USF HEALTH MORSANI COLLEGE OF MEDICINE
UNIVERSITY OF SOUTH FLORIDA

Human Papillomavirus

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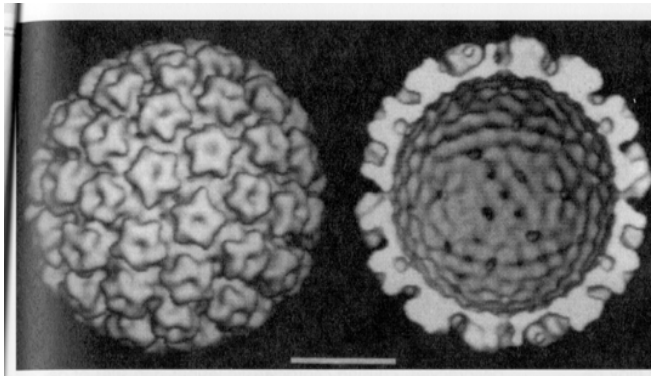
Objectives

1. Recall the basic science of HPV
2. Discuss the natural history of HPV infections
3. Evaluate pap smear and cervical biopsy results
4. Explain the HPV vaccine
5. Determine risk factors for cervical cancer

Basic Science of HPV

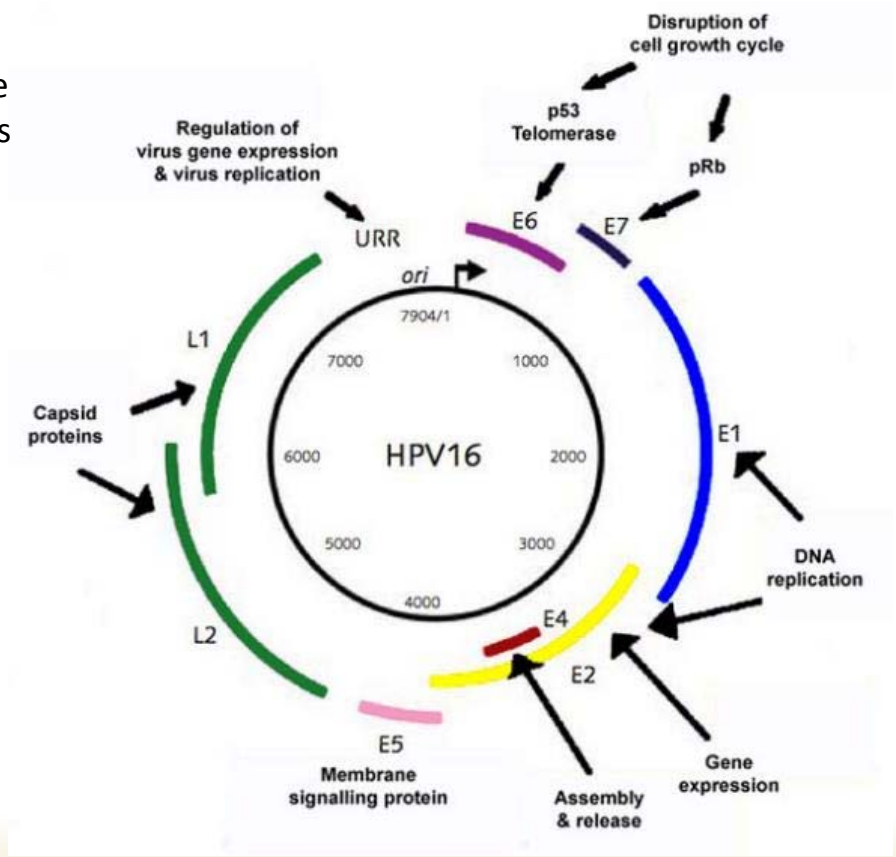
Human papillomaviruses; Classification

- Naked icosahedral symmetry, double stranded small circular DNA genome



Papillomavirus 16; Early (E) and late (L) genes

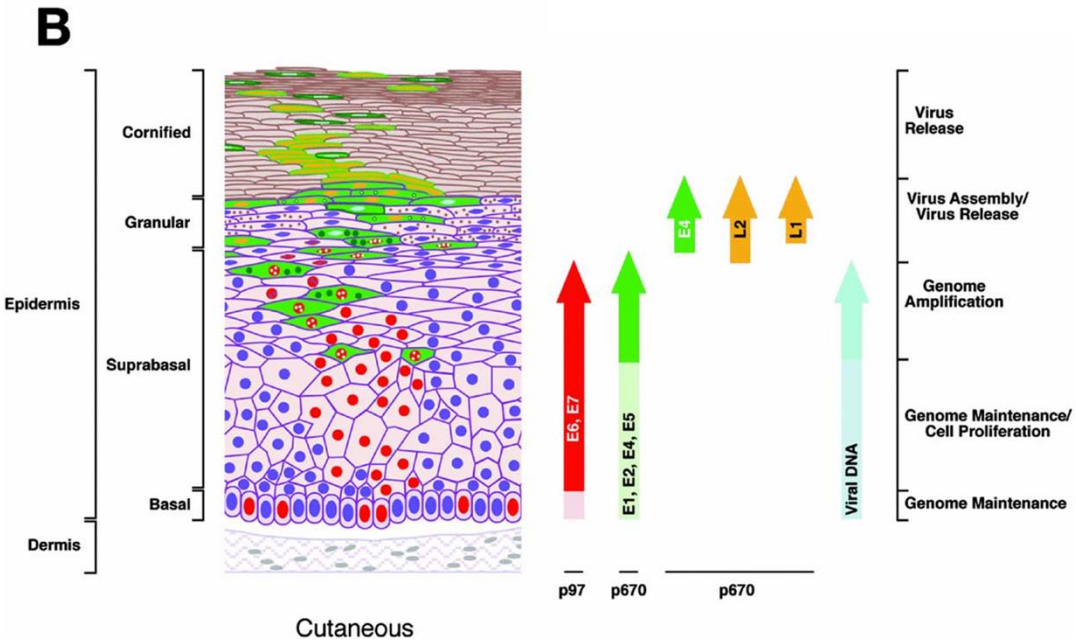
Circular genome encodes 8 genes



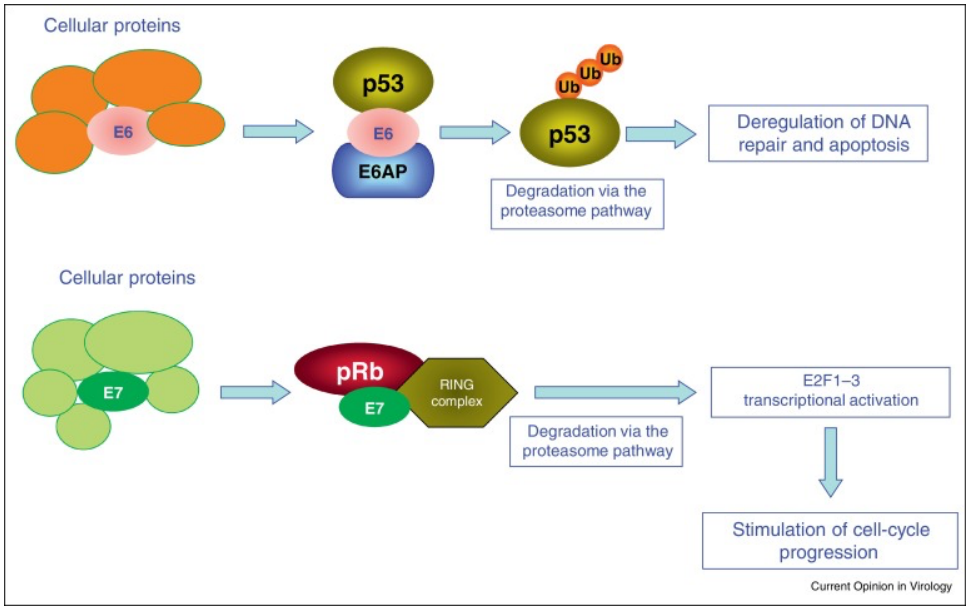
Human papillomaviruses; Virus replication

- Latency in basal cell layers, latent episomal DNA in nucleus
  - Replicates in the differentiating epithelium/mucosa

HPV replication



Carcinogenesis by HPV



Pathogenesis of papillomavirus infection leading to cancer

- (1) Infection with papillomavirus DNA types 16, 18, 31, 33
- (2) Integration of the viral genome into a chromosome and increased expression of early genes E6 and E7
- (3) Development of secondary mutations in cellular proto-oncogenes, chromosomal instability, telomerase activation = cancer

Pathogenesis of papillomavirus infection leading to cancer

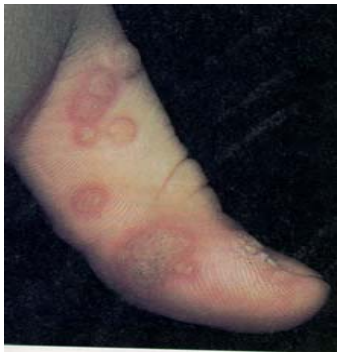
- In the presence of other carcinogens such as products of **tobacco** exposure, the increased DNA damaged sustained by the cell is allowed to go relatively unchecked by the HPV coinfection which has disabled tumor suppressor function
- Cell-mediated immunity is important
  - HIV inhibits clearance of the virus through T cell-mediated immunosuppression and directly enhances expression of E6 and E7 proteins in the HIV and HPV coinfected cell, HIV+ less likely to clear HPV infection
  - Other immunosuppressed patients, Pregnancy
- Neutralizing antibodies also play a role in immunity

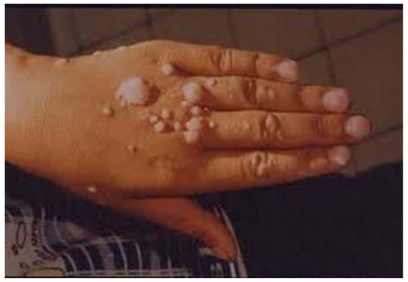
Clinical Aspects of HPV

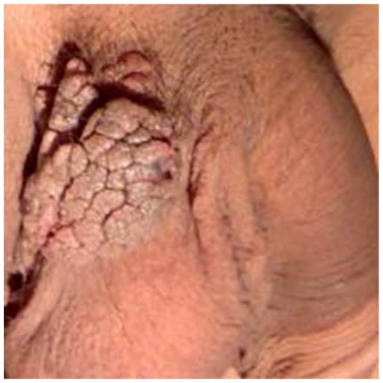
HPV types

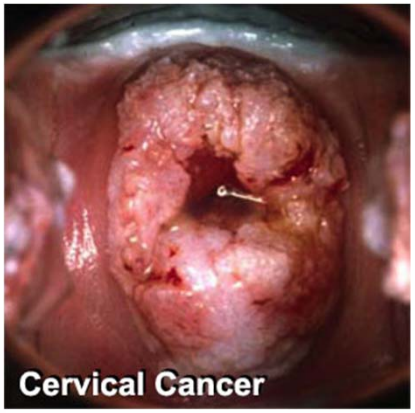
- Different HPV types (>200) have a propensity to infect different body sites and cause different benign or malignant tumors
  - Plantar wart 1
  - Common wart 2,4
  - Flat warts 3,10
  - Butcher's warts 7,2
  - Condylomata acuminata (genital warts) 6,11
  - Respiratory papillomatosis 6,11

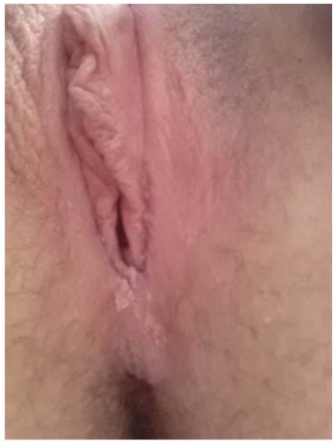
  - Oropharyngeal cancer 16
  - Anal cancer 16, 18
  - Squamous intraepithelial lesions and/or carcinoma of the vagina, vulva, cervix, anus, or penis
    - Low grade 16, 31, 6, 11
    - High grade 16, 31, 52, 18

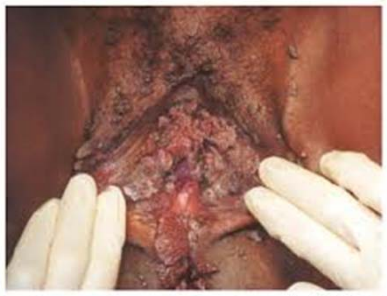







Cervical Cancer





QUESTION

- Which cancer is the most likely to be associated with HPV?
  A. Oral
  B. Vaginal
  C. Penile
  D. Cervical

HPV-Attributable Cancer

CDC

Number of HPV-Associated and HPV-Attributable Cancer Cases per Year

Cancer site	Average number of cancers per year in sites where HPV is often found (HPV-associated cancers)	Percentage probably caused by any HPV type[a]	Number probably caused by any HPV type[a]	Percentage probably caused by HPV types 16/18[b]	Number probably caused by HPV types 16/18[b]	Percentage probably caused by HPV types 31/33/45/52/58[c]	Number probably caused by HPV types 31/33/45/52/58[c]
Cervix	11,693	91%	10,600	66%	7,700	15%	1,700
Vagina	819	75%	600	55%	500	18%	100
Vulva	3,671	69%	2,500	49%	1,800	14%	500
Penis	1,181	63%	700	48%	600	9%	100
Anus	5,229	91%	4,800	79%	4,200	8%	400
Female	3,416	93%	3,200	80%	2,700	11%	400
Male	1,813	89%	1,600	79%	1,400	4%	100
Rectum	772	91%	700	79%	600	8%	100
Female	528	93%	500	80%	400	11%	100
Male	244	89%	200	79%	200	4%	<100
Oropharynx	16,479	70%	11,600	60%	9,900	6%	900
Female	3,203	63%	2,000	51%	1,600	10%	300
Male	13,276	72%	9,600	63%	8,400	4%	600
TOTAL	**39,844**	**79%**	**31,500**	**63%**	**25,300**	**10%**	**3,800**
Female	**23,330**	**83%**	**19,400**	**63%**	**14,700**	**13%**	**3,100**
Male	**16,514**	**73%**	**12,100**	**64%**	**10,600**	**4%**	**700**

[a]HPV types detected in genotyping study; most were high-risk HPV types known to cause cancer (Saraiya M et al. U.S. assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. *Journal of the National Cancer Institute* 2015;107:djv086).

QUESTION

- Which HPV type causes the most cervical cancer?

  A. 16

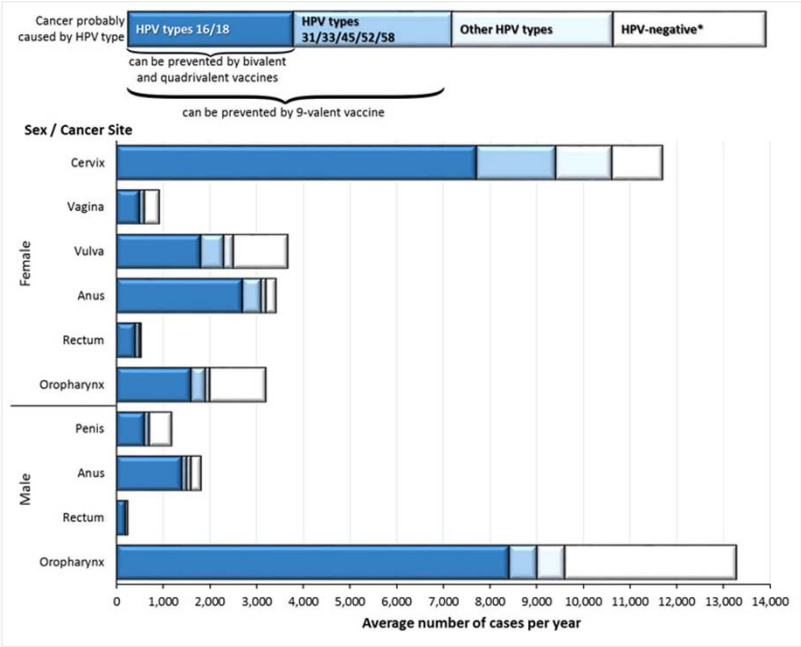
  B. 18

  C. 31

  D. 33

HPV-Attributable Cancer

CDC



*HPV DNA was not detected in a percentage of cancers (Saraiya M et al. U.S. assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. *Journal of the National Cancer Institute* 2015;107:djv086).

Data are from population-based cancer registries participating in the CDC National Program of Cancer Registries and/or the NCI Surveillance, Epidemiology, and End Results Program, meeting criteria for high data quality for all years 2009 to 2013 and cover about 99% of the U.S. population.

Female Genital Tract HPV Infection

- Over 40 mucosal HPV genotypes infect the lower female genital tract
  - "Low-risk" types HPV 6 and HPV 11 cause ~90% of genital warts
  - ~15 HPV types "oncogenic" or "high-risk"
    - HPV 16 (50%) and HPV 18 (~20%) cause ~70% of all cervical cancers, 31/33/45/52/58 another 19%
    - Usually a necessary but not sufficient factor for the development of squamous cervical neoplasia, only a small fraction
    - In addition to cervical cancer- cancer of anus, vagina, penis, mouth, and throat

Transmission

- HPV is spread from skin surface to skin surface during vaginal, anal, or oral sex
  - Respiratory during passage through birth canal

- Genital HPV
  - Usually asymptomatic
  - Risks:
    - Early onset of sexual activity
    - Multiple sexual partners
    - A high-risk sexual partner
    - Sex with a new partner
    - History of STDs
    - Immunosuppression ex. HIV infection
    - Absence of condom use
    - Circumcision status – incidence, clearance
    - Smoking

QUESTION

- What percentage of sexually active adults will acquire a genital tract HPV infection before age 50?

  A. 15%

  B. 25%

  C. 50%

  D. 75%

HPV as an STD

- Globally, HPV is the most common STD
  - Estimated that 75-80% of sexually active adults will acquire a genital tract HPV infection before age 50
  - HPV positivity is most commonly present within the first 10 yrs after sexual debut, then incidence increases again at menopause
  - Older women may be reactivation vs. new recent infection
  - Many sexually active young women have sequential infections with different oncogenic types of HPV
  - Geographic variation in distribution of HPV genotypes
  - There may be racial differences in the type and turnover of HPV infection in women, in a study black women had a slightly higher incidence of infection with high-risk HPV types, more persistent infections

Natural History of HPV Infections

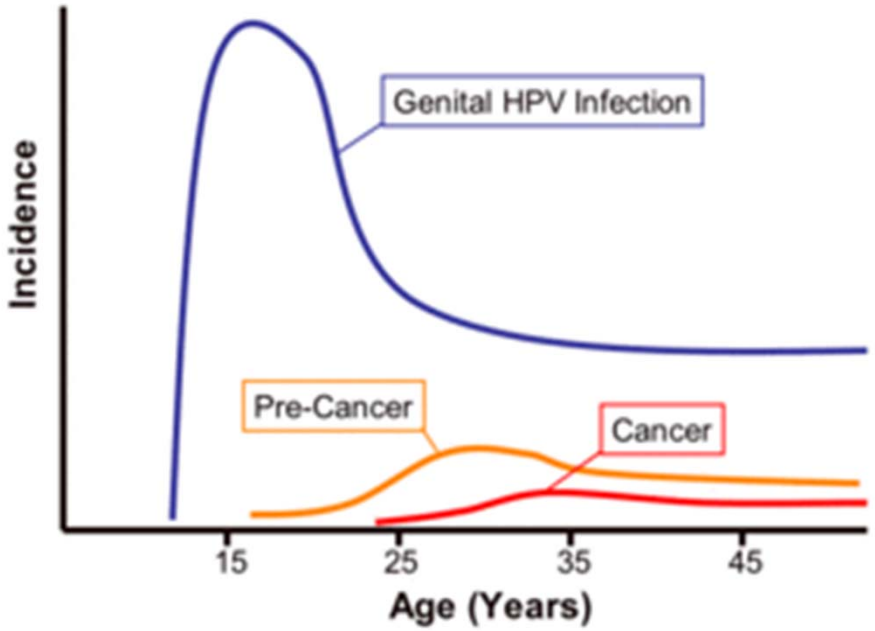
- Most HPV infections including oncogenic typically resolve within 6-12 months = transient infection
  - Most <21 years old clear the infection in an average of 8 months, most CIN will also resolve spontaneously
  - Those that don't clear are called persistent infections
  - Any age can clear but HPV detected in women >30 years old is more likely to reflect persistent infection

- If persistent oncogenic HPV infection then risk of developing precancerous lesions and cancer, although not all progress
  - Still positive 1-2 years after initial infection strongly predicts risk of CIN3 or cancer
  - The HPV genotype is most important determinant of persistence and progression: #1 is HPV-16, #2 is HPV-18, then ~13 others
    - Other factors are cigarette smoking, a compromised immune system, HIV+

Natural History of HPV Infections

- In the U.S. the median age of cytologically-detected precancerous lesions occurs ~10 yrs after the median age of sexual debut
- Then ~10 yrs from CIN3 to cancer
- Cervical cancer occurs a median of 15-25 years after HPV infection, mean age of cervical cancer diagnosis 48

Natural History of HPV Infections



Cervical Cancer

- Most cases of cervical cancer occur in women who were either never screened or were screened inadequately

Natural History of HPV Infections

- Increasing evidence that HPV can enter a latent state including HIV-infected and older women
  - Unknown whether all become latent or whether re-emergent HPV infections carry a significant cancer risk

- The importance of the immune response in the natural history of HPV is illustrated by the increased risk of cancer among immunosuppressed or immunocompromised patients

HPV Detection

- By several molecular methods
- Only testing of cervical cytological or biopsy specimens is currently clinically available
- In the U.S. there are no FDA-approved tests clinically available to detect HPV infection of oropharyngeal, anal, or male genital specimens
- No FDA-approved serological or blood tests to detect HPV infection

Cervical Cytology: The Bethesda System

Specimen adequacy
Satisfactory for evaluation
Presence or absence of endocervical or transformation zone components or other quality indicators such as partially obscuring blood or inflammation
Unsatisfactory for evaluation (specify reason)
Specimen rejected or not processed (specify reason)
Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormalities (specify reason)

General categorization (optional)
Negative for intraepithelial lesion or malignancy
Epithelial cell abnormality
Other
Interpretation/result
Negative for intraepithelial lesion or malignancy

Organisms
Trichomonas vaginalis
Fungal organisms morphologically consistent with Candida species
Shift in flora suggestive of bacterial vaginosis
Bacteria morphologically consistent with Actinomyces species
Cellular changes consistent with herpes simplex virus
Other non-neoplastic findings (optional to report)
Reactive cellular changes associated with:
Inflammation (includes typical repair)
Radiation
Intrauterine contraceptive device
Glandular cells status posthysterectomy
Atrophy

Epithelial cell abnormalities

Squamous cell
Atypical squamous cells (ASC)
ASC of undetermined significance (ASC-US)
ASC, cannot exclude high-grade squamous intraepithelial lesion (ASC-H)
Low-grade squamous intraepithelial lesion (LSIL)
Encompassing: human papillomavirus, mild dysplasia, and cervical intraepithelial neoplasia (CIN) 1
High-grade squamous intraepithelial lesion (HSIL)
Encompassing: moderate and severe dysplasia, carcinoma in situ, CIN 2, and CIN 3
Squamous cell carcinoma

Glandular cell
Atypical glandular cells (AGC)
Specify endocervical, endometrial, or glandular cells not otherwise specified
Atypical glandular cells, favor neoplastic
Specify endocervical or not otherwise specified
Endocervical adenocarcinoma in situ (AIS)
Adenocarcinoma
Other (list not comprehensive)
Endometrial cells in a women 40 years or older

Cytological classification (used for screening)		Histological classification (used for diagnosis)	
	Bethesda system	CIN	WHO descriptive classifications
	Normal	Normal	Normal
	ASC-US ASC-H	Atypia	Atypia
	LSIL	CIN 1 including flat condyloma	Koilocytosis
	HSIL	CIN 2	Moderate dysplasia
	HSIL	CIN 3	Severe dysplasia
	HSIL	CIN 3	Carcinoma in situ
	Invasive carcinoma	Invasive carcinoma	Invasive carcinoma

The 2001 Bethesda system update is standard. Until recently histolopathologic terminology was much less standardized

Cervical Cancer Screening

- Evolution of new technologies and recommendations for managing the results
  - In 2011 the ACS, the American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology (ASCP) updated their joint guidelines as did the U.S. Preventive Services Task Force (USPSTF)
  - In 2015 the ASCCP and the Society of Gynecologic Oncology (SGO) issued interim guidance for the use of a HPV test for primary screening which had been approved by the FDA in 2014
- Recent revisions have balanced cancer detection with harms of screening by incorporating the powerful negative predictive value of HPV testing and lengthening screening intervals

HPV Testing

- No role for testing for low-risk genotypes
- Most test for 13-14 of the most common high-risk genotypes (+ or -)
- Indication for HPV testing:
  - Determination of the need for colposcopy in women with an ASCUS cytology result
  - Use as an adjunct to cytology for cervical cancer screening in women age 30-65+ “co-testing”
  - One HPV test was FDA approved in 2014 for primary cervical cancer screening in women 25+
- Genotyping tests for HPV-16, HPV-18, HPV-45
  - Mainly women age 30-65+ that have negative pap but +HRHPV results

Cervical Cancer Screening

Table 1. Screening Methods for Cervical Cancer for the General Population: Joint Recommendations of the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology*

Population	Recommended Screening Method	Comment
Women younger than 21 years	No screening	
Women aged 21–29 years	Cytology alone every 3 years	
Women aged 30–65 years	Human papillomavirus and cytology cotesting (preferred) every 5 years Cytology alone (acceptable) every 3 years	Screening by HPV testing alone is not recommended*
Women older than 65 years	No screening is necessary after adequate negative prior screening results	Women with a history of CIN 2, CIN 3, or adenocarcinoma in situ should continue routine age-based screening for a total of 20 years after spontaneous regression or appropriate management of CIN 2, CIN 3, or adenocarcinoma in situ
Women who underwent total hysterectomy	No screening is necessary	Applies to women without a cervix and without a history of CIN 2, CIN 3, adenocarcinoma in situ, or cancer in the past 20 years
Women vaccinated against HPV	Follow age-specific recommendations (same as unvaccinated women)	

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

*After the Joint Recommendations were published, a test for screening with HPV testing alone was approved by the U.S. Food and Drug Administration. Gynecologic care providers using this test should follow the interim guidance developed by the American Society for Colposcopy and Cervical Pathology and the Society for Gynecologic Oncology (Huh WK, Ault KA, Chelmow D, Davey DD, Goulart RA, Garcia FA, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. Obstet Gynecol 2015;125:330–7.).

Modified from Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. ACS-ASCCP-ASCP Cervical Cancer Guideline Committee. CA Cancer J Clin 2012;62:147–72.

Epithelial atrophy common after menopause likely predisposes women to false-positive cytology screening test results

Management of Cervical Cancer Screening Results

Table 2. Management of Cervical Cancer Screening Results ⇦

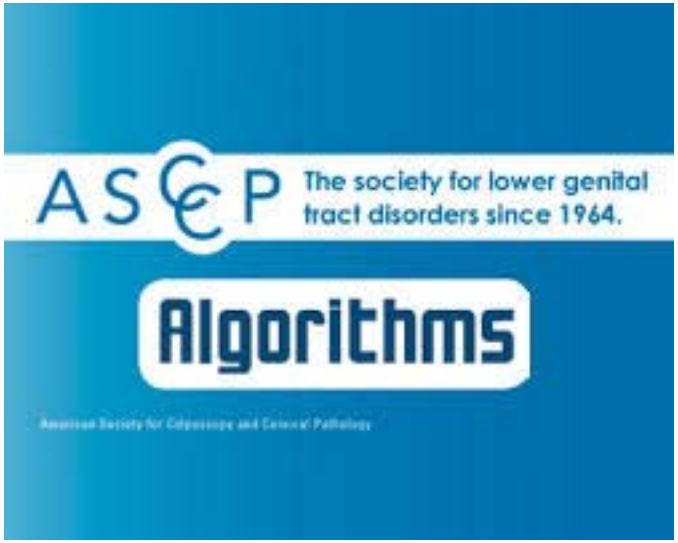
Screening Method	Result	Management
Cytology screening alone	Cytology negative	Screen again in 3 years
	ASC-US cytology and reflex HPV negative	Cotest in 3 years
	All others	Refer to ASCCP guidelines*
Cotesting	Cytology negative, HPV negative	Screen again in 5 years
	ASC-US cytology, HPV negative	Screen again in 3 years
	Cytology negative, HPV positive	Option 1: 12-month follow-up with cotesting Option 2: Test for HPV-16 or HPV-18 genotypes • If positive results from test for HPV-16 or HPV-18, referral for colposcopy • If negative results from test for HPV-16 and HPV-18, 12-month follow-up with cotesting
	All others	Refer to ASCCP guidelines*

Abbreviations: ASCCP, American Society for Colposcopy and Cervical Pathology; ASC-US, atypical squamous cells of undetermined significance; HPV, human papillomavirus.

*Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al, for the 2012 ASCCP Consensus Guidelines Conference. 2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors. J Low Genit Tract Dis 2013;17:S1–S27.

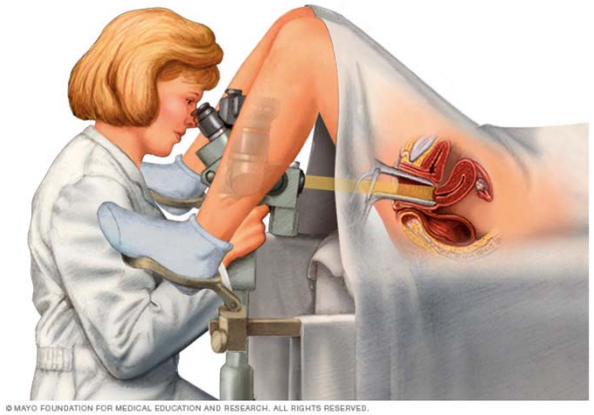
Modified from Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. ACS-ASCCP-ASCP Cervical Cancer Guideline Committee. CA Cancer J Clin 2012;62:147–72, with additional modifications based on Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al, for the 2012 ASCCP Consensus Guidelines Conference. 2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors. J Low Genit Tract Dis 2013;17:S1–S27.

Management of Cervical Cancer Screening Results



Management of Cervical Cancer Screening Results – Colposcopy

Colposcopy for most abnormal paps



Management Options

- Observation
  - Repeat pap smear and/or HPV test
- Excisional therapy
  - LEEP, laser conization, cold-knife conization
- Ablative treatments
  - Cryotherapy or laser vaporization

General Rules for Management

- Low-grade neoplasia or CIN1 is a manifestation of acute infection, high rate of regression to normal histology → recommendations for observation
- CIN3 significant risk of progression to cancer ~30% at 30 years if untreated, true cancer precursor
- CIN2 approach is controversial (thought to be a mix of low-grade and true precancers) so now two-tiered histologic classification:
  - LSIL and HSIL (getting away from CIN)

Management

- Many potential combos of cervical cytology and HPV results, some not in guidelines
- Some lab tests not in guidelines
  - Molecular markers highly associated with clinically relevant cervical neoplasia, such as p16/Ki-67 and E6 and E7

Management

- Recurrent HPV-positive
  - Likely that the HPV has not cleared but in a latent subclinical state below the threshold of the testing being positive
  - Impossible to prove or disprove if a current HPV infection is a new infection or reactivation of an old latent infection
  - Most probably reactivations of latent infections acquired at or near sexual debut
  - Reactivation of latent could imply waning immunity and might be at risk of persistence
- Long history of occasionally positive and occasionally negative HPV and cytology results suggests borderline latent infection

QUESTION

- Which of the following is true about HPV vaccines?
  A. Contains recombinant protein
  B. It contains live virus
  C. You should test for HPV prior to administration
  D. It cannot be given to immunosuppressed patients

HPV Prevention – HPV vaccine

- Vaccine contains recombinant virus-like particles (L1 capsid proteins) (noninfectious)

HPV Vaccines

- More effective before sexual debut
- Prophylactic vaccines
  - › 3 vaccines:

    1. **Gardasil** 4-valent 2006 (only distributed until end 2016)
    2. **Cervarix** 2-valent 2009
    3. **Gardasil 9** 9-valent 12/2014 (Only one available in U.S.)
  - › FDA approved for females ages 9-26 *11-12 and males *11-21

GARDASIL 9

- Males and females
- 9-valent vaccine targets HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58
- Three doses over 6 months
  – 0,2,6 months*

Vaccine Efficacy

- Many studies have reported declining prevalence and incidence of HPV infection and HPV-related disease
- Population decreases in HPV-related disease may reflect herd immunity
- Large decreases seen in other countries like Australia where vaccine coverage is higher

Cervical Cancer Screening After Vaccination?

- Screening recommendations apply regardless of HPV vaccination status
  - Many receive the vaccine when they're older and after viral exposure
  - The 9-valent vaccine immunizes against 7 high-risk subtypes but does not cover all
  - Rate of vaccine administration is far from 100%
  - Long-term efficacy of the vaccine remains incompletely established

In Conclusion: Predicting Cervical Cancer

- High risk women may require more frequent cervical cancer screening:
  - HIV+
  - Immunocompromised such as received a solid organ transplant
  - Exposed to diethylstilbestrol in utero
  - Previously treated for CIN2, CIN3, or cancer
    - Previous CIN2 or higher at risk of persistent or recurrent disease for at least 20 yrs after treatment
- Cytology is a marker for current risk of clinically relevant disease (CIN 2+) while HPV testing is an excellent marker for predicting future risk
  - HPV-16 or HPV-18 positive?
  - Persistent HPV+?
- Did the patient get the HPV vaccine?
- Tobacco use?
- Long history of abnormal results mixed with normal results?

Resources

- The American College of Obstetricians and Gynecologists Practice Bulletin Number 168 “Cervical Cancer Screening and Prevention,” October 2016
- The American College of Obstetricians and Gynecologists Practice Bulletin Number 140, “Management of Abnormal Cervical Cancer Screening Test Results and Cervical Cancer Precursors,” December 2013
- UpToDate “Human papillomavirus infections: Epidemiology and disease associations” accessed 1/22/2018.
- UpToDate “Human papillomavirus testing of the cervix: Management of abnormal results” accessed 1/22/2018.
- CDC website.

Questions??