Highest rates of cervical cancer incidence and mortality are in sub-Saharan Africa, Central America and South-East Asia
  - Increased rates reflect inequalities in access to vaccination, screening and treatment services, risk factors including HIV prevalence, and social and economic determinants such as sex, gender biases and poverty
- 2 major subtypes
  - Squamous cell carcinoma accounts for approximately 70% of invasive cervical cancer
  - Adenocarcinoma and its variants account for about 25%
  - Neuroendocrine carcinomas and other rare cell types comprise the remaining 3% to 5% of cases
- Despite decrease in squamous cell carcinoma seen over past 5 decades, incidence of cervical adenocarcinoma increasing, especially in younger women
- Adenocarcinoma associated with greater probability of distant recurrence, and poorer overall survival

Risk Factors

- Most important risk factor for development of invasive cervical cancer – **Infection with HPV**
- Other risk factors:
  - Cigarette smoking
  - Lower socioeconomic status
  - Multiple sexual partners
  - Early age of first intercourse
  - High parity
  - Coinfection with other sexually transmitted diseases
  - Presence of immunocompromised conditions (HIV or pharmacologic)

HPV

- Most common STI in US
- At least 200 genotypes of HPV have been described
- Detected in 99.7% of cervical cancers
- Typically self-limited, asymptomatic, and not diagnosed
- Most HPV infections are transient, with little risk of progression
- Persistent cervical infection with high-risk HPV strongly predicts subsequent risk of high-grade dysplasia or cancer
  - 10-year risk for development of precancerous lesions – 13%-17%
  - Risk of progression from precancerous lesions to invasive disease – 31% over 30 years

History of Screening and Where Evidence Took Us

- Previous traditional screening – periodic screening using cytology-based methods alone
- Currently in US, liquid-based cytology used in more than 90% of cytology testing – improved sample quality compared with conventional cytology
- Turning point – ability to test for high-risk HPV DNA
  - Allowed detection of viral strains most commonly associated with development of cancer (even with negative cytology)
- U.S. Preventive Services Task Force - independent group of national experts in prevention and evidence-based medicine
  - Make evidence-based recommendations about clinical preventive services such as screenings, counseling services, or preventive medications
- 2012 USPSTF made initial recommendations
  - Systematic review of the evidence of liquid-based cytology and high-risk HPV screening
  - Review included studies meeting criteria for fair and good-quality and focused on routine screening in populations in developed countries
  - In addition, USPSTF in 2015 commissioned decision analysis modeling study to evaluate:
    - Optimal ages at which to begin and end screening
    - Optimal screening intervals
    - Benefits and harms of different screening strategies

Screening in Women < 21 Years Old

USPSTF considered following types of evidence to determine when screening for cervical cancer should begin:

- Rare among women < 20 years - 0.1% of all incident cancer cases occur in this age group
- Precancerous lesions uncommon
- Estimated prevalence of CIN 3 among women < 20 years is 0.2%
- Concurrent false-positive cytology rate of about 3.1%

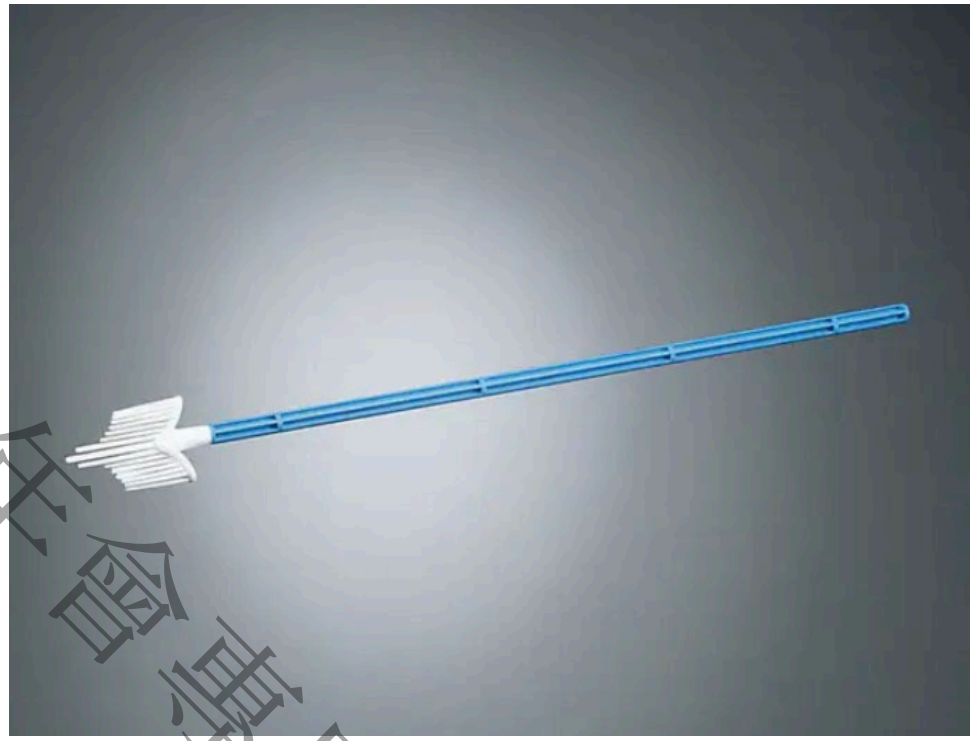
Decision analysis model commissioned for the 2012 USPSTF recommendation showed no net benefit to starting screening before age 21 years

- USPSTF did not look at evidence for women younger than 21 years living with HIV or who are otherwise at higher risk of cervical cancer - outside the scope of this recommendation

Screening in Women 21-29 Years Old

- Knew screening with cytology should start at age 21, but given high prevalence of transient HPV infection among adolescents and young adults, when should HPV testing begin?
  - 4 trials compared screening with high-risk HPV testing alone vs cytology alone found consistently higher detection rate among younger women (< 30 or 35 years)
    - ➢ Concern for overdiagnosis and overtreatment of transient infection
    - ➢ Modelled screening with cytology alone to high-risk HPV testing alone at 25, 27 and 30 years
    - ➢ Found minimal differences in terms of life years gained 30 vs 25
    - ➢ But increased number of colposcopies when start at 25

- **Switching from cytology alone to high-risk HPV testing alone at age 30 appears to offer similar benefits in terms of cancer reduction as switching at younger ages but with fewer associated tests and procedures**



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Screening in Women 30-65 Years Old

- USPSTF found 8 trials of cervical cancer screening:
  - 4 RCTs compared screening with high-risk HPV testing alone vs cytology alone
  - 4 RCTs compared screening with cytology alone vs cotesting (cytology in combination with high-risk HPV testing)

- No trials directly compared using high risk HPV testing alone vs contesting

- Given low mortality rate in countries with screening, impractical to directly measure effects on mortality through clinical trials
- Therefore, trials measured rate of CIN 3+ (CIN 3 or worse) detection
  - Some trials also reported the rate of invasive cervical cancer

- Cytology alone has:
  - Lower sensitivity than primary high-risk HPV testing or cotesting
  - A lower false-positive rate and rate of additional testing

- Primary high-risk HPV testing has adequate sensitivity

- **Cotesting may detect slightly more cases of CIN than screening with high-risk HPV testing alone but with a significant increase in the number of tests and procedures**

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Screening in Women >65 Years Old

- No direct evidence on when to stop screening
- None of the screening trials enrolled women > 65 years

- USPSTF considered the incidence of cervical cancer in older women and whether the pattern of cervical cancer incidence differs in screened vs unscreened women
  - Incidence and prevalence of CIN peak in the mid-reproductive years and begin to decline in approximately the fourth decade of life, seen in both screened and unscreened women
  - Cervical cancer not more aggressive or rapidly progressive in older vs younger women
  - Rate of HGSIL lesions diagnosed by cytology is low in older women who have had adequate prior screening

- Decision model commissioned by the USPSTF showed extending screening beyond age 65 would have no significant benefit - maintained the current practice **of stopping screening at age 65 years in adequately screened women**

- *KP registry study found majority of cases of invasive cervical cancer in women > 65 years occurred in those who had not met criteria for stopping screening*

- *Suggested that the decision to stop screening at age 65 years should only be made after confirming that the patient has received prior adequate screening*

Updated Screening Guidelines

Table 1. USPSTF Recommendations for Routine Cervical Cancer Screening

Population*	Recommendation	USPSTF Recommendation Grade†
Aged less than 21 years	No screening	D
Aged 21–29 years	Cytology alone every 3 years‡	A
Aged 30–65 years	Any one of the following: • Cytology alone every 3 years • FDA-approved primary hrHPV testing alone every 5 years • Cotesting (hrHPV testing and cytology) every 5 years	A
Aged greater than 65 years	No screening after adequate negative prior screening results§	D
Hysterectomy with removal of the cervix	No screening in individuals who do not have a history of high-grade cervical precancerous lesions or cervical cancer	D

Abbreviations: FDA, U.S. Food and Drug Administration; hrHPV, high-risk human papillomavirus testing.

The American College of Obstetricians and Gynecologists (ACOG) joins ASCCP and the Society of Gynecologic Oncology (SGO) in endorsing the U.S. Preventive Services Task Force (USPSTF) cervical cancer screening recommendations [1], which replace ACOG Practice Bulletin No. 168, *Cervical Cancer Screening and Prevention*, as well as the 2012 ASCCP cervical cancer screening guidelines [2].

"Management of abnormal cervical cancer screening results should follow current ASCCP guidelines"

Do not screen
- *Women post hysterectomy with removal of cervix without history of high-grade precancerous lesion or cervical cancer (not at risk for cervical cancer)*

Adequate prior negative screening
- *Documentation (or a reliable patient report) of 3 consecutive negative cytology results or 2 consecutive negative co-test results within the previous 10 years with the most recent test within the past 5 years*

Individualized follow up for women with...
- *Previous diagnosis of high-grade precancerous cervical lesion or cervical cancer*
- *Treated for CIN 2 or higher within the past 20 years*
- *In utero exposure to diethylstilbestrol*
- *Immunocompromised*
  - *HIV+*
  - *Received solid organ transplantation*

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Updated Cervical Cancer Screening Guidelines. ACOG Practice Advisory. April 2021, Reaffirmed April 2023.

Management of Abnormal Screening Test Results
Risk-Based Management: A New Framework

- Previous 2012, American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines relied on test results-based algorithms
- 2019 consensus ASCCP guidelines follow a risk-based approach (defined as treating patients according to estimated precancer risk) to determine follow up and management
  - Also, recommend consideration of a patient's screening history, along with current test results, to guide clinical decision making.
- Precancer risks precisely estimated using current and past cytology and HPV test and biopsy results from more than 1.5 million individuals who were followed up for up to 15 years at KP No CA
- Reduces testing in low-risk patients while increasing testing in high-risk patients
  - Results in fewer procedures and better cancer prevention
- When implementing, clinicians will more frequently encounter abnormal results because:
  1. high-risk individuals screen more often than low-risk individuals
  2. colposcopy is deferred for some patients, but these individuals require follow-up in 1 year
  3. a higher proportion of patients undergoing colposcopy will be diagnosed with precancer requiring treatment because colposcopy is deferred for lower-risk patients

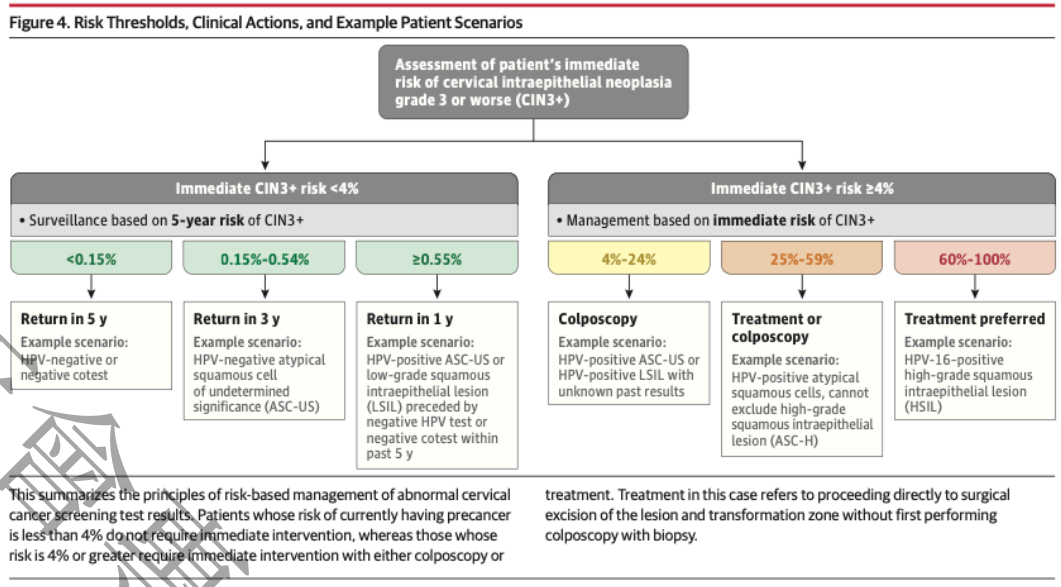

Figure 4. Risk Thresholds, Clinical Actions, and Example Patient Scenarios

This summarizes the principles of risk-based management of abnormal cervical cancer screening test results. Patients whose risk of currently having precancer is less than 4% do not require immediate intervention, whereas those whose risk is 4% or greater require immediate intervention with either colposcopy or treatment. Treatment in this case refers to proceeding directly to surgical excision of the lesion and transformation zone without first performing colposcopy with biopsy.

Perkins, RB. Cervical Cancer Screening. A Review. JAMA, : 330(6);547-558.

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Management of Abnormal Screening Test Results

Table. Management Recommendations for Patients Aged 25 Years or Older (2019 ASCCP Risk-Based Management Consensus Guidelines)

Current HPV test result	Current cytology (Papanicolaou test) or biopsy result	Prior results	Management recommendation	Risk of CIN3+[10,49]
Recommendation for 5-y follow-up				
Negative	NILM or no cytology	Unknown or HPV-negative	HPV test or HPV/cytology cotest in 5 y	≤0.14% at 5 y
Negative	NILM	ASCUS HPV-negative	HPV or HPV/cytology cotest in 5 y	0.14% at 5 y
Negative	NILM	3 consecutive negative HPV tests after colposcopy confirming low-grade abnormality (eg, 7-y normal follow-up)	HPV or HPV/cytology cotest in 5 y	0.03% at 5 y
Recommendation for 3-y follow-up				
Negative	ASC-US	Unknown	HPV test or HPV/cytology cotest in 3 y	0.40% at 5 y
Negative	NILM	Low-grade abnormal cytology (ASC-US, LSIL) and colposcopy with no CIN2+ (HSIL) found	HPV test or HPV/cytology cotest in 3 y for 3 consecutive negative results before returning to a 5-y screening interval	0.18% at 5 y
Negative	NILM	HIV+ or immunosuppressed	HIV+ and immunosuppressed: screen at 3-y intervals	Special situation: opportunistic infection guidelines[33]
Negative	NILM or no cytology	Treatment of CIN2+ followed by 3 consecutive negative HPV tests or HPV/cytology cotests	Following initial surveillance after CIN2+ treatment: screen every 3 y for at least 25 y through 65 y; may continue at 3-y intervals while patient is in good health	0.35% at 5 y for HPV-negative NILM; 0.44% at 5 y for HPV-negative only
Recommendation for 1-y follow-up				
Negative	LSIL	Unknown or HPV-negative[a]	HPV test or HPV/cytology cotest in 1 y	0.44%-1.1% current risk; 0.79%-2.0% at 5 y
Positive	NILM	Unknown or HPV-negative[a]	HPV test or HPV/cytology cotest in 1 y	0.74%-2.1% current risk; 2.3-4.8% risk at 5 y
Positive	ASC-US or LSIL	Negative screening results with HPV testing or negative HPV/cytology cotesting within past 5 y[b]	HPV test or HPV/cytology cotest in 1 y	2.0%-2.1% current risk; 3.8% at 5 y
Positive	ASC-US or LSIL	Colposcopy within the past year with no CIN2+ (HSIL) found and preceded by NILM, ASC-US, or LSIL cytology	HPV test or HPV/cytology cotest in 1 y	2.1%-3.1% current risk; 6.0% at 5 y
Positive	p16/Ki-67 dual-stain negative[c]	Noncontributory	HPV test in 1 y	0.75% current risk, 1.5% at 3y
	Colposcopy with normal or CIN1 (LSIL) biopsy results	NILM, ASCUS, or LSIL cytology	HPV test or HPV/cytology cotest in 1 y (Note observation is preferred to treatment for persistent results of CIN1 [LSIL])	0.53% current risk; 2.6% at 5 y
	Colposcopy with normal or CIN1 (LSIL) biopsy results	HSIL cytology	Colposcopy plus either HPV test or HPV/cytology cotest at year 1, HPV test or HPV/cytology cotest at year 2, then HPV test or HPV/cytology cotest at 3-y intervals for at least 25 y through age 65 y and may continue while in good health	Special situation[10,d]
	Colposcopy with normal or CIN1 (LSIL) biopsy results	ASC-H cytology	HPV test or HPV/cytology cotest at 1 and 2 y, then HPV test or HPV/cytology cotest at 3-y intervals for at least 25 y through age 65 y and may continue while in good health	Special situation[10,d]
	Colposcopy with normal or CIN1 (LSIL) biopsy results	AGC cytology	Repeat HPV/cytology cotest at years 1 and 2, then HPV/cytology cotest in 3 y, then HPV test or HPV/cytology cotest at 3-y intervals for at least 25 y through age 65 y and may continue while in good health	Special situation[10,d]
Recommendation for repeat testing				
Unsatisfactory cytology			Repeat cytology as soon as convenient and no later than 4 mo; If both Papanicolaou and HPV test were performed, repeat both; A negative HPV result is not considered valid in the setting of an unsatisfactory cytology result Note: absent transformation zone is not unsatisfactory and should be managed as a NILM result	Special situation[10,d]

(continued)

Table. Management Recommendations for Patients Aged 25 Years or Older (2019 ASCCP Risk-Based Management Consensus Guidelines) (continued)

Current HPV test result	Current cytology (Papanicolaou test) or biopsy result	Prior results	Management recommendation	Risk of CIN3+[10,49]
Recommendation for 6-mo follow-up				
	CIN2: observation[e]		If observation is elected for CIN2, colposcopy plus either HPV test or HPV/cytology cotest is recommended at 6-mo intervals for up to 2 y Treatment is recommended if CIN3 develops at any time or CIN2 persists for 2 y If CIN2 regresses at 6 and 12 mo visits, repeat HPV test or HPV/cytology cotest in 1 y If negative, repeat HPV test or HPV/cytology cotest at 3-y intervals for at least 25 y through age 65 y and may continue while in good health	Special situation[10,d]
	CIN2+ (HSIL): after treatment		Repeat HPV test or HPV/cytology cotest at 6 mo, 18 mo, 30 mo (until 3 consecutive negative results obtained) then move to 3-y intervals for at least 25 y through age 65 y and may continue while in good health	Multiple-risk estimates[49]
	AIS: after treatment		HPV test, cytology, and ECC at 6-mo intervals for 3 y, then annually for 2 y, then HPV testing or HPV/cytology cotesting at 3 y intervals for at least 25 y or while in good health Hysterectomy preferred when childbearing complete	Special situation[10,d]
Recommendation for colposcopy				
Negative or no HPV test	ASC-H	Noncontributory	Colposcopy	Special situation[10,d]
Noncontributory	AGC	Noncontributory	Colposcopy with ECC and perform endometrial biopsy if age ≥35 y or age <35 y with obesity or anovulation	Special situation[10,d]
Noncontributory	Atypical endometrial cells	Noncontributory	Endometrial and endocervical biopsy; if both negative, colposcopy	Special situation[10,d]
Positive	Noncontributory	HPV positive[f]	Colposcopy recommended for HPV-positive results occurring twice consecutively due to elevated CIN3+ risk associated with persistent HPV infection	Risk varies by situation[10]
Positive for genotype HPV-16 and/or HPV-18	Noncontributory	Noncontributory	Colposcopy for all HPV-16 or HPV-18 results	Risk varies by situation[10]
Positive	ASC-US or LSIL	Unknown or HPV-positive	Colposcopy	4.4% current risk
No HPV test	LSIL[g]	Noncontributory	Colposcopy	Special situation[10,d]
Positive	p16/Ki-67 dual-stain positive[c]	Noncontributory	Colposcopy	12% current risk
Recommendation for colposcopy or expedited treatment[h]				
Positive	ASC-H	Noncontributory	Colposcopy or expedited treatment	26% current risk
Positive: untyped Positive: genotype other than HPV-16 negative No HPV test	HSIL	Noncontributory	Colposcopy or expedited treatment	49% current risk for HPV-positive untyped
Recommendation for expedited treatment[i]				
Positive: genotype HPV-16	HSIL	Noncontributory	Expedited treatment	60% current risk
Positive	HSIL	No screening in >5 y	Expedited treatment	64% current risk

Abbreviations: AGC, atypical glandular cells; AIS, adenocarcinoma in situ; ASC-H, atypical squamous cells cannot exlude high-grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; ECC, endocervical curettage; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion or malignancy.

[a] Colposcopy may be warranted for patients with a history of high-grade lesions. These include: AIS, CIN3, histologic HSIL, CIN2, cytologic HSIL, ASC-H, AGC.

[b] Negative HPV test or HPV/cytology cotest results only reduce risk sufficiently to defer colposcopy if performed for screening purposes within the last 5 years. Colposcopy is still warranted if negative HPV test or cotest results occurred in the context of surveillance for a prior abnormal result.

[c] World Health Organization guidelines support dual stain for triage of HPV-positive screening test results; US guidelines were pending at the time of this review.

[d] Special situation refers to scenarios for which CIN3+ risk estimates were not available or when other criteria were used for guidelines.

[e] Patients should be counseled on their preference for treatment vs serial colposcopy. Considerations include but are not limited to age, future pregnancy considerations, ability and desire to undergo repeated colposcopy vs treatment.

[f] Prior cytology results do not modify the recommendation; colposcopy is always recommended for 2 consecutive HPV-positive tests (note if colposcopy is performed between the 2 HPV tests, they are not considered consecutive).

[g] Patients aged 24 y or younger are managed differently: after ASC-US or LSIL results, repeat cytology is recommended at 1 y and 2 y with colposcopy if ASC-US or LSIL persists at 2 y. Colposcopy is recommended for cytology results of AGC, ASC-H, HSIL.

[h] Expedited treatment is defined as proceeding to excisional treatment without first performing colposcopy with biopsy. See footnote e for considerations related to shared decision-making.

[i] Expedited treatment is preferred for nonpregnant patients aged 25 y or older. Colposcopy with biopsy is an acceptable option if desired by patient after shared decision-making. Considerations are described in footnote e. Note that if referring for treatment would delay diagnosis, colposcopy should be performed because up to 8% of patients with these results will have invasive cancer.

Perkins, RB. Cervical Cancer Screening. A Review. JAMA, : 330(6);547-558.

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Implementation

- New management guidelines are lengthy
- To help navigate this information and to facilitate implementation, a free web-based decision management tool has been developed (https://app.asccp.org/)
- In addition, a smartphone app is available (https://www.asccp.org/mobile-app)

Prevention Vaccination!

Box 4
Human papillomavirus Advisory Committee on Immunization Practices vaccine recommendations

- Routine HPV vaccination at age 11 or 12 years (can be given as early as 9 years).
- Vaccination for girls and women through age 26 years and for boys and men through age 21 who were not adequately vaccinated previously. Transgender persons and men who have sex with men should be vaccinated through age 26 years if they were not adequately vaccinated previously.
- For persons initiating vaccination before their 15th birthday, the recommended immunization schedule is 2 doses of HPV vaccine (0, 6–12 month schedule).
- For persons initiating vaccination after their 15th birthday, the recommended immunization schedule is 3 doses of HPV vaccine (0, 1–2, 6 month schedule).
- If the vaccination schedule is interrupted, the series does not need to be restarted. The number of recommended doses is based on age at administration of the first dose.

From Meites E, Kempe A, Markowitz LE. Use of a 2-dose schedule for human papillomavirus vaccination - updated recommendations of the advisory committee on immunization practices. MMWR Morb Mortal Wkly Rep 2016;65:1405–8.

- Staples JN, Duska LR. Cancer Screening and Prevention Highlights in Gynecologic Cancer. Obstet Gynecol Clin N Am 46 (2019) 19–36.

HPV vaccine – effective method for preventing infection with HPV

- 2 HPV vaccines are licensed in the United States
- 6 HPV vaccines available globally

Vaccines are prophylactic

- Do not have therapeutic effect on HPV-related disease or disease progression in those already infected with HPV

WHO's Strategy for Elimination

- Adopted unanimously by the World Health Assembly in August, 2020
- Set three targets to meet by 2030 to put countries on the path to elimination of cervical cancer
  - 90% of girls vaccinated with the human papillomavirus (HPV) vaccine by age 15 years;
  - 70% of women screened with a high-performance test by age 35 years and again at 45 years
  - 90% of women with cervical disease receiving treatment.
- All countries made a commitment to eliminate cervical cancer as public health problem
- Defined elimination as reducing the number of new cases annually to 4 or fewer per 100 000 women
- Modelling estimates:
  - 74 million new cases of cervical cancer can be averted
  - 62 million deaths can be avoided

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Work towards Best Practice Guidelines

- Centers for Disease Control and Prevention recognized need for educational materials for clinicians on prevention and early diagnosis of gynecologic cancer
- Awarded funding to ACOG
- Convened panel of experts in evidence review from:
  - Society for Academic Specialists in General Obstetrics and Gynecology
  - Society of Gynecologic Oncology
- Reviewed relevant literature, best practices, and existing practice guidelines to work to develop evidence-based educational materials for women's health care clinicians about gynecologic cancer
- Published 3 executive summaries in 2023 in our Green Journal

Uterine Cancer

- Common cancer in female reproductive organs, mainly occurring in postmenopausal women
  - Globally, 435,041 new incident cases and 91,640 deaths from uterine cancer in 2019
  - Uterine cancer-related mortality has increased by an average of 1.9% per year from 1971 to 2014
  - Incidence of uterine cancer higher in high-income regions or countries, especially in North America and Europe
- 4th most common cancer in the US, accounting for 7% of cancers affecting women
  - Rates rose on average 1.3% per year from 2007 to 2016
- Most cases are confined to the uterus at diagnosis
- Good prognosis typically
  - Accounts for only 4% of female cancer-related deaths
- Divided into endometrial cancers affecting the epithelial lining and much less common mesenchymal malignancies, which represent only 3% of uterine cancers

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Endometrial Cancer – Epidemiology and Classification

Can affect women of all ages	Incidence and mortality rates increasing since 2007	Type 1 cancers	Type 2 cancers	New Classification

• Most commonly diagnosed 55 – 64 years, median age of 63 years	• Aggressive high-risk subtypes more frequent
	  • Mortality rate increased more than the incidence rate
	• Increasing significantly in Hispanic women < 50
	• Traditionally, classified into type 1 and type 2 cancers
		• Estrogen-driven, low-grade (grade 1–2) endometrioid tumors
		  • Account for approximately 65–80% cases
		  • Usually diagnosed at an early stage
		  • 80% limited to the uterus at diagnosis
		• Good prognosis, 5-year survival rates 80–90% in stage I disease
		• Rates of type 1 cancer highest in White women in Western populations
			• More common in older women
			  • Characterized by more aggressive behavior and worse prognosis
			  • Disproportionately affect non-Hispanic Black women
			  • Extrauterine disease more common at diagnosis
			  • Risk of recurrence of both local and distant disease higher
				• Type 1 and 2 classification useful framework for categorizing endometrial cancer
				  • Recent trends shifted toward molecular-based risk stratification systems
				  • May eventually replace decision making based on histology alone
				  • Being evaluated in an ongoing prospective trial

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Endometrial Cancer Subtypes

Characteristics of Type 1 and 2

Table 1
Characteristics of type 1 and type 2 endometrial carcinomas

Characteristic	Type 1 (85%)	Type 2 (15%)
Histology	Endometrioid grades 1–2	Endometrioid grade 3, serous, clear cell, carcinosarcoma, otherwise undifferentiated carcinomas
Genetic alteration	Loss of PTEN function, KRAS, CTNNB1 and PIK3CA and MLH1 promoter hypermethylation	P53, Her-2/neu overexpression and amplification, inactivation of p16, loss of E-cadherin
Background histology	Hyperplasia	Atrophy
Preceding histology	Atypical hyperplasia Endometrial intraepithelial neoplasia (EIN)	Endometrial intraepithelial carcinoma (EIC)
Association with estrogen stimulation	+++	+
Differentiation	Well to moderate	Poor
Growth	Slow-growing	Rapid progression
Invasion	Superficial	Deep
Typical patient	Perimenopausal, obese	Older women, thin
Clinical course	Indolent	Aggressive
Stage at diagnosis	Early	Later
Prognosis	Good	Poor

Data from Refs.[6–8]

Type 2 Endometrial Cancer Subtypes

- Serous carcinoma
  - Most common high-risk histology, accounts for 10% of endometrial cancer cases, but up to 40% of deaths
- Clear cell carcinoma
- Carcinosarcoma
- Most grade 3 endometrioid carcinomas
- Undifferentiated or dedifferentiated cancers

Despite nuances, often group subtypes together because of their aggressive behavior and relatively poor prognoses compared with type I cancers

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Chelmow D et al. Executive Summary of the Uterine Cancer Evidence Review Conference. Obstet Gynecol 2023;142:4. 626-643.

See increasing risk of Endometrial Cancer with…

- Higher BMI/Obesity (increases risk for uterine sarcoma as well)
- High glycemic index diets, diets high in saturated fats, and pro-inflammatory diets
- High meat consumption
- Increased length of exposure to endogenous hormones
  - Early menarche and later menopause
  - Late menarche inversely associated with uterine sarcoma risk
- Unopposed estrogen
- Several genetic cancer syndromes
  - Lynch syndrome
  - Cowden syndrome
- Diabetes
- Hypertension
- PCOS

Potential decreased risk with…

- Increased physical activity
- Diets with:
  - High fruit and vegetable intake
  - Higher isoflavone consumption and dietary fiber and endometrial cancer
  - Anti-inflammatory characteristics
- Combined hormone therapy (reduced risk of endometrial cancer compared with nonusers)
- Combined oral contraceptives
  - Risk reduction increased with longer duration of use and persisted more than 10 years after discontinuation
  - Decreased endometrial cancer risk in cohort of women with Lynch syndrome using COCs
- Tubal sterilization
- Aspirin and bisphosphonate use

Of note: Infertility treatments do not appear to increase risk

Reducing Endometrial Cancer Risk

Lifestyle Modifications

- No protective effect from dietary modifications
- No interventional trials specifically looking at risk reduction with physical activity
- **Given the health benefits of healthy diet and physical activity, patients should be counseled to follow national recommendations**

Weight Reduction

- No specific intervention trials of weight reduction
  - Bariatric surgery was associated with decreased risk
- **Given the benefits of weight reduction, patients with BMIs 30 or higher should receive behavioral counseling**

Progestins and Oral Contraceptives

- No specific interventional trials or recommendations for progestins or COCs
  - Based on epidemiologic evidence, patients using these methods for clinical indications likely experiencing endometrial cancer risk reduction as an ancillary benefit

Other Medications

- No interventional trials or recommendations for use of aspirin, metformin, or bisphosphonates

Risk Reduction – Special Populations

Lynch Syndrome

- **Consider hysterectomy for women who have completed childbearing**
  - **Significantly reduces endometrial cancer incidence but not mortality**
- National Comprehensive Cancer Network (NCCN) recommends considering risk-reducing hysterectomy for Lynch syndrome patients, with timing, "individualized based on whether childbearing is complete, comorbidities, family history, and [Lynch syndrome] gene, as risks for endometrial cancer vary by pathogenic variant"
  - **ACOG recommends discussing hysterectomy by a patient's early to mid-40s**

Individuals With the BRCA Mutation

- NCCN recommends discussing the risks and benefits of concurrent hysterectomy at the time of risk-reducing BSO, but further clarification of the magnitude of risk of serous uterine cancer is needed

Other Genetic Syndromes

- No studies evaluating risk-reducing hysterectomy among women with Cowden syndrome, PTEN hamartoma tumor syndrome, or Peutz-Jeghers syndrome (pathogenic STK11 variants)
  - For patients with Cowden syndrome or PTEN hamartoma tumor syndrome, the NCCN recommends, "discuss option of hysterectomy upon completion of childbearing and counsel regarding the degree of protection, extent of cancer risk, and reproductive desires"

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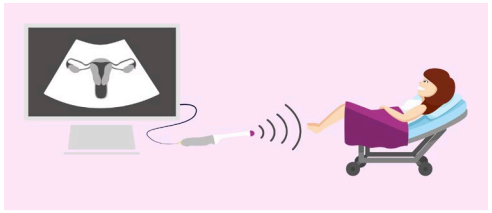
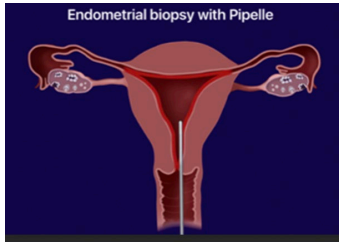
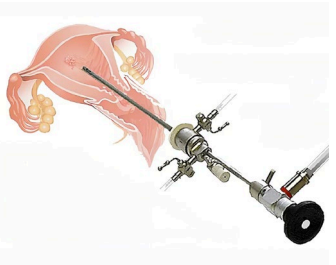
Screening Methods







- **Transvaginal Ultrasonography**
  - Commonly used for first-line evaluation in patients with postmenopausal bleeding
  - In a meta-analysis, sensitivity and specificity for endometrial cancer detection in postmenopausal patients with an endometrial thickness threshold of 5 mm, 90% and 54%, respectively
  - ACOG states that ultrasonographic measurement of endometrial thickness in premenopausal women has no diagnostic value and should not be performed
- **Office Endometrial Sampling**
  - Minimally invasive and cost-effective
  - Pipelle catheter - accurate method of endometrial sampling
    - Detection rates for endometrial cancer:
      - 99.6% in postmenopausal women
      - 91% in premenopausal women
  - SGO and ACOG both recommend that persistent AUB should be further evaluated, with the SGO specifying use of hysteroscopic-guided biopsy
- **Diagnostic hysteroscopy**
  - Highly accurate for diagnosing endometrial cancer among premenopausal and postmenopausal women with AUB when adequate visualization of the uterine cavity (LR for positive result 60.9, 95% CI 52.1–72.5)

Screening Asymptomatic Average-Risk Patients

- Limitations to effective screening in asymptomatic individuals
  - Low prevalence of disease
  - Most common symptom, Anovulatory Uterine Bleeding (AUB), usually arising at an early disease stage when high cure rates are possible

- **Review found no study or major society recommendation supporting endometrial cancer screening in asymptomatic women at usual risk**
  - Studies of ultrasound in women with postmenopausal bleeding demonstrated low PPV, varying between 0 and 0.2
  - No studies assessing use of endometrial sampling, hysteroscopy, or SIS in asymptomatic women at usual risk

Screening Indicated

High-Risk Populations

- **Several professional societies recommend screening patients with Lynch syndrome**
  - **ACOG and SGO recommended offering EMB every 1-2 years starting age 30-35**
  - **Recommendations largely based on expert opinion, and ACOG, the NCCN, and the American Cancer Society state recommendations have not been validated**
- No guidelines or studies to support screening in these populations: Cowden syndrome, Peutz-Jeghers syndrome, and Li-Fraumeni syndrome,
- No guidelines or studies supporting endometrial cancer screening in individuals with the BRCA mutation

Patients Using Tamoxifen

- Increased risk of benign polyps and endometrial cancer, increasing with duration of use and associated with endometrial thickening
  - No established thresholds for measuring endometrial thickness with TVUS in this population
  - 2 studies found TVUS of asymptomatic premenopausal and postmenopausal women taking tamoxifen yields a high false-positive rate, leading to unnecessary intervention
- **ACOG, the National Cancer Institute, and the American Cancer Society recommend against routine screening**
- **Given evidence suggesting tamoxifen users with baseline endometrial polyps more likely to develop atypical hyperplasia, ACOG states there may be a role for pretreatment screening before initiation of tamoxifen therapy**

Table 2. Recommendations for Endometrial Cancer Screening in People With Lynch Syndrome

Source	Screening Recommendations
American Cancer Society*	Offer annual screening with endometrial biopsy beginning at age 35 y.
NCCN†	Consider screening using endometrial biopsy every 1–2 y starting at age 30–35 y. Transvaginal ultrasonography can be considered at the clinician's discretion in postmenopausal women. Transvaginal ultrasonography is not recommended as a screening tool in premenopausal women.
ACOG and SGO‡	Offer endometrial biopsy every 1–2 y starting at age 30–35 y.

NCCN, National Comprehensive Cancer Network; ACOG, American College of Obstetricians and Gynecologists; SGO, Society of Gynecologic Oncology.

* Smith RA, von Eschenbach AC, Wender R, et al. American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers. CA Cancer J Clin 2001: Jan-Feb; 51(3):38–75.

† National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: genetic/familial high-risk assessment: colorectal (version 1.2020). Accessed November 30, 2020. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf

‡ Lynch syndrome. Practice Bulletin No. 147. American College of Obstetricians and Gynecologists. Obstet Gynecol 2014;124:1042–54. doi:10.1097/01/AOG/0000456325.50739/72

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Evaluation

Evaluation of Postmenopausal Bleeding

- ACOG and SGO recommend initial evaluation with either TVUS or endometrial sampling
  - If insufficient sampling, TVUS can be used
  - If sampling is negative and the bleeding persists or recurs, hysteroscopy with D&C is recommended
- ACOG recommends using an endometrial thickness of greater than 4 mm to prompt endometrial sampling if starting evaluation with TVUS

Detecting Endometrial Cancer in Premenopausal Patients

- ACOG recommends endometrial sampling in patients with AUB who are older than 45 years as a first-line test
- ACOG also recommends sampling in patients younger than age 45 years with risk factors, including history of unopposed estrogen exposure (such as seen in obesity or PCOS), failed medical management, and persistent AUB

Evaluation

Evaluation of Incidental Findings in Asymptomatic Patients

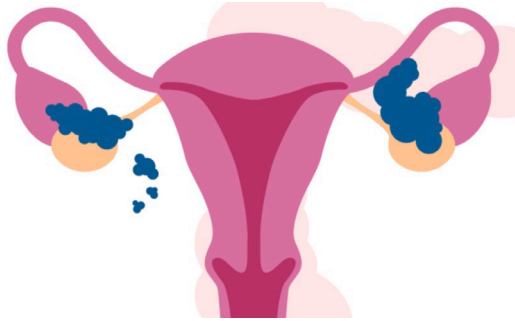
- **NO GUIDELINES**
- In asymptomatic postmenopausal women, endometrial thickness >=4 mm on TVUS - poor accuracy for the diagnosis of endometrial cancer
- **ACOG states that management of endometrial polyps can be expectant or surgical depending on patient symptoms and risk factors for malignancy**
  - Abnormal uterine bleeding indication for polypectomy
  - No guidelines regarding evaluation or treatment of asymptomatic postmenopausal women with incidental endometrial polyps

Evaluation

Cervical Cytology Findings Prompting Uterine Cancer Evaluation

- **2019 ASCCP Risk-Based Management Consensus Guidelines recommend endometrial sampling for postmenopausal women with endometrial cells on cytology**
  - No recommendation for evaluation of asymptomatic premenopausal women with benign appearing endometrial cells
  - Recommend endometrial sampling with colposcopy and endocervical sampling in nonpregnant patients 35 years or older with all categories of atypical glandular cells or adenocarcinoma in situ on cytology
  - Recommend endometrial sampling for nonpregnant patients younger than age 35 years with these findings and risk factors for endometrial neoplasia
- For patients with atypical endometrial cells, preferred management is endometrial and endocervical sampling alone, but colposcopy is acceptable as part of the initial evaluation

Ovarian Cancer – Epidemiology



- Relatively rare
  - 313,000 new cases of ovarian cancer in 2020 worldwide
  - Ranks 17th among all cancers in the US
  - Incidence of 10.6 per 100,000 from 2015 to 2019
  - 5th most common cause of cancer death in women in the US - the deadliest form of gynecologic cancer

- Usually typically advanced stage at diagnosis
  - At least 50% of cases presenting with distant disease

- Overall 5-year survival in the United States is 49.7%
  - Strongly correlated with stage at the time of diagnosis
  - Five-year survival depending on stage is:
    - 93.1% - localized
    - 74.2% - regional
    - 30.8% - distant
    - 28.2% - unstaged

- Recurrence risk correlates strongly with stage at diagnosis
- Fewer than 10% of women with stage I disease will have recurrence
- 90% of women with stage IV disease will have recurrent disease

Ovarian Cancer Classification

- Ovarian cancers are classified by the tissue from which they originate:
  - Epithelial - most common, accounting for 90% of malignant ovarian neoplasms
  - Germ-cell tumors - about 5% of ovarian cancers
  - Sex cord–stromal - account for 3–5%
  - All of these types can be further subdivided
- New cases of ovarian cancer in the US have been falling by an average of 3.3% each year since 2009
- Age-adjusted death rates have been falling by about 2.7% annually since 2010

Box 2. Ovarian Cancer Types

Epithelial ovarian cancer
- Serous carcinoma
  - –High-grade serous carcinoma
  - –Low-grade serous carcinoma
- Endometrioid carcinoma
- Mucinous carcinoma
- Clear-cell carcinoma
- Borderline or low-malignant-potential neoplasms
- Carcinosarcoma
- Undifferentiated or dedifferentiated
- Transitional cell carcinoma (Brenner tumor)

Germ-cell tumors
- Dysgerminoma
- Immature teratoma
- Embryonal carcinoma
- Endodermal sinus or yolk sac tumors

Sex cord–stromal tumors
- Granulosa cell tumors
- Thecomas
- Sertoli-Leydig cell tumors

What Increases and Lowers Risk?

Increases Risk

- Tobacco increases mucinous
- Inactivity
- Postmenopausal HRT
- Genetic mutations
- BRCA1, BRCA2
- 10–25% of ovarian cancers are associated with a hereditary genetic abnormality
- Endometriosis

Table 1. Ovarian Cancer Risk by Genetic Mutation

Gene	Epithelial Ovarian Cancer Absolute Risk*
ATM	<3%
BRCA1	39%–58%
BRCA2	13%–29%
BRIP1	>10%
MLH1, MSH2	>10%
MSH6	≤13%
PMS2	<3%
EPCAM	<10%
PALB2	3%–5%
RAD51C	>10%
RAD51D	>10%

* Modified with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for genetic/familial high-risk assessment: breast, ovarian and pancreatic v2.2022. © 2022 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Lowers Risk

- Increased physical activity associated with decreased risk (20% if active)
- Tobacco decreases clear cell
- Endogenous hormones
  - Parity
  - Later menarche and earlier menopause
  - Breastfeeding
- COCs
  - 50% reduction noted after 10 or more years of use
  - Risk reduction increased with longer duration of COC use
- Tubal Ligation
- Aspirin Use

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Is there anything that is no risk…

Inconsistent risk

- Obesity
- Heterogeneity in the studies on the use of talcum powder
- Infertility
  - Independent risk factor or whether the observed effect is mediated by nulliparity, endometriosis, decreased contraceptive use, and other risk factors

No risk

- Diet
- Alcohol use
- IUD
- POPs

RISK REDUCTION

- 2009 meta-analysis
  - 80% reduction in the incidence of ovarian cancer after risk-reducing BSO in BRCA1 and BRCA2 carriers (95% CI 0.12–0.39)
- ACOG, the National Comprehensive Cancer Network, and the Society of Gynecologic Oncology recommends risk-reducing BSO for women at increased risk of ovarian cancer
- **ACOG – Risk reducing BSO**
  - **Recommend at age 35–40 years for BRCA1 mutation carriers**
  - **Women with BRCA2 mutations may consider delaying until age 40–45 years**
  - **Opportunistic salpingectomy with hyst or sterilization appears to be safe and does not increase the risk of complications but should not alter the intended route of hysterectomy**
  - **OC use appropriate for women with mutations in BRCA1 or BRCA2 if indicated. Use for cancer prophylaxis is reasonable.**

National Comprehensive Cancer Network*
Risk-reducing BSO:
- "*BRCA* pathogenic/likely pathogenic variant-positive management: Recommend risk-reducing salpingo-oophorectomy, typically between 35 and 40 years, and upon completion of childbearing. Because ovarian cancer onset in patients with *BRCA2* pathogenic/likely pathogenic variants is an average of 8–10 years later than in patients with *BRCA1* pathogenic/likely pathogenic variants, it is reasonable to delay RRSO for management of ovarian cancer risk until age 40–45 years in patients with *BRCA2* pathogenic/likely pathogenic variants unless age at diagnosis in the family warrants earlier age for consideration of prophylactic surgery." (page BRCA-A 2 of 3)
- Consider between the ages of 45 and 50 years in carriers of a *BRIP1* variant (12% lifetime risk), an *RAD51C* variant (11% lifetime risk), and an *RAD51D* variant (13% lifetime risk).
- Total hysterectomy or BSO may be considered in those who have completed childbearing and carry a mismatch repair gene linked to Lynch syndrome.

SDO: Salpingectomy alone is not recommended for risk reduction.

Society of Gynecologic Oncology†
Risk-reducing BSO: Recommend risk-reducing BSO "be performed between 35 and 40 years of age in women with *BRCA1* and *BRCA2* mutations. Guidance for women who are at high risk according to strong family histories or who have been identified with a genetic mutation other than *BRCA1* or *BRCA2* generally follows the guidelines for *BRCA1* and *BRCA2* mutation carriers, but there are fewer data for these groups to support the value of salpingo-oophorectomy. Some syndromes such as Peutz-Jeghers syndrome are associated with cancer at a younger age, so the timing of RRSO should be individualized according to the age of incident cancers in the family or the specific mutation. Flexibility in the timing of RRSO may also be appropriate for *BRCA2* carriers who present with ovarian cancer at a later age than BRCA1 carriers." (page 2112)
SDO: "Can be considered at the completion of childbearing in women at increased genetic risk of ovarian cancer who do not agree to salpingo-oophorectomy. However, this is not a substitute for oophorectomy, which should still be performed as soon as the woman is willing to accept menopause, preferably by the age of 40 years." (page 2116)
OS: "Can be considered in average-risk women undergoing hysterectomy, other pelvic surgery, or sterilization at the completion of childbearing." (page 2116)
OC use: "Women with *BRCA1* or *BRCA2* mutations should consider taking oral contraceptive pills to reduce their ovarian cancer risk." (page 2112)

American College of Obstetricians and Gynecologists‡
Risk-reducing BSO: recommend at age 35–40 years for *BRCA1* mutation carriers; women with *BRCA2* mutations may consider delaying until age 40–45 years.
OS: Salpingectomy at the time of hysterectomy or as a means of tubal sterilization appears to be safe and does not increase the risk of complications. OS should not alter the intended route of hysterectomy.
OC use: Appropriate for women with mutations in *BRCA1* or *BRCA2* if indicated. Use for cancer prophylaxis is reasonable.

BSO, bilateral salpingo-oophorectomy; RRSO, risk-reducing salpingo-oophorectomy; SDO, salpingectomy with delayed oophorectomy; OS, opportunistic salpingectomy; OC, oral contraceptive.
*National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Genetic/familial high-risk assessment: breast, ovarian, and pancreatic version 2.2021. Accessed May 15, 2022. https://nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf
†Walker JL, Powell CB, Chen LM, Carter J, Bae Jump VL, Parker LP, et al. Society of Gynecologic Oncology recommendations for the prevention of ovarian cancer. Cancer 2015;121:2108–20. doi: 10.1002/cncr.29321
‡Hereditary breast and ovarian cancer syndrome. Practice Bulletin No. 182. American College of Obstetricians and Gynecologists.

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Screening

Most common methods studied

- Transvaginal ultrasonography
- Bimanual palpation
- Measurement of the serum tumor marker CA 125

Algorithms using a combination of transvaginal ultrasonography and tumor markers studied and include:

- ROCA (Risk of Ovarian Cancer Algorithm) and the parametric empirical Bayes model
- ROCA estimates the risk of ovarian cancer on the basis of age and change in CA 125
- Makes recommendations for repeat assessment of CA 125 or transvaginal ultrasonography on the basis of the calculated risk
- Specificity for epithelial ovarian cancer of 99.8% (95% CI 99.7–99.9%)
- Positive predictive value of 19% (95% CI 4.1– 45.6%)

Screening in Asymptomatic Women at Average Risk

No major professional society has recommended use of ovarian cancer screening in asymptomatic women at average risk, nor did any individual study show clear overall benefit

In 2018, USPSTF conducted systematic review for its updated publication on screening for ovarian cancer

Found screening offered no benefit in terms of ovarian cancer mortality

No high-quality evidence supporting the use of other serum markers, circulating tumor cells, or algorithms in ovarian cancer screening

USPSTF recommends against screening for ovarian cancer in asymptomatic women who are not known to have a high-risk hereditary cancer syndrome

Concluded that “there is at least moderate certainty that the harms of screening for ovarian cancer outweigh the benefits”

Screening in Patients at High Risk

- Due to lack of efficacy of ovarian cancer screening in patients at high risk, many professional societies do not recommend ovarian cancer screening for high-risk populations
- Routine ovarian cancer screening is not recommended
- **ACOG recommends genetic counseling based on family and personal histories of breast or ovarian cancer or both**
- Genetic testing can then discover pathogenic mutations in genes that increase the risk of epithelial ovarian cancer
  - Transvaginal ultrasonography or CA 125 level assessment can be considered starting at age 30–35 y until RRSO
  - No consensus on ovarian cancer screening in patients with Lynch syndrome

Box 2
Patients with increased likelihood of having an inherited predisposition to breast and ovarian cancer who should receive genetic counseling and be offered genetic testing

An individual affected with any of the following:

- High-grade EOC/tubal/peritoneal cancer
- Breast cancer in a patient no more than 45 years old
- Breast cancer with close relative with breast cancer at no more than 50 years old or close relative with EOC/tubal/peritoneal cancer at any age
- Breast cancer in a patient no more than 50 years old with a limited family history
- Breast cancer with at least 2 close relatives with breast cancer at any age
- Breast cancer with at least 2 close relatives with pancreatic cancer or aggressive prostate cancer (Gleason score ≥7)
- Two breast primaries, with the first diagnosed prior to age 50
- Triple negative breast cancer at an age of no more than 60 years
- With breast cancer and Ashkenazi Jewish ancestry
- Pancreatic cancer with at least 2 close relatives with breast, EOC/tubal/peritoneal, pancreatic, or aggressive prostate cancer

An individual with no personal history of cancer but with the following:

- First-degree or several close relatives who meet one of the above criteria
- Close relative carrying a known BRCA1 or BRCA2 mutation
- Close relative with male breast cancer

Adapted from Lancaster JM, Powell CB, Chen LM, et al. Society of Gynecologic Oncology Statement on risk assessment for inherited gynecologic cancer predispositions. Gynecol Oncol 2015;136(1):5; with permission.

Table 2. Identification and Screening of High-Risk Patients

Source	Recommendations
ACOG*	Recommends genetic counseling based on family and personal histories Routine ovarian cancer screening is not recommended, but transvaginal ultrasonography or CA 125 level assessment can be considered starting at age 30–35 y until RRSO. No consensus on ovarian cancer screening in patients with Lynch syndrome
ACR 2017 Appropriateness criteria†	No effective ovarian cancer screening Ovarian cancer screening with pelvic ultrasonography may be appropriate for some premenopausal or postmenopausal women at increased risk for ovarian cancer, which includes those with a personal history or family history of ovarian cancer, known or suspected genetic predisposition, or elevated CA 125 level.
ASRM/SGO‡	No strong evidence for effective ovarian cancer screening Transvaginal ultrasonography and CA 125 level assessment may be an option for women who decline or defer RRSO.
ESMO§	No strong evidence for effective ovarian cancer screening Transvaginal ultrasonography and CA 125 every 6 mo can be considered from age 30 with proper counseling on the lack of efficacy.
NCCN‖	Recommends genetic counseling based on family and personal histories No strong evidence for effective ovarian cancer screening If RRSO is not chosen, transvaginal ultrasonography and CA 125 assessment for ovarian cancer screening may be considered starting at age 30–35.
NICE¶	Recommends a risk assessment for patients with a family history of ovarian cancer or breast cancer in first- or second-degree relatives
RCOG#	Ovarian cancer screening should not be offered as an alternative to RRSO.
SOGC**	Recommends genetic counseling No strong evidence for effective ovarian cancer screening

ACOG, American College of Obstetricians and Gynecologists; RRSO, risk-reducing salpingo-oophorectomy; ACR, American College of Radiology; ASRM, American Society for Reproductive Medicine; SGO, Society of Gynecologic Oncology; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; RCOG, Royal College of Obstetricians and Gynaecologists; SOGC, Society of Obstetricians and Gynaecologists of Canada.

* Hereditary breast and ovarian cancer syndrome. Practice Bulletin No 182. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e110–26. doi:10.1097/AOG.0000000000002296; *and* Lynch syndrome. Practice Bulletin No. 147. American College of Obstetricians and Gynecologists and the Society of Gynecologic Oncology. Obstet Gynecol 2014;124:1042–54. doi:10.1097/01.AOG.0000456325.50739.72

† Expert Panel on Women's Imaging; Pandharipande PV, Lowry KP, Reinhold C, Atri M, Benson CB, et al. ACR Appropriateness Criteria® Ovarian Cancer Screening. J Am Coll Radiol 2017;14:S490–9. doi: 10.1016/j.jacr.2017.08.049

‡ Chen L, Blank SV, Burton E, Glass K, Penick E, Woodard T. Reproductive and hormonal considerations in women at increased risk for hereditary gynecologic cancers: Society of Gynecologic Oncology and American Society for Reproductive Medicine evidence-based review. Fertil Steril 2019;112:1034–42. doi:10.1016/j.fertnstert.2019.07.1349

§ Paluch-Shimon S, Cardoso F, Sessa C, Balmana J, Cardoso MJ, Gilbert F, et al. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. Ann Oncol 2016;27(suppl 5):v103–10.

‖ National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Genetic/familial high-risk assessment: breast, ovarian, and pancreatic version 2.2021. Accessed May 15, 2022. https://nccn.org/login?ReturnURL=https://nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

¶ National Institute for Health and Care Excellence. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. Clinical Guideline 164. 2013, updated 2019. Accessed April 8, 2022. https://www.nice.org.uk/guidance/cg164

Management of women with a genetic predisposition to gynaecological cancers. Scientific Impact Paper No. 48. Royal College of Obstetricians and Gynaecologists. Obstet Gynaecol 2015;17:140. doi: 10.1111/tog.12182

** Jacobson M, Bernardini M, Sobel ML, Kim RH, McCuaig J, Allen L. Gynaecologic management of heeditary breast and ovarian cancer. Committee Opinion No. 366. Society of Obstetricians and Gynaecologists of Canada. J Obstet Gynaecol Can 2018;40:1497–510. doi: 10.1016/j.jogc.2018.05.046

93%).[94] Sensitivity and specificity are poorer in premenopausal patients than postmenopausal patients, likely because benign conditions that can cause CA 125 elevation occur more frequently in premenopausal patients than postmenopausal patients and the ovarian cancer incidence is lower in premenopausal patients than in postmenopausal patients.[94]

The International Ovarian Tumour Analysis Phase 5 study was a prospective, multicenter cohort study with patients selected for surgery or conservative management on the basis of morphology and symptoms.[100] In this study, 1,919 patients with a new diagnosis of a mass that was assessed as benign on ultrasonography had outcomes examined at 24 months after

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Early Diagnosis

ACOG recommendations:

➢Patients and clinicians “should maintain an appropriate level of suspicion when signs and symptoms of ovarian cancer are present”

- Abdominal mass
- Abdominal distention or increased girth
- Abdominal or pelvic pain
- Specificities associated with these symptoms: 88%-99%
- Sensitivities: < 50%

➢“Transvaginal ultrasonography is the recommended imaging modality for a suspected or and incidentally identified pelvic mass.

➢ No alternative imaging modality has demonstrated sufficient superiority to transvaginal sonography to justify routine use.”

CA 125 most frequently measured serum marker for evaluation and early diagnosis of ovarian cancer despite variation in its measured sensitivity (61–90%) and specificity (71–93%)

➢*Sensitivity and specificity poorer in premenopausal than postmenopausal patients*

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Vulvar and Vaginal Cancer

- **Vulvar cancer accounts for approximately 5% of all gynecologic cancers worldwide**
  - 2019 - 5,579 cases diagnosed
- **Vaginal cancer even more rare, accounting for only 1% to 3% of gynecologic malignancies**
  - 2019 - 1,368 cases diagnosed
- Annual incidence of vulvar and vaginal malignancies
  - Approximately 2.5 cases and 1 case in 100,000 women, respectively
- **Squamous cell carcinoma**
  - **Most common histologic type**
  - Accounts for about 90% of vulvar cancers and 80–90% of vaginal cancers
- **Share many of the risk factors associated with cervical cancer**
- HPV DNA was detected in 69% of vulvar cancers and 75% of vaginal cancers
  - HPV-16 most common type, present in > 75% of HPV-positive vulvar, vaginal, and anal carcinomas
- Incidence increased in patients with immune compromise and impaired viral clearance

Table 1. New Cases and Deaths

	United States			Global
Cancer Site	New Cases	Deaths	5-y Relative Survival (%)	Incident Cases
Vagina	1,368*	431*	51.0†	15,000‡,§
Vulva	5,579*	1,347*	70.3†	34,000‡,§
Anus (female)	5,339‖	806‖	72.6†	20,000‡

Data are n unless otherwise specified.

* Cases in 2019 from the Centers for Disease Control and Prevention. Vaginal and vulvar cancers statistics. Accessed February 6, 2023. https://cdc.gov/cancer/vagvulv/statistics/index.htm

† The 5-year survival from 2012 to 2018 from National Cancer Institute Surveillance, Epidemiology, and End Results Program. Cancer Statistics Explorer Network SEER*Explorer. SEER 5-year relative survival rates, 2012–2018 (by cancer site). Accessed April 2, 2023. https://seer.cancer.gov/statistics-network/explorer/application.html

‡ de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Cancer 2017;141:664–70. doi: 10.1002/ijc.30716

§ Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424. doi: 10.3322/caac.21492

‖ Cases in 2019 from U.S. Cancer Statistics Working Group. U.S. Cancer Statistics data visualizations tool, based on 2021 submission data (1999–2019). Accessed March 21, 2023. https://cdc.gov/cancer/dataviz

Epidemiology

Vulvar cancer

- **HPV–related vulvar cancer - increasing in incidence**
  - In US, overall incidence increased by 1.2% each year from 2001 to 2017
  - Most rapid rise s between ages 50–59 years
- Median age at diagnosis 68 years
  - 24.8% of cases occur between 65 and 74 years
- According to a large retrospective study of U.S. cancer data from 2008
  - < 50 years, the age-specific incidence rates of invasive vulvar squamous cell carcinoma similar among White and Black people
  - > 50 years, incidence rates rose more rapidly among White women than Black women
- 2016 to 2020, median age at death from vulvar cancer was 77 years
  - 55.7% of deaths occurring after age 75 years
- 2018 meta-analysis found HPV-positive vulvar cancer associated with better overall survival and recurrence-free survival than HPV-negative vulvar cancer

Vaginal Cancer

- **Incidence rates stable over time, despite a high HPV- attributable fraction**
- < 60 - more likely to be positive for HPV-16 or -18 than in older women
  - 77.3% compared with 44.7% (P5.038)

Table 2. Rates of New Cases Per 100,000 Women Per Year

Cancer Site	All Races	Hispanic	Non-Hispanic American Indian or Alaska Native	Non-Hispanic Asian or Pacific Islander	Non-Hispanic Black	Non-Hispanic White
Anal*						
Incidence	2.3	1.6	1.2	0.5	1.8	2.8
Deaths	0.3	0.2	0.3	0.1	0.3	0.4
Vaginal†						
Incidence	NR	0.6	NC	0.4	0.9	0.6
Deaths	NR	0.2	NC	NC	0.3	0.2
Vulvar†						
Incidence	2.5	1.7	2.3	1.0	1.7	3.0
Deaths	0.6	0.3	NC	0.2	0.4	0.7

NR, not reported; NC, not calculated (too few people).
* Data from Cancer Stat Facts: anal cancer. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Accessed November 9, 2022. https://seer.cancer.gov/statfacts/html/anus.html (incidence rates were age-adjusted from 2015 to 2019 SEER data; death rates were age-adjusted 2016–2020.)
† Data from Centers for Disease Control and Prevention. Vaginal and vulvar cancers statistics. Accessed February 6, 2023. https://cdc.gov/cancer/vagvulv/statistics/index.htm (2019 statistics reported).

- Incidence and death rates for anogenital cancers for women across different races and ethnicities

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Risk Factors

HPV –Associated Conditions

- **Vaginal and vulvar cancers most strongly associated with HPV-16**
- HPV–associated cancers and pre-cancers of cervix associated with increased risk of cancer at other lower anogenital tract sites
- Preinvasive and invasive disease of the cervix associated with increased risk of vaginal cancer

Immune Compromise

- **Alterations in immune function mediate HPV risk**
- Receipt of a solid-organ transplant was associated with increased risk of vaginal and vulvar cancer
- Association strongest for vulvar cancer
- End-stage renal disease (before or without kidney transplantation) also associated with increased risk of vulvar cancer

Other Vulvar Diseases

- **Lichen sclerosis, lichen planus, and Paget disease of the vulva associated with vulvar cancer (not involved with HPV)**
- Differentiated vulvar intraepithelial neoplasia **(VIN**) associated with incident cancer and progression to vulvar cancer over many years
- Risk of associated vulvar cancer persisted beyond 5 years after a diagnosis of lichen sclerosis

Lifestyle Factors

- No confirmed, consistent associations for vulvar and vaginal cancers with tobacco use, alcohol consumption, or sexual activity
- **Higher risk of clear-cell carcinoma of the vagina associated with in utero diethylstilbestrol exposure**
- No confirmed associations of intrinsic or extrinsic hormone exposure

Genetic Disorders

- Some very rare genetic disorders (e.g. warts, hypogammaglobulinemia , infections, and myelokathexis syndrome; Fanconi anemia) are associated with increased risk according to small case series
- No other studies show association with family history

Prevention and Risk Reduction

Behavior Modification

- In literature search, **no intervention trials of behavioral modification,** including dietary changes, condom use, or tobacco cessation, **for lower anogenital tract cancer risk reduction**
- Prospective trial of 82 newly sexually active women
  - 70% less likely to have HPV infection if they reported condom use 100% rather than less than 5% of the time (adjusted hazard ratio 0.3, 95% CI 0.1–0.6)
- Tobacco cessation is recommended for all adults
- **ACOG recommends smoking cessation for all people with VIN**

Lower Anogenital Tract Cancer Precursor Lesions

- No studies with vaginal or vulvar cancer outcomes after surveillance for or treatment of VAIN or VIN
- History of cervical cancer or CIN 2–3 increases risk of vaginal cancer
- ASCCP guidelines recommend surveillance with HPV-based testing for 25 years in patients after hysterectomy who have a diagnosis of CIN 2 or worse
- **ACOG recommends treating all vulvar high-grade squamous intraepithelial lesions (HSIL)**

Lichen Sclerosis

- **Long-term steroid use in lichen sclerosis patients demonstrated significant decrease in VIN 2 or worse**
- Recommend initial treatment with clobetasol propionate 0.05% ointment for 3 months with topical steroids as needed for recurrent symptoms after that time

Human Papillomavirus Vaccination

- **HPV vaccination, especially if completed before sexual initiation, extremely effective against lower anogenital tract cancer precursor**
- In RCT with quadrivalent vaccine given ages 16-26
  - 100% reduction in VAIN and VIN 2 or worse in those without prior exposure
  - 62% reduction in the group with previous HPV exposure
- Similar in RCT of nanovalent HPV vaccine
  - No cases of VAIN 2 or worse or VIN 2 or worse in participants without prior HPV exposure
  - Vaccine performance noninferior to the quadrivalent vaccine in patients with prior HPV exposure
- Vaccination had no effect on HPV infection in a study of patients with HPV-16 or -18 DNA positivity

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Screening

Asymptomatic Women at Average Risk

- **No evidence for routine screening**
- USPSTF concluded insufficient evidence for screening pelvic exam in asymptomatic women
- **ACOG states pelvic examinations in asymptomatic, non-pregnant individuals involve shared decision making and should be performed when indicated by history or symptoms**

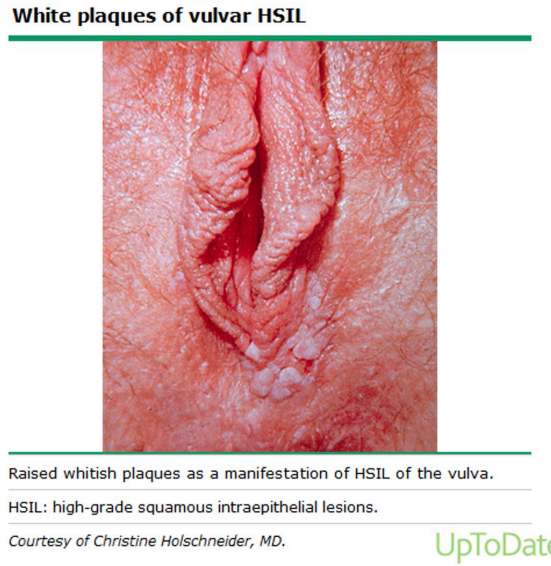
Populations at High Risk For Vulvar Cancer

- **No studies or guidelines about screening for vulvar cancer or cancer precursors in populations at high risk**
- **ASCCP colposcopy standards include gross examination of the vulva and vagina at time of colposcopy**
- Department of Health and Human Services HIV guidelines note that "no screening procedure is available for vulvar cancer" and that biopsy or referral is indicated for suspicious lesions
- American Society of Transplantation Infectious Diseases and The Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group do not have specific recommendations but encourage careful inspection of vulva, vagina, cervix and anus

Populations at High Risk for Vaginal Cancer

- **No studies about screening for vaginal cancer or cancer precursors in populations at high risk**
- **ASCCP recommends that women who have undergone hysterectomy and have a history of CIN 2, CIN 3, or adenocarcinoma in situ have ongoing surveillance at 3-year intervals for a total of 25 years**
- Women with HIV
  - U.S. Department of Health and Human Services - routine vaginal cancer screening is not recommended after a hysterectomy for benign disease
  - Recommend annual vaginal cuff Pap tests in patients after hysterectomy for high- grade CIN, adenocarcinoma in situ, or invasive cervical cancer
  - Recommend continued screening in patients not known to have had a hysterectomy for benign indications.
- Recommendations for solid- organ transplantations - inspection of the vagina at the time of cervical screening

Early Diagnosis



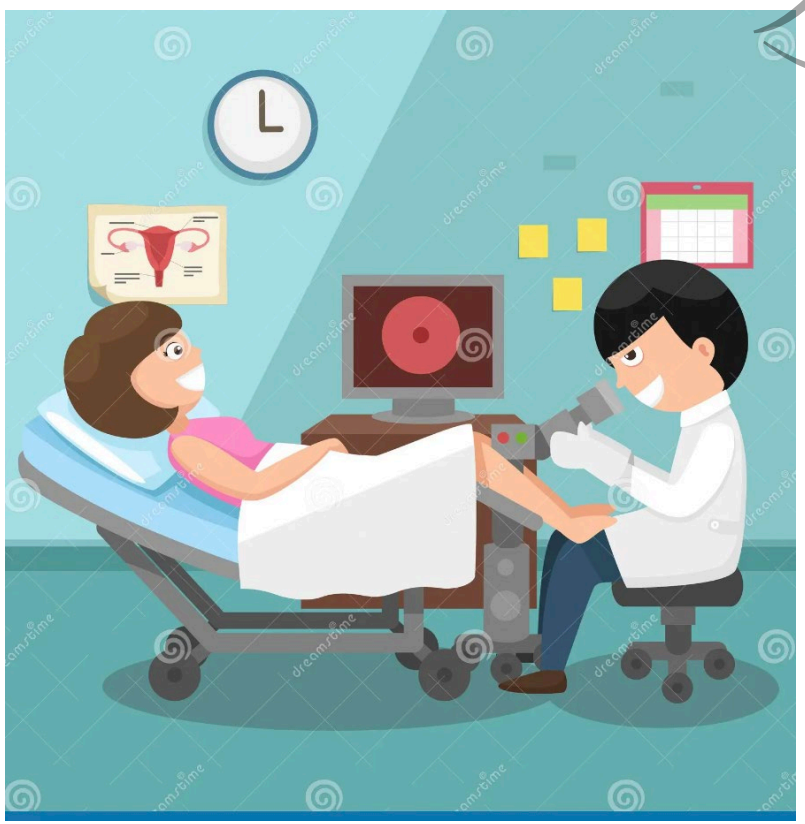
Vulvar Cancer

- **No studies of the predictive value of symptoms for vulvar cancer or its precursors**
- **Most with vulvar cancer present with at least one symptom**
  - **Pain**
  - **Pruritus**
  - **Visible lesion**
- 60% vulvar cancers diagnosed without distant spread, likely because of the symptomatic nature of these lesions
- Symptoms of vulvar precancers - similar but less severe
- Nonhealing vulvar ulcers - particularly high risk.
  - In one study of non-healing ulcers, 63% were diagnosed with vulvar squamous cell carcinoma, and 36% had at least HSIL

Vaginal Cancer

- **No studies of the predictive value of symptoms for vaginal cancer or its precursors**
- **VAIN - predominantly asymptomatic**
- Cancer more commonly symptomatic
  - Vaginal bleeding (painless bleeding most common in most studies)
  - Unexplained vaginal discharge
  - Pain
  - Palpable mass
  - Other nonspecific symptoms

Techniques for Evaluation



No studies evaluating the diagnostic performance of any lower genital tract evaluation tool

Most commonly used tools found

- Pelvic examination
- Cytology
- Vaginal or vulvar colposcopy

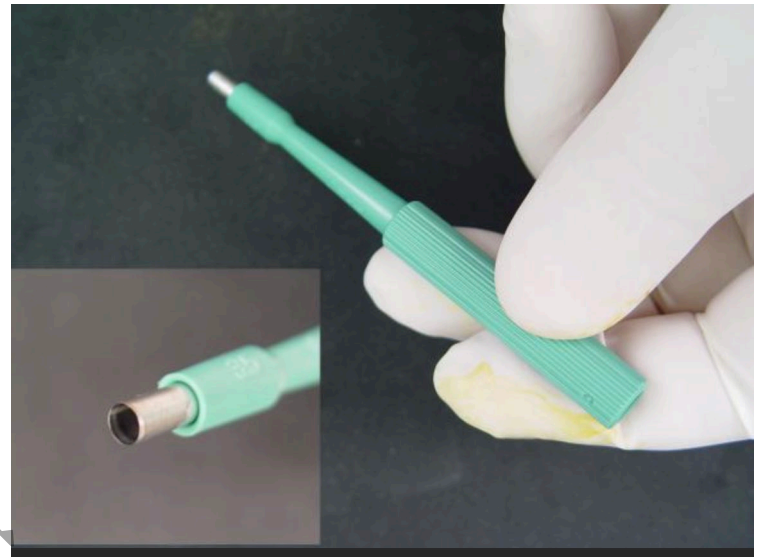
ACOG recommends pelvic examination when indicated by medical history or symptoms including but not limited to

- Abnormal bleeding
- Dyspareunia
- Pelvic pain
- Vaginal bulge

Detection of vulvar cancers or precancers is limited to visual assessment and confirmation by histopathology

When to Biopsy

ACOG	Recommends biopsy when lesions are: •Atypical (e.g. new pigmentation, indurated, affixed to underlying tissue, bleeding, or ulcerated) •Concerning for malignancy •In immunocompromised patient (including those living with HIV) •Uncertain of diagnosis •Not responding to standard therapy •Worsening during therapy Recommends biopsy in postmenopausal women with apparent genital warts and in women of all ages with suspected condyloma in whom topical therapies have failed
Society of Obstetricians and Gynaecologists of Canada	Recommends a biopsy of any worrisome vulvar lesion through a punch biopsy of adequate size (at least 4 mm wide) and depth (to subcutaneous fat)
European Society of Gynaecological Oncology	Recommends a punch or incisional biopsy of any lesion suspicious for a vulvar cancer In patients with multiple vulvar lesions, they recommend that all lesions be biopsied separately to accurately map all disease.



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Thoughts…

- US and ACOG standards of care for screening
  - Frameworks of which are heavily based on Western culture and populations
- Differences in health service infrastructures, human resources, service delivery, and accessibility to services
- Does not take into account and differences in socioeconomic factors, cultural diversity and any geographic barriers of other countries
- Any recommendations create costs which create obstacles
  - In many countries, significant proportion of patients unable to access preventative or therapeutic services due to inadequate health care services and financing/coverage
- To reduce burden of gynecologic cancer, must formulate appropriate cancer control policies and invest in education, supply resources and provide infrastructure
- Commonality - need to understand first and foremost what would cause someone to be willing to understand and express concerns for any the symptoms, have desire and motivation for preventative care and seek and accept health care

Start with Patient Education – The Why

Español | Other Languages

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Gynecologic Cancers

Gynecologic Cancers Home

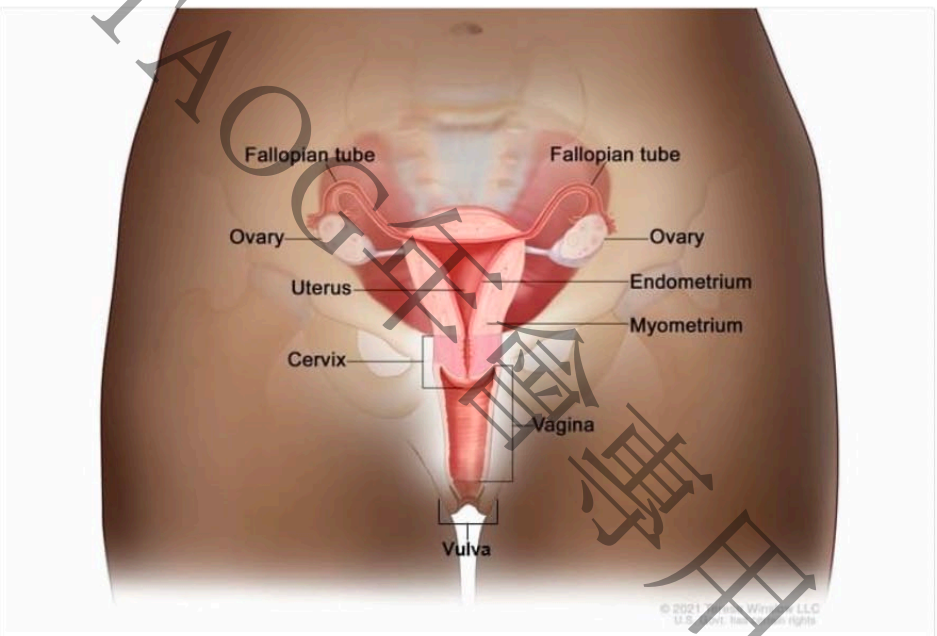
What Is Gynecologic Cancer?

Gynecologic cancer is any cancer that starts in a woman's reproductive organs. Cancer is always named for the part of the body where it starts. Gynecologic cancers begin in different places within a woman's pelvis, which is the area below the stomach and in between the hip bones.

Types of Gynecologic Cancer

- Cervical cancer begins in the *cervix,* which is the lower, narrow end of the uterus. (The uterus is also called the womb.)
- Ovarian cancer begins in the *ovaries,* which are located on each side of the uterus. Some ovarian cancers can also begin in the fallopian tubes or peritoneum.
- Uterine cancer begins in the *uterus,* the pear-shaped organ in a woman's pelvis where the baby grows when she is pregnant.
- Vaginal cancer begins in the *vagina,* which is the hollow, tube-like channel between the bottom of the uterus and the outside of the body.
- Vulvar cancer begins in the *vulva,* the outer part of the female genital organs.

Each gynecologic cancer is unique, with different signs and symptoms, different risk factors (things that may increase your chance of getting a disease), and different prevention strategies. All women are at risk for gynecologic cancers, and risk increases with age. When gynecologic cancers are found early, treatment is most effective.



This diagram shows different parts of a woman's reproductive system.

Last Reviewed: June 13, 2023
Source: Division of Cancer Prevention and Control, Centers for Disease Control and Prevention

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Thank you Dr. Shee-Uan Chen and the Taiwan Association of Obstetrics and Gynecology

Please visit Portland, Oregon

Kaohsiung, Taiwan – Portland's Sister City
June Annual Dragon Boat Race

Please come to Minneapolis, Minnesota for ACOG Annual Clinical and Scientific Meeting May 16-18, 2025

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References

- Burke, W et al. Executive Summary of the Ovarian Cancer Evidence Review Conference. Obstet Gynecol 2023;142:1. 179-195.
- Chelmow, D et al. Executive Summary of the Lower Anogenital Tract Cancer Evidence Review Conference. Obstet Gynecol 2023;142:3. 708-724.
- Chelmow, D et al. Executive Summary of the Uterine Cancer Evidence Review Conference. Obstet Gynecol 2023;142:4. 626-643.
- Committee on Gynecologic Practice, Society of Gynecologic Oncology. ACOG Committee Opinion No. 716: The Role of the Obstetrician–Gynecologist in the Early Detection of Epithelial Ovarian Cancer in Women at Average Risk. Obstet Gynecol 2017;130:3. 146-149.
- Curry, SJ et al. US Preventive Services Task Force. Screening for cervical cancer: US Preventive Services Task Force recommendation statement. JAMA. 2018;320(7):674-686.
- Grossman, DC. Screening for Ovarian Cancer US Preventive Services Task Force Recommendation Statement. JAMA, 2018; 319(7): 588-594.
- Perkins, RB. Cervical Cancer Screening. A Review. JAMA, : 330(6);547-558.
- Staples JN, Duska LR. Cancer Screening and Prevention Highlights in Gynecologic Cancer. Obstet Gynecol Clin N Am 46 (2019) 19–36.
- Su, Shih-Yung., 2023. Mortality trends and disease burdens of cervical, endometrial and ovarian cancers from 1981 to 2020 in Taiwan. Preventative Medicine. 172; 107551.
- Updated Cervical Cancer Screening Guidelines. ACOG Practice Advisory. April 2021, Reaffirmed April 2023.
- Updated Guidelines for Management of Cervical Cancer Screening Abnormalities. ACOG Practice Advisory. Oct 2020, Reaffirmed Sept 2022.
- Recommendations for Well-Woman Care 2023.
- Yang, L et al. Time trend of global uterine cancer burden: an age-period-cohort analysis from 1990 to 2019 and predictions in a 25-year period. BMC Womens Health. 2023; 23: 384.