HPV-Informed Cervical Cancer Screening and Prevention

Utah Academy of Family Physicians, 11/7/20
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THE University of Vermont MEDICAL CENTER

Objectives

After this activity, I hope you will be able to …

- Summarize the natural history of HPV as it relates to cervical cancer screening.
- Use the ASCCP mobile application or web application to manage cervical cancer screening results.
- Increase uptake of HPV vaccination within your adolescent practice.

Agenda

This content is divided into three primary sections:

- Human papillomavirus (HPV)
  - Focusing on the natural history of carcinogenesis
- Cervical cancer screening
  - Reviewing past, present, and future strategies
- Vaccination
  - Proof that it works
  - Strategies to increase uptake

Agenda

- **Human papillomavirus (HPV)**
  - **Natural history**
- Cervical cancer screening
  - Past, present, future
- Vaccination
  - Efficacy
  - Strategies to increase uptake

What is HPV?

- The human papillomavirus is a small dsDNA virus, specific to humans, which infects epithelial cells.
- Once incorporated into cells, the viral proteins decrease apoptosis, leading to unregulated cell growth.
  - This can cause either benign or malignant tumors, depending on the infected location and the strain of virus.
- More than 100 types of HPV have been identified.
  - Over 40 types affect the anogenital area.

Types of HPV

Different HPV types cause unregulated cell growth in different parts of the body.

- Plantar warts - type 1
- Common warts - types 2, 4
- Flat warts - types 3, 10
- Low-risk AG - types **6, 11,** 40, 42, 43, 44, 53, 54, 61, 72, 73, 81
- High-risk AG - types **16, 18,** *31, 33,* 35, 39, *45,* 51, *52,* 56, *58,* 59, 66, 68
  - **Bold:** in the HPV4 vaccine
  - **Italics:** in the HPV9 vaccine

HPV causes cervical cancer

- The transformation zone of the cervix is an area of metaplasia prone to develop dysplasia in the presence of HPV.
  - This is analogous to Barrett's esophagus:
    - Cells of the distal esophagus exposed to acid from the stomach change over time through *dysplasia*, making them more like stomach cells and more able to tolerate exposure to acid.
    - Because the cells are actively changing, the area of *dysplasia* is more likely to progress to *neoplasia* so people with Barrett's esophagus are monitored for esophageal cancer.

HPV causes cervical cancer

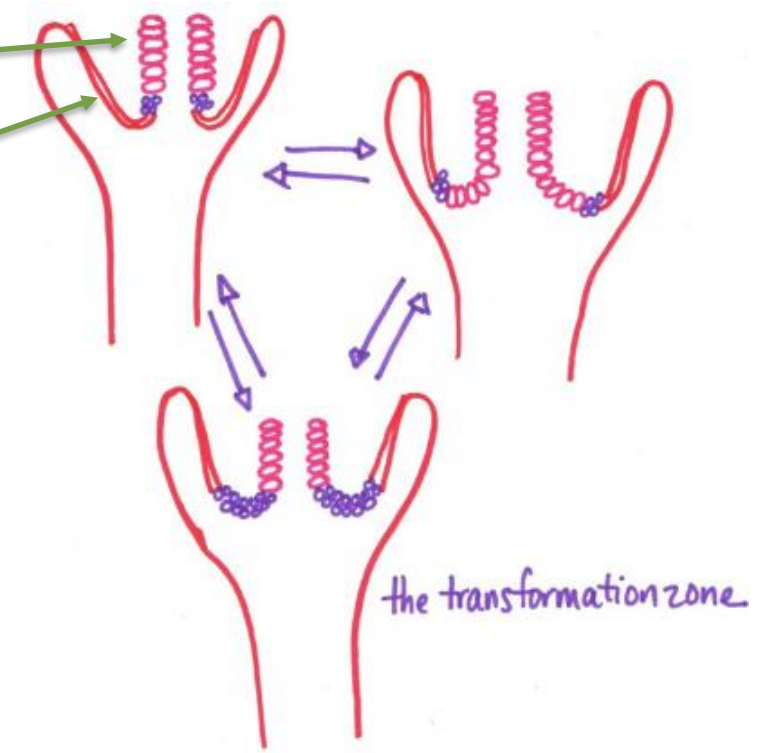
- HPV infection is associated with changes called low-grade squamous intraepithelial lesion (LSIL).
- Persistent LSIL progresses to high-grade squamous intraepithelial lesion (HSIL) in 8-28% of people over 5-10 years.
- Without intervention, HSIL progresses to cancer in 3-5% of people over 10-30 years.
- HPV is detectable in almost 100% of cervical cancers.

Squamous Metaplasia (the transformation zone)

- During puberty, columnar cells from the endocervix begin to migrate to the ectocervix, which previously only had squamous cells.
- Environmental factors in the vagina lead to metaplasia of the columnar cells.
  - These factors include pH, infection/inflammation, and changing levels of sex hormones.
- Metaplastic columnar cells convert into mature squamous cells.
- This creates the appearance of squamous cells migrating toward the cervical os.

Squamous Metaplasia (the transformation zone)

1. Columnar cells in the endocervix, squamous cells on the ectocervix



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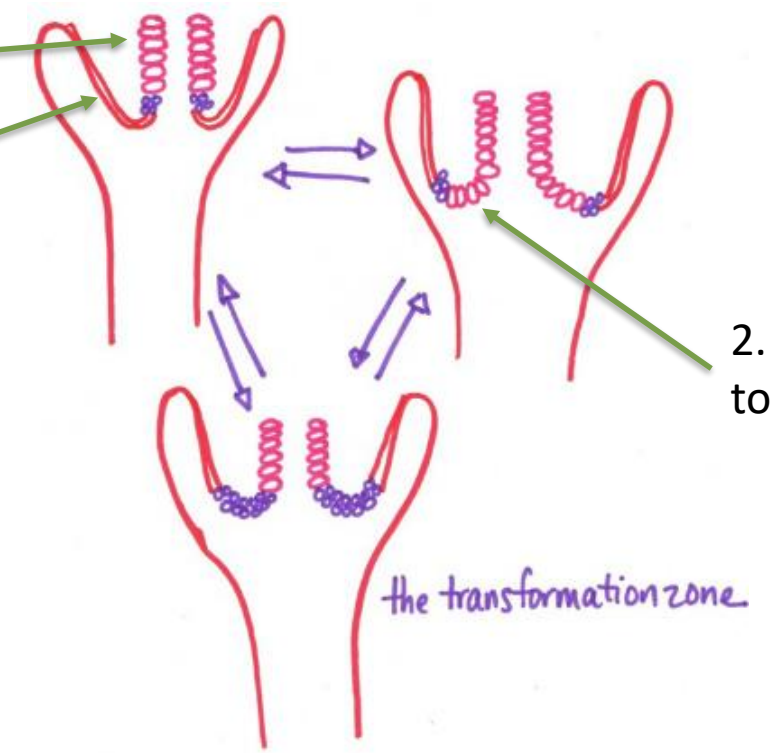

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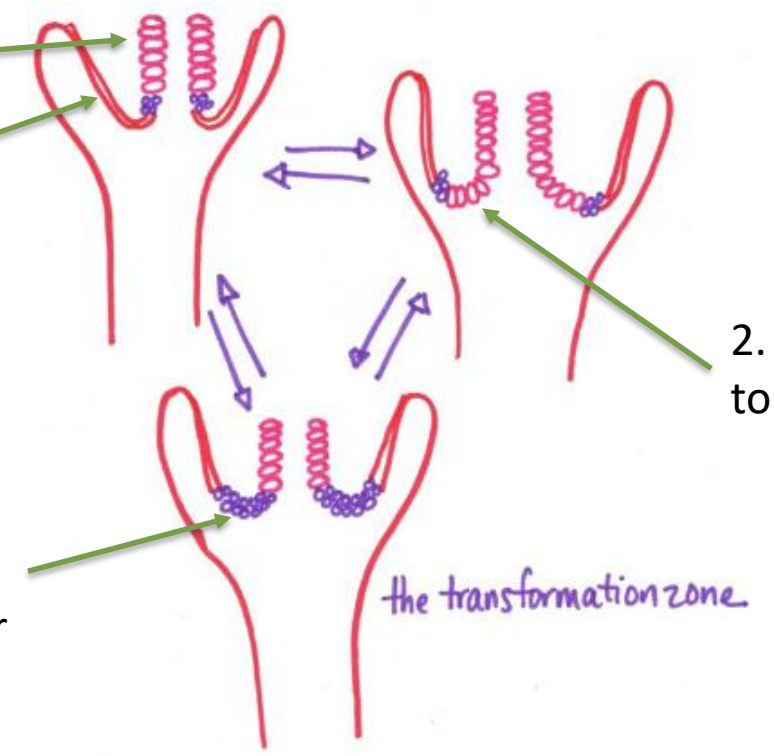

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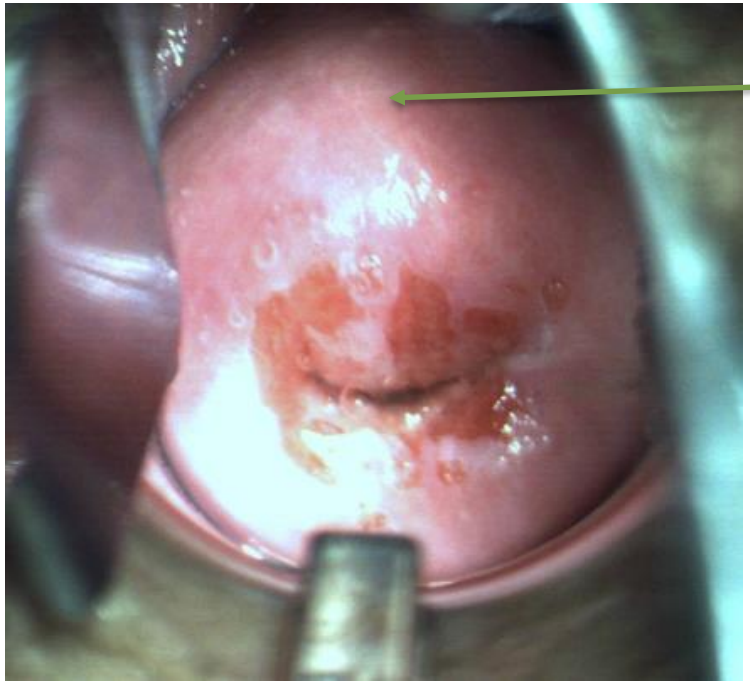
3. The transformation zone is the area where columnar cells are changing into squamous cells

Squamous metaplasia is NORMAL



Original squamous epithelium

PHOTO: CLARA KEEGAN MD

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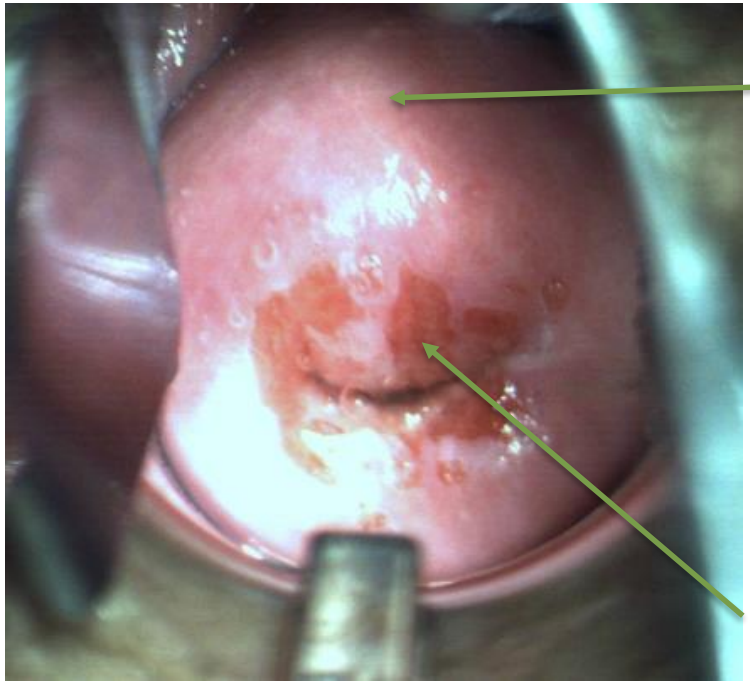

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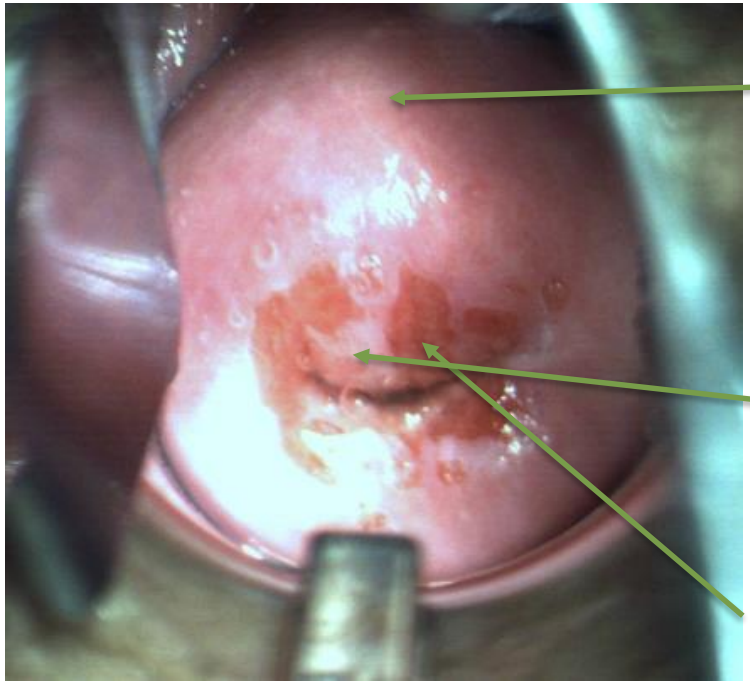

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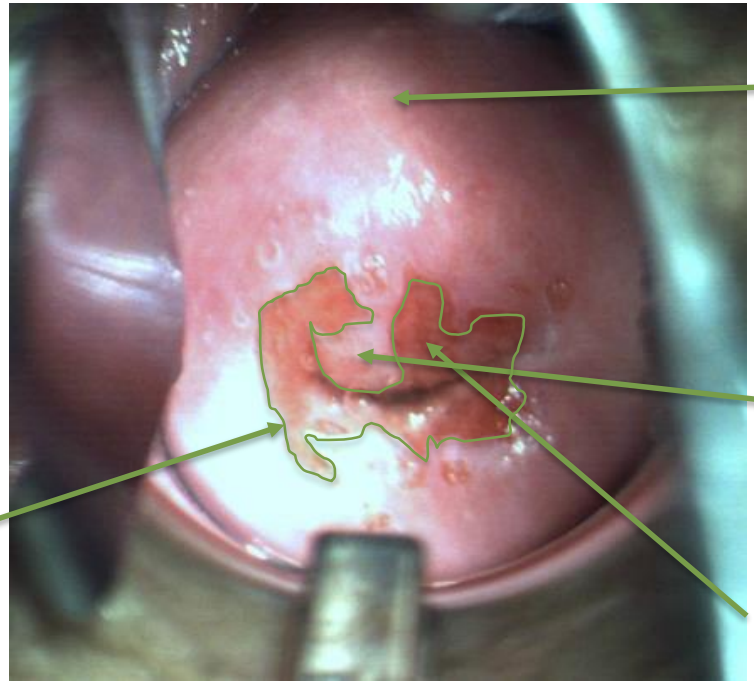

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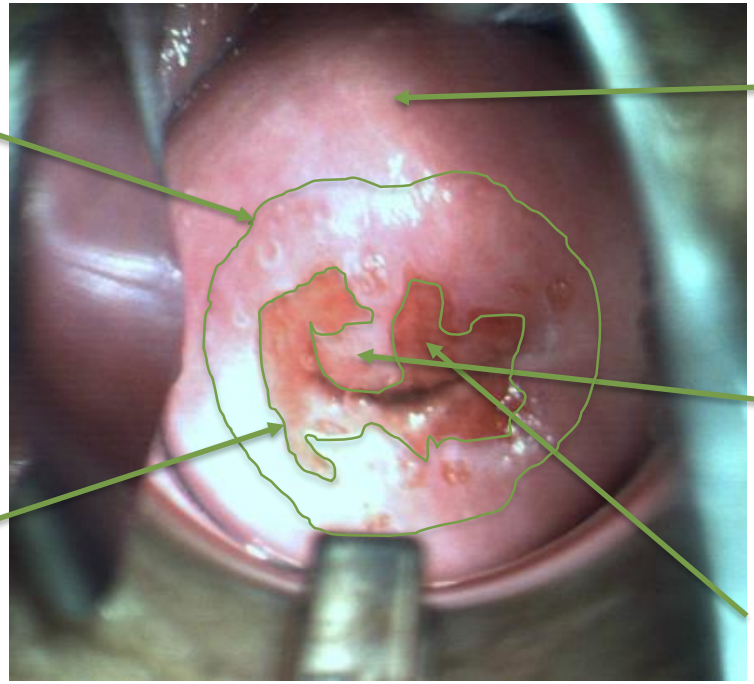

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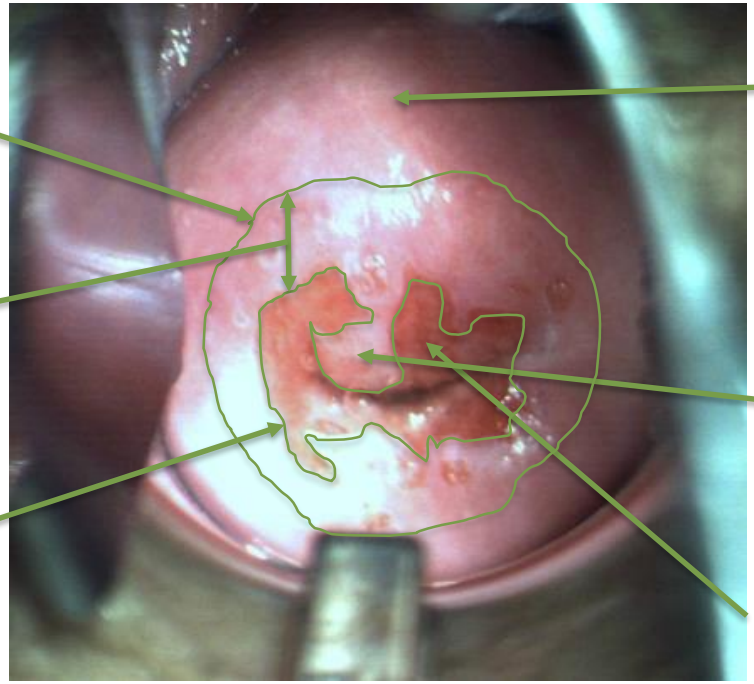

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HPV infection of the transformation zone causes dysplasia that can progress to cancer

Equivalent to HPV infection

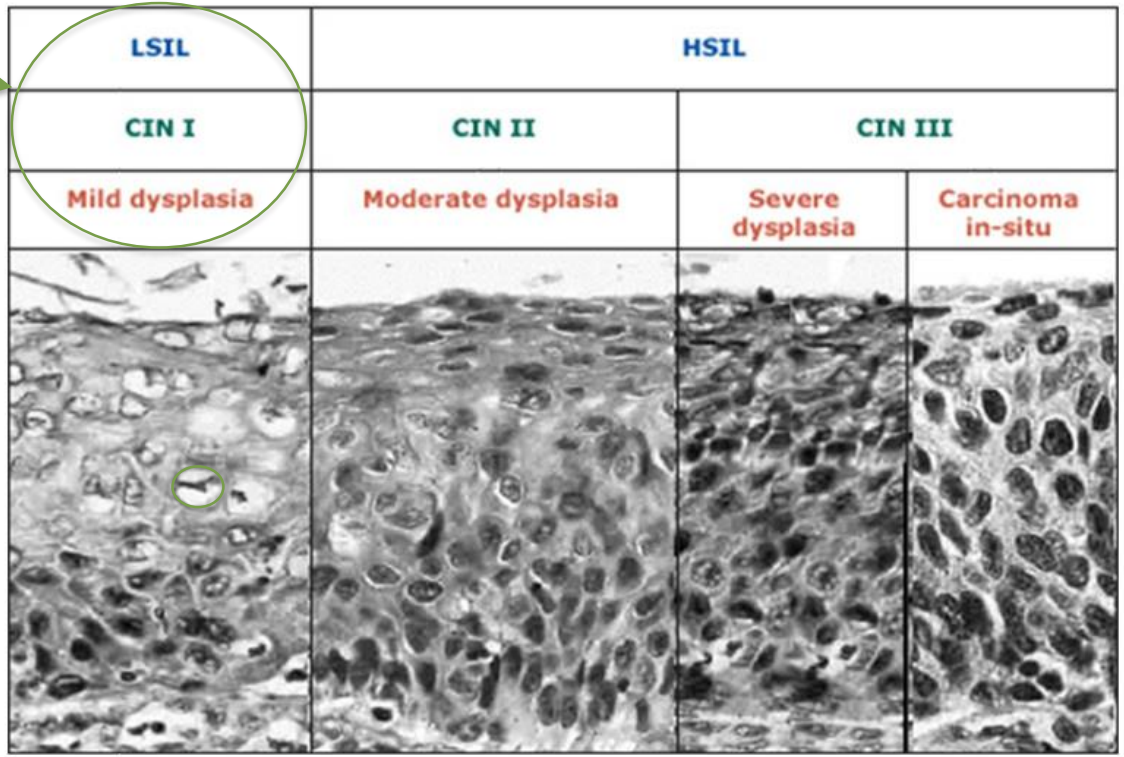
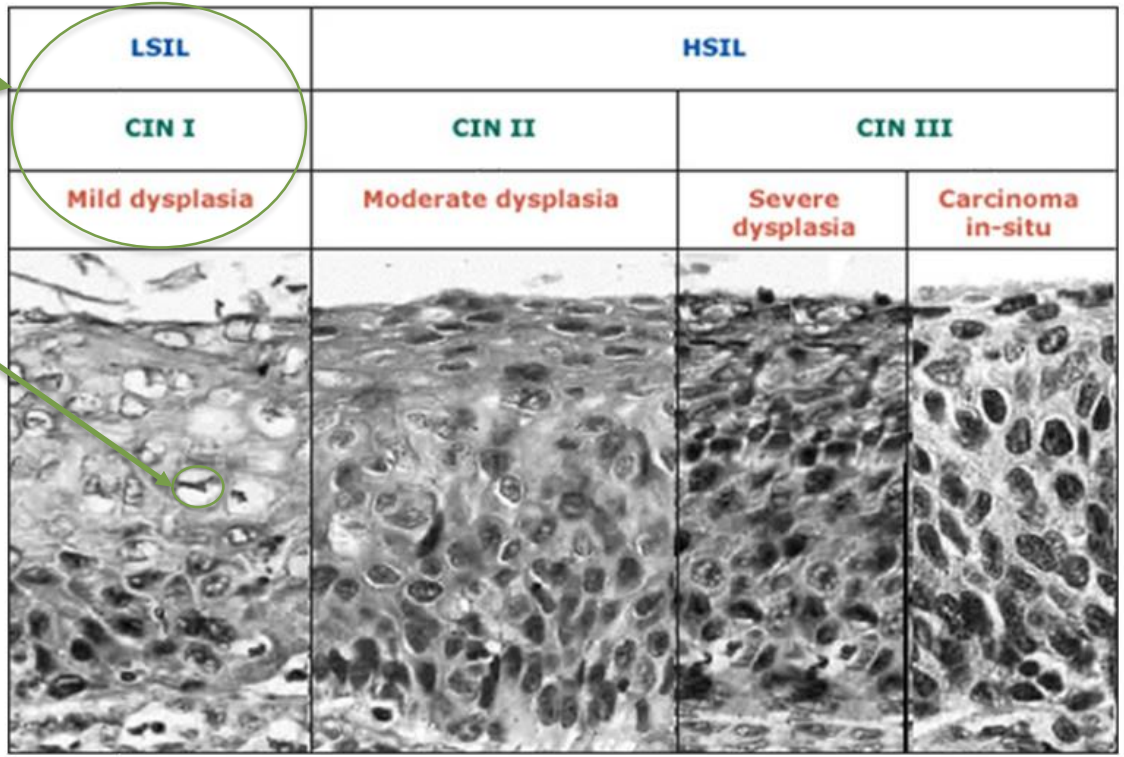


FIGURE: UPTODATE

HPV infection of the transformation zone causes dysplasia that can progress to cancer

Equivalent to HPV infection

Koilocyte: classic finding in HPV infection



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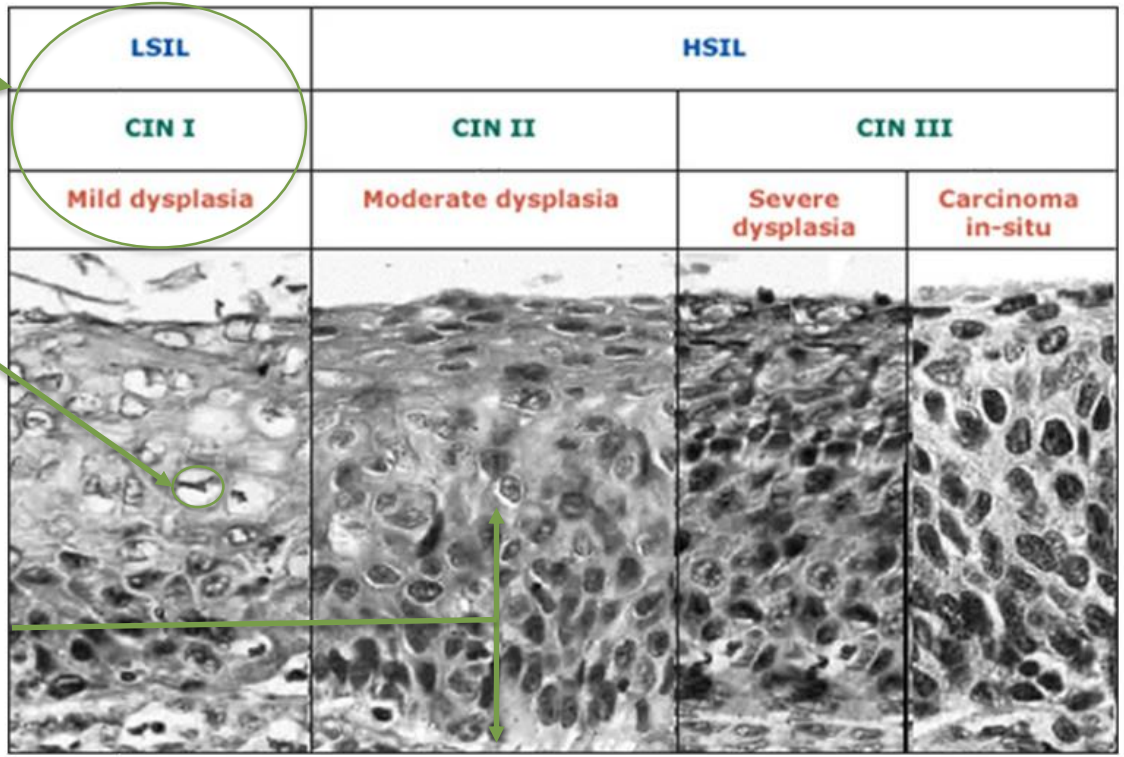

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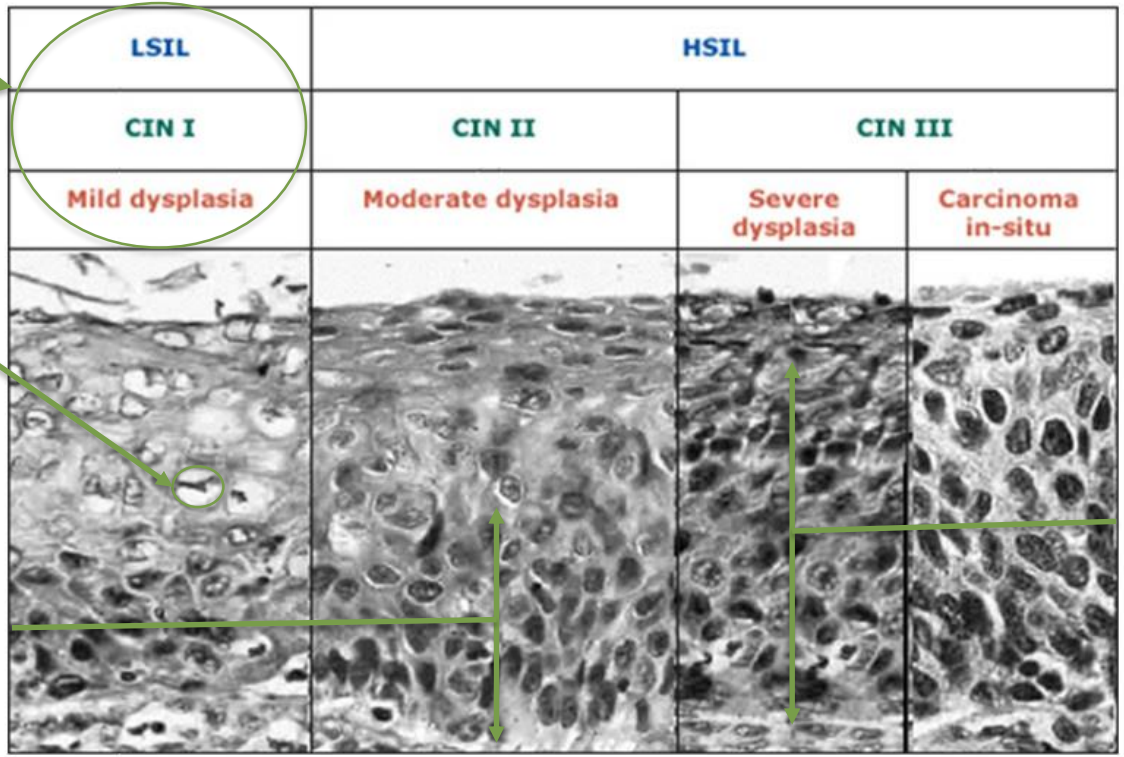
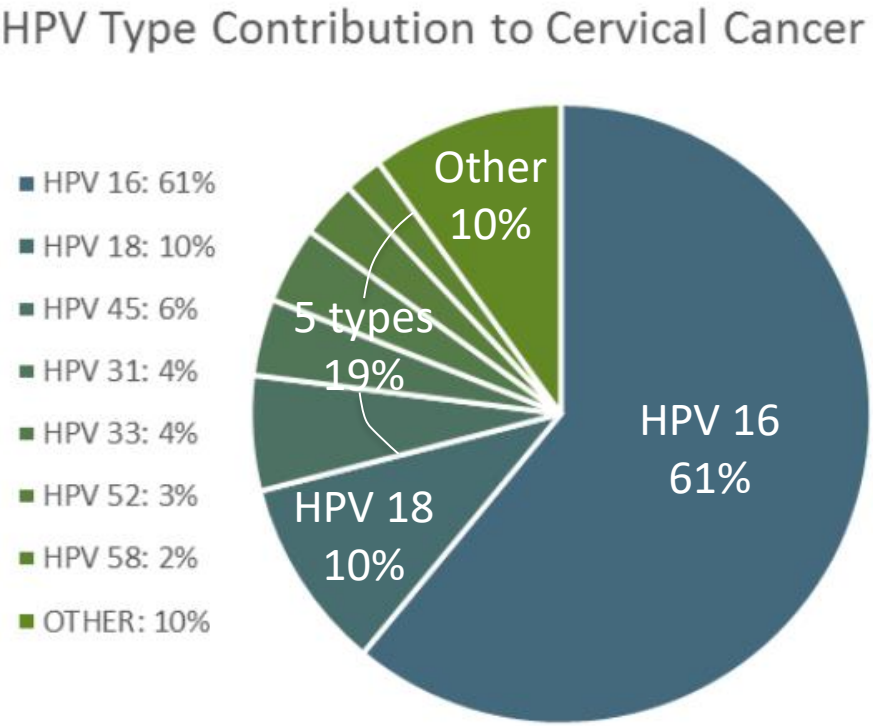


Dysplasia more than 2/3 of the epithelial thickness

FIGURE: UPTODATE

HPV types 16 & 18 cause most cases of cervical cancer



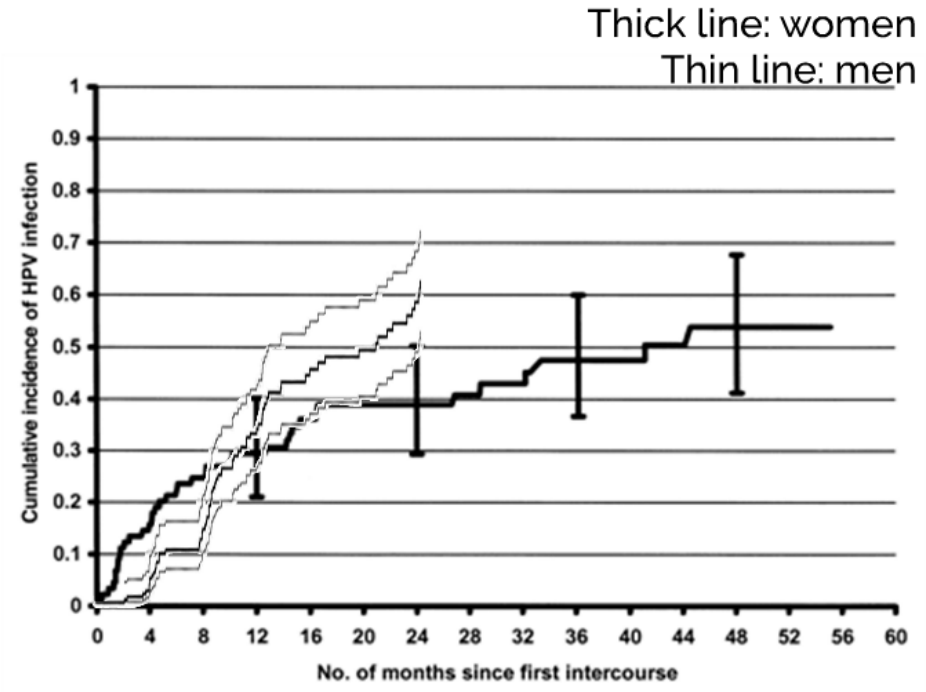
HPV is easy to get and essentially ubiquitous

- 79 million Americans are currently infected with some type of HPV.
  - Incidence: 14 million new cases per year
  - Prevalence: women 42.5%, men 61% (all HPV types)
    - hrHPV types: women 29%, men 23% (oncogenic HPV types)
- High risk HPV (hrHPV) infection is usually asymptomatic.
- Intercourse is not necessary for transmission of hrHPV.

Everybody has HPV

Acquisition of HPV Infection after Sexual Debut

College students were tested for hrHPV before and then periodically after first sexual intercourse.



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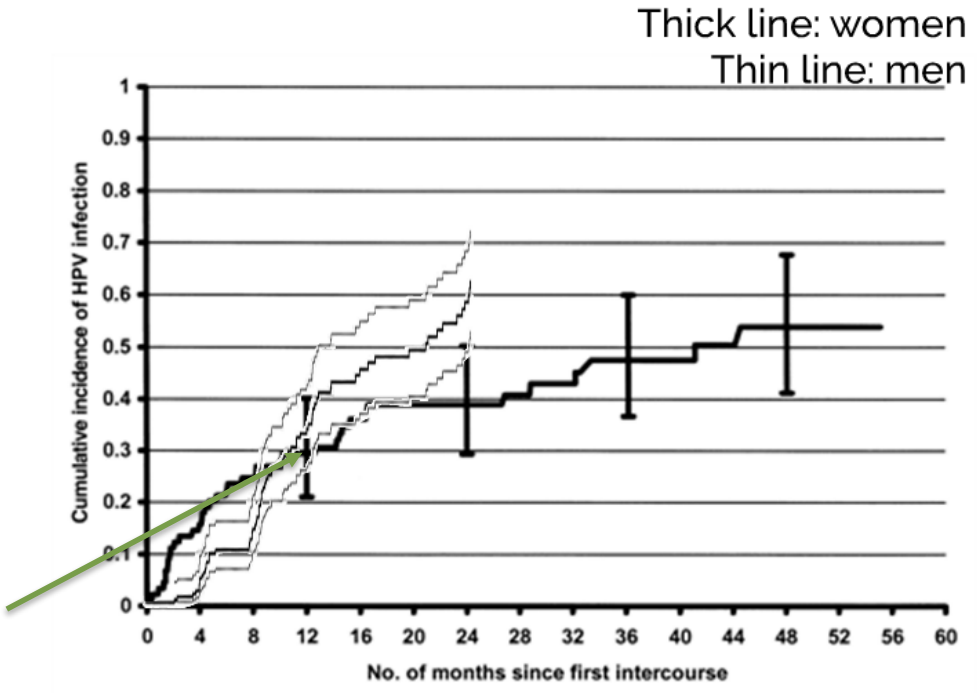

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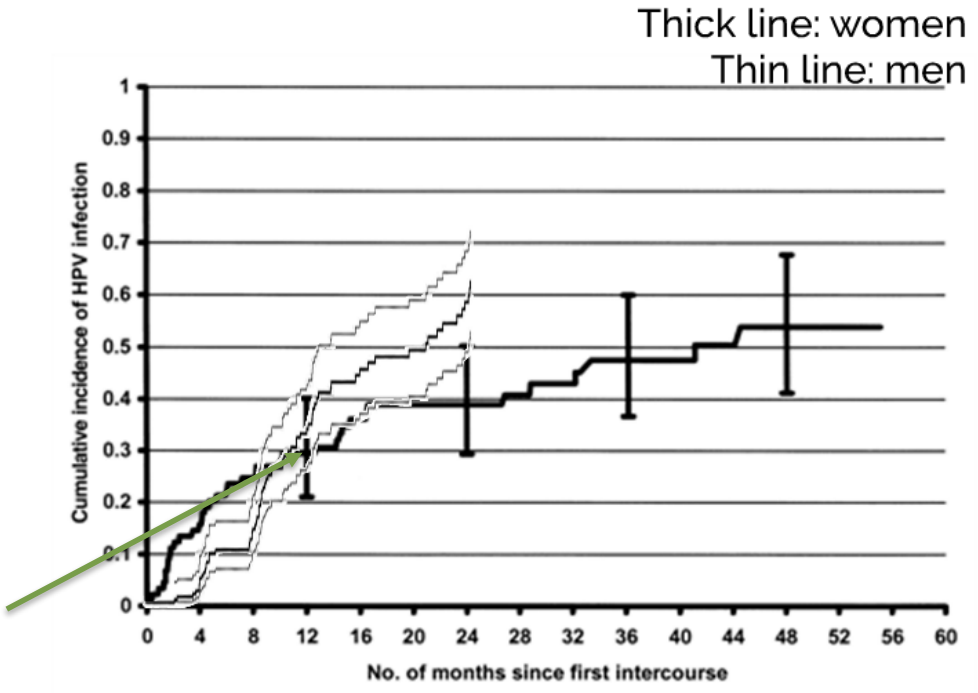


Cumulative incidence continued to rise over the next 1-3 years.

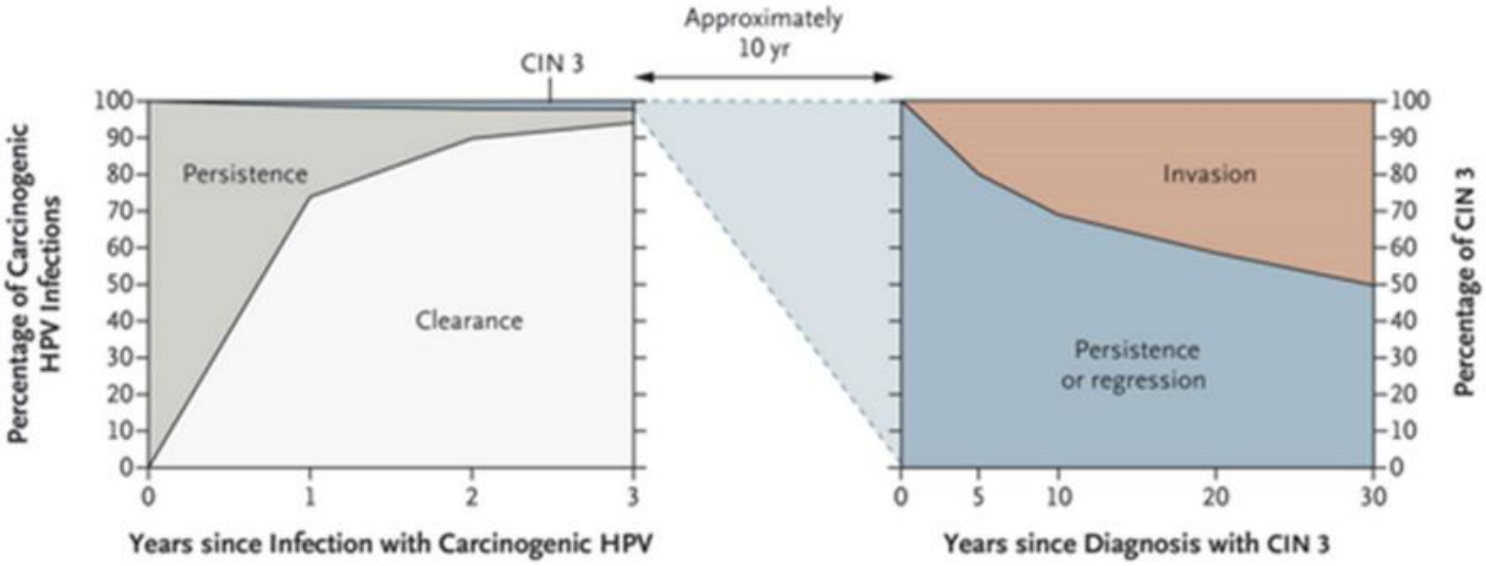
HPV is found in virgins with rapid increase in prevalence after sexual debut

- We know that vertical transmission occurs, though most neonatal infections have resolved by 12 months old.
- HPV has been detected in 46% of women before first intercourse.
  - 70% of infected women reported noncoital sexual activity.
- About 50% of high-school students have engaged in vaginal-penile intercourse.
  - 1/3 of 9th graders, 2/3 of 12th graders
  - 24% of high school seniors have had 4+ partners
- 40-60% partner concordance: about half the time both partners have the same strain; half the time they have different strains or one is infected and the other isn't

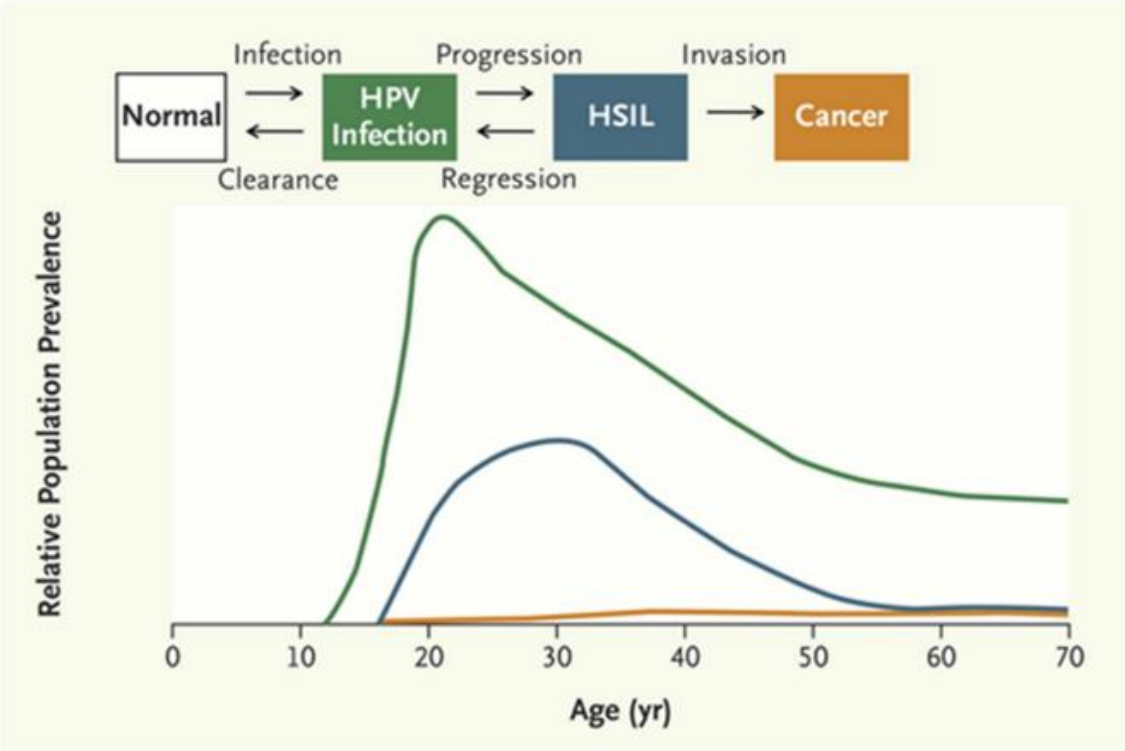
The HPV infection is often cleared before it is clinically significant

- 40-70% of infections resolve in one year.
- 70-100% of infections in young women resolve in 2-5 years.
  - Infection may persist at undetectable levels.
  - More likely, women make antibodies to specific HPV types.
- Men clear 75% of infections in one year.

Typical time course of infection with carcinogenic human papillomavirus, from acquisition to the development of squamous-cell cancer



Age at peak prevalence for each stage in cervical carcinogenesis



Agenda

- Human papillomavirus (HPV)
  - Natural history
- **Cervical cancer screening**
  - **Past, present, future**
- Vaccination
  - Efficacy
  - Strategies to increase uptake

Cervical Cancer Screening

- Characteristics of a good screen
  - Disease is prevalent
  - Test is tolerable and inexpensive with good sensitivity
  - Treatment after detection makes a difference in patient outcomes
- Approaches to cervical cancer screening have changed based on new understanding of the natural history of HPV.

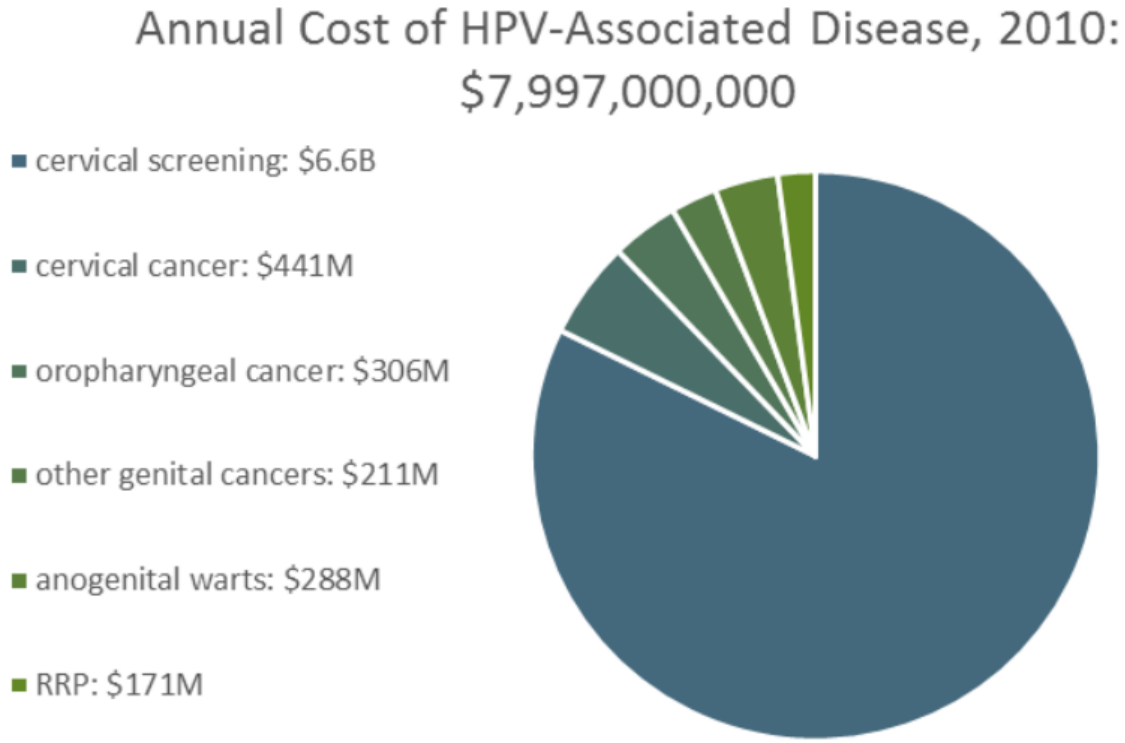
Traditional Strategy: Cytology alone

- Great specificity (98%) but sensitivity is only 51%.
- This works because high grade dysplasia persists for years before progression to cancer.
- The limited sensitivity requires annual screening with a low threshold for additional testing and treatment.
- This approach detects early disease that would resolve spontaneously, leading to unnecessary cost and risk (treatment can be associated with preterm labor and low birth weight).

High-risk HPV testing reduces unnecessary testing

- In 1999, we started adding reflex hrHPV testing on ASCUS Paps.
  - hrHPV negative: continue annual screening
  - hrHPV positive: immediate colposcopy
- In 2004, we began routine hrHPV cotesting for women 30 and over.
  - Normal cytology with negative hrHPV testing allowed us to extend the Pap interval to 3 years.

Pap testing is expensive



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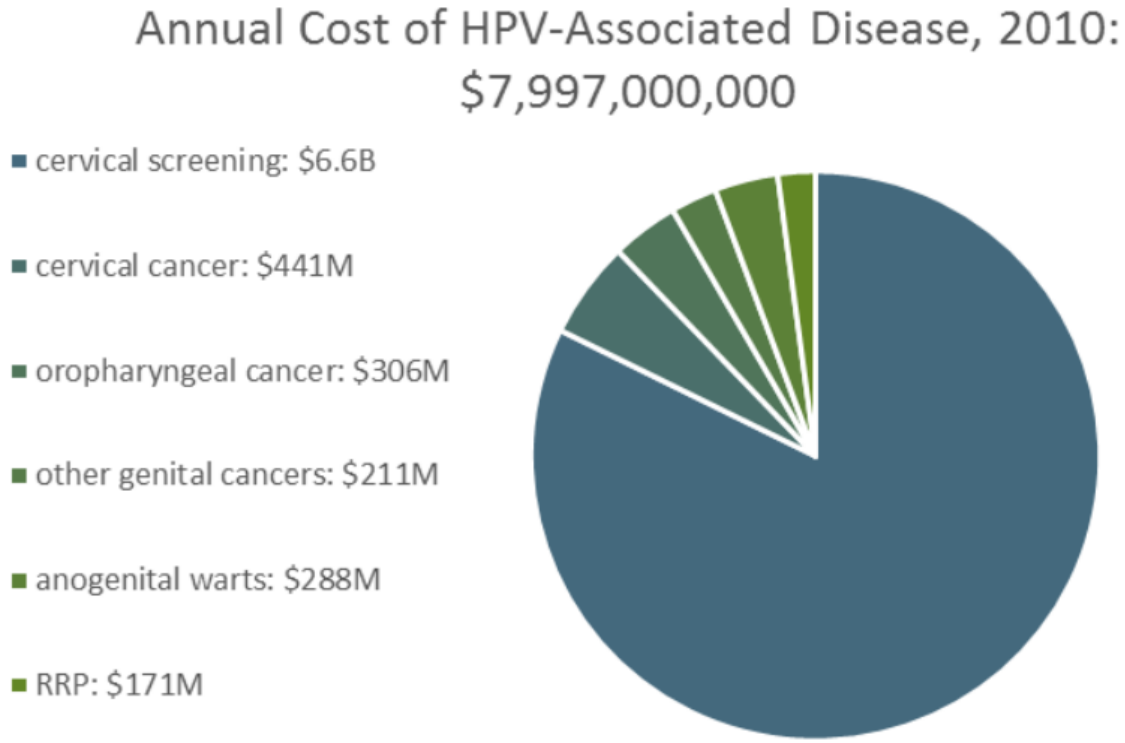

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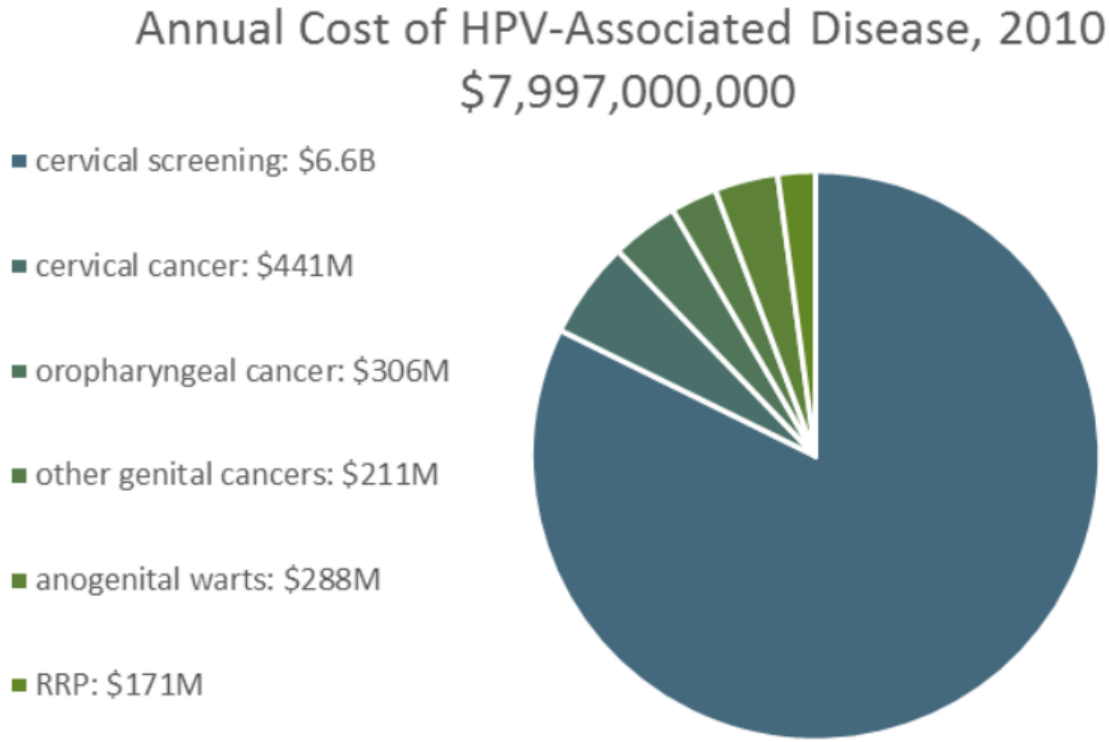
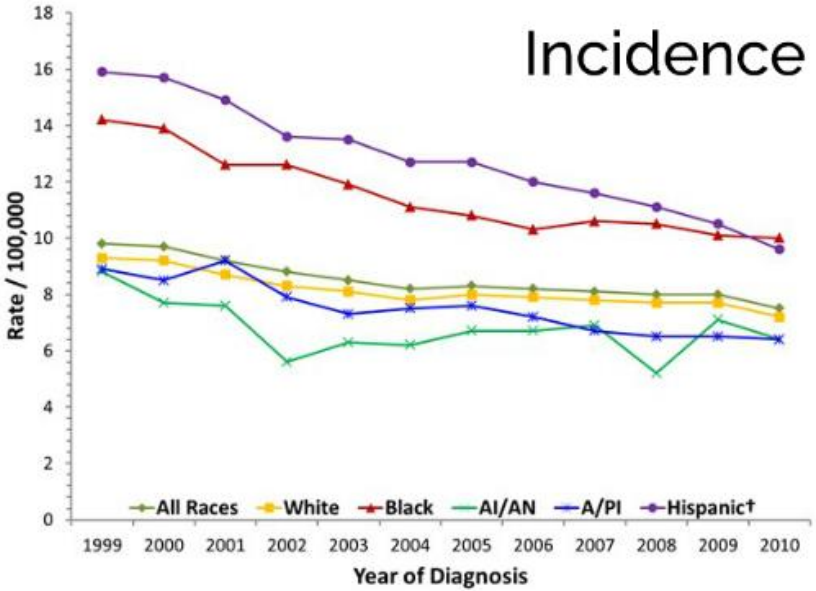
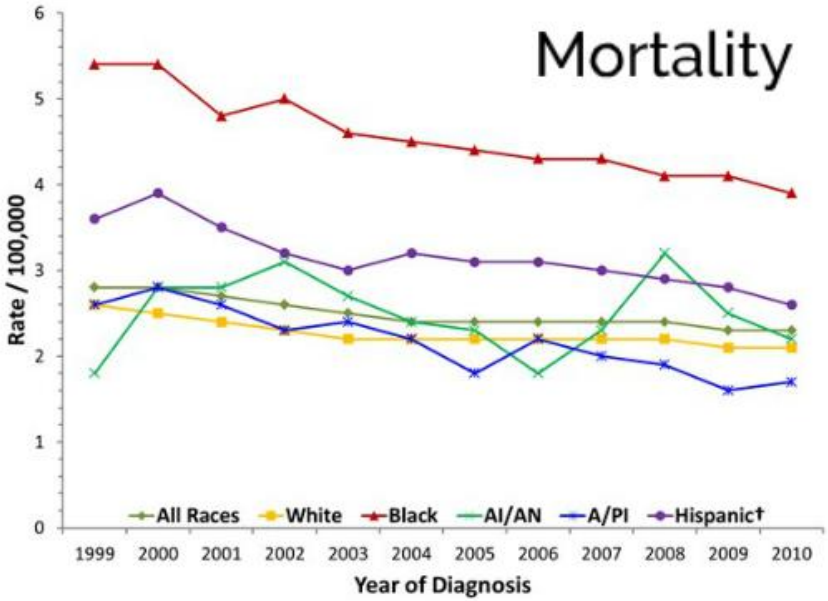


Recurrent respiratory papillomatosis is a rare effect of vertically transmitted HPV. Papillomas along the trachea can interfere with breathing and require episodic resection under bronchoscopy.

Pap testing has decreased the incidence and mortality of cervical cancer





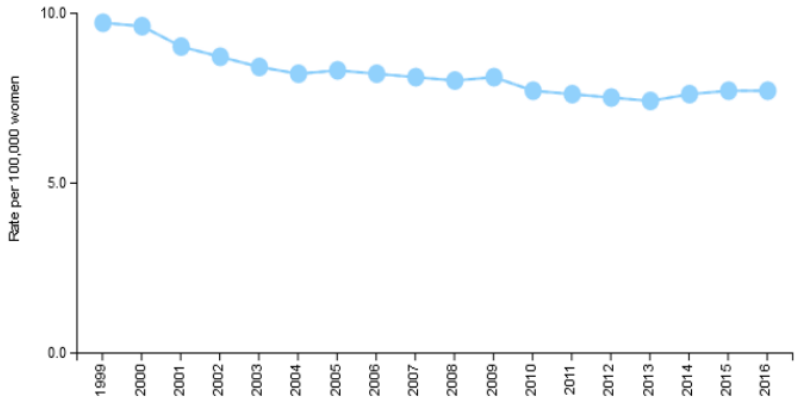
Racial disparities exist in both incidence and mortality of cervical cancer.

Updated data: trends 2009 to 2016

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

Annual Rates of New Cancers, 1999-2016

Cervix, United States



Data source – U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on November 2018 submission data (1999-2016): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; https://www.cdc.gov/cancer/dataviz, June 2019.

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Annual Rates of Cancer Deaths, 1999-2016

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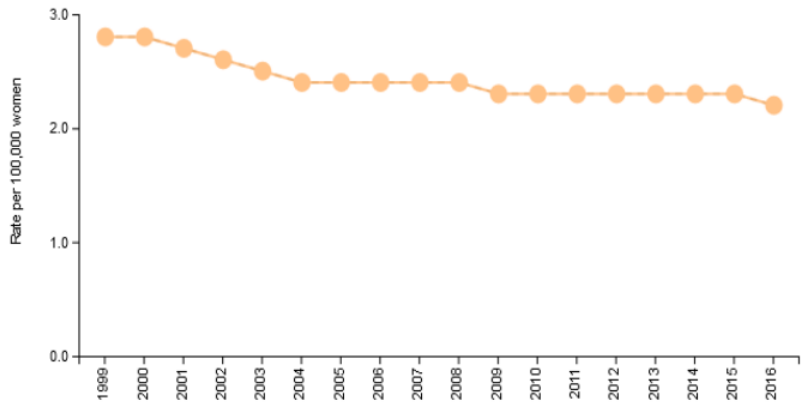

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Updated data: racial disparities in 2016

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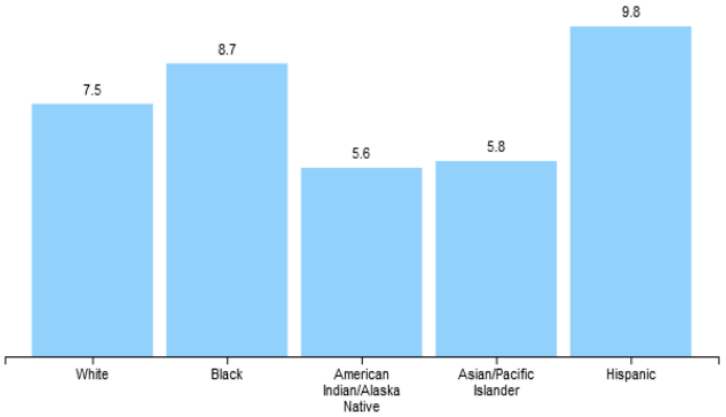
Rate of New Cancers by Race/Ethnicity, Female

Cervix, United States, 2016



Rate per 100,000 women

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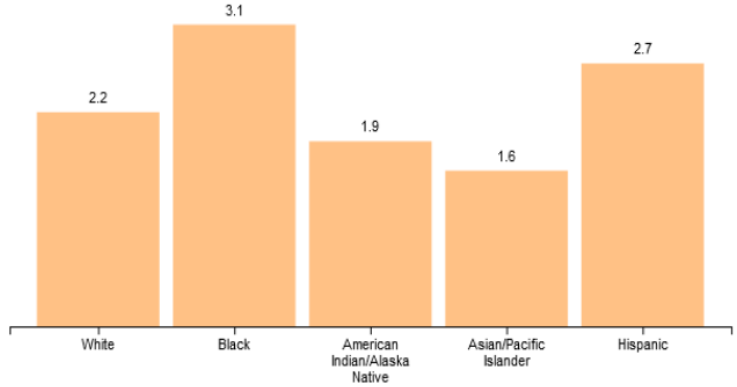

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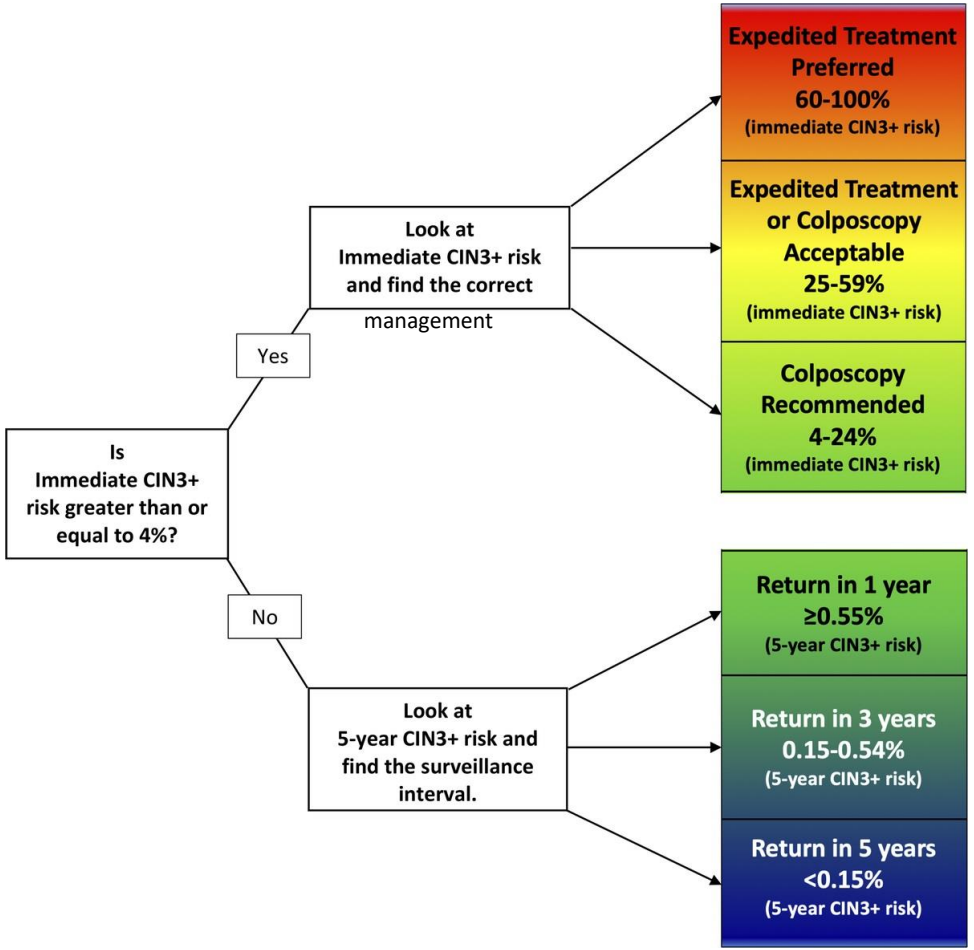
Current ASCCP Guidelines

- Screen:
  - Age 21-29 with cytology, q3yr
  - Age 30-65 with cytology and hrHPV, q5yr
    - cytology alone q3yr is acceptable
  - After diagnosis of CIN2+, screen q3yr for 25 years
- Do not screen:
  - Age < 21 yo
  - Age > 65 yo
  - After hysterectomy without CIN3

Management recommendations are based on risk of developing CIN3+. This allows new data to be entered “behind the scenes” so instead of using static algorithms, we can use a more dynamic application.



Adolescents under 21 years old:
DO NOT SCREEN

- In this group, the prevalence of HPV is high but cervical cancer is rare (0.1 cases per 100,000 people).
- We would need to screen 1 million adolescents to prevent one case of cancer.
- The incidence of cervical cancer in this age group is unchanged since the 1970s, indicating that screening has not affected cancer rates.

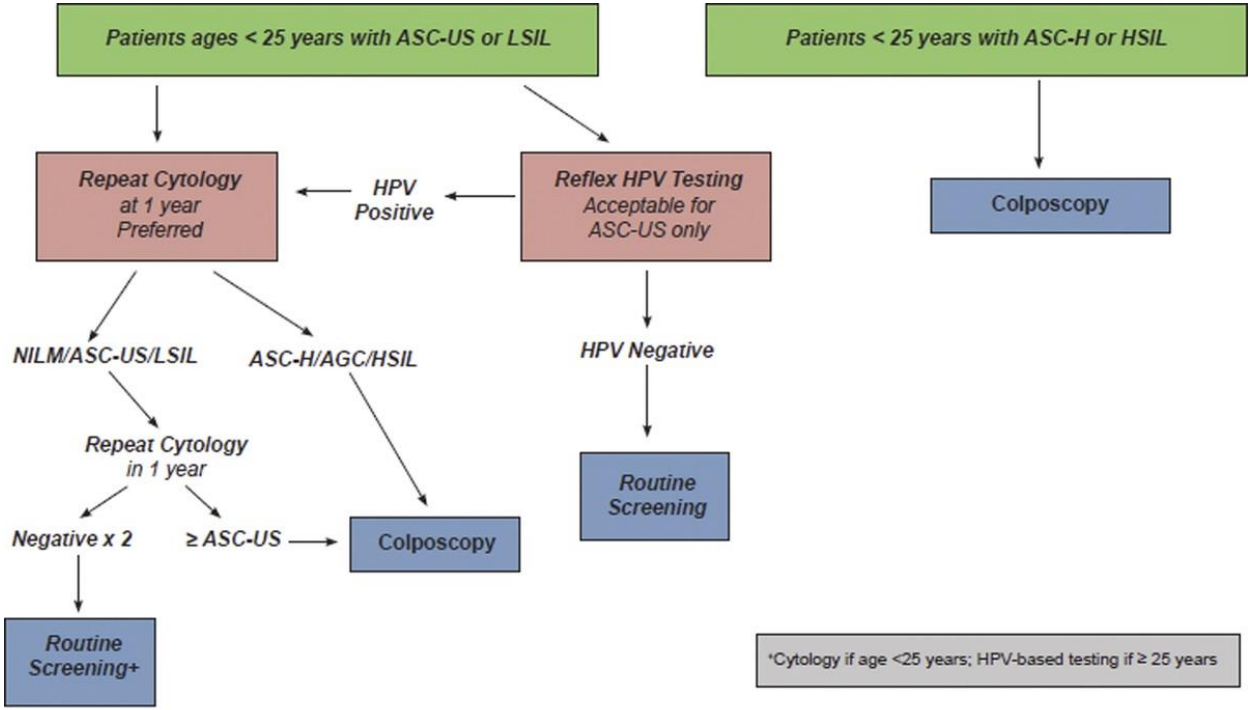
Young women 21 to 29 years old:
SCREEN EVERY 3 YEARS

- The HPV prevalence is about 50% in this age group.
- Cancer rates are low.
  - 21-24: 1.2-1.4/100,000
  - 25-29: 5.1/100,000
- Screening every 2 years leads to more colposcopy compared to 3 years, without reducing the mortality rate of 5 per 100,000.
- Extending the screening interval beyond 3 years increases rates of CIN3.

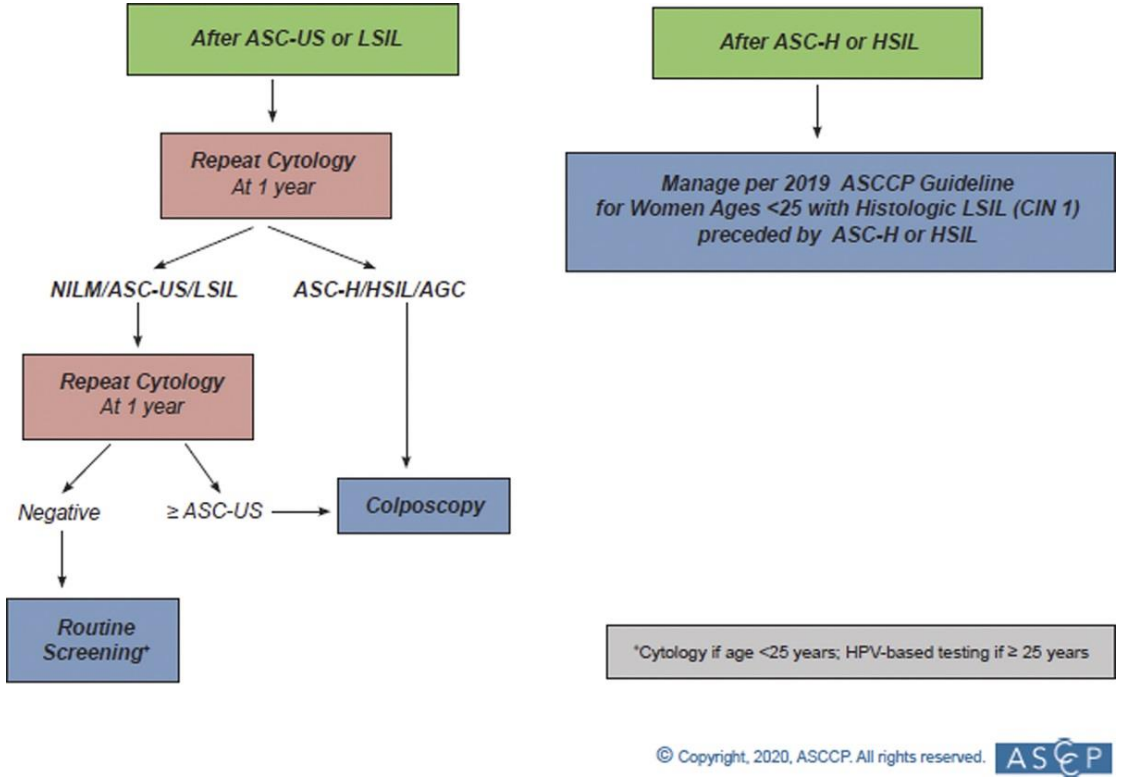
Management is less aggressive at 21-24 yo

- Because HPV is very common and often clears spontaneously, we can wait to see if the infection persists.
- The three year risk of CIN3 is 3%, compared to 5.2% after age 30.
- Treatment can lead to complications with further pregnancy, so being more aggressive can worsen outcomes overall.

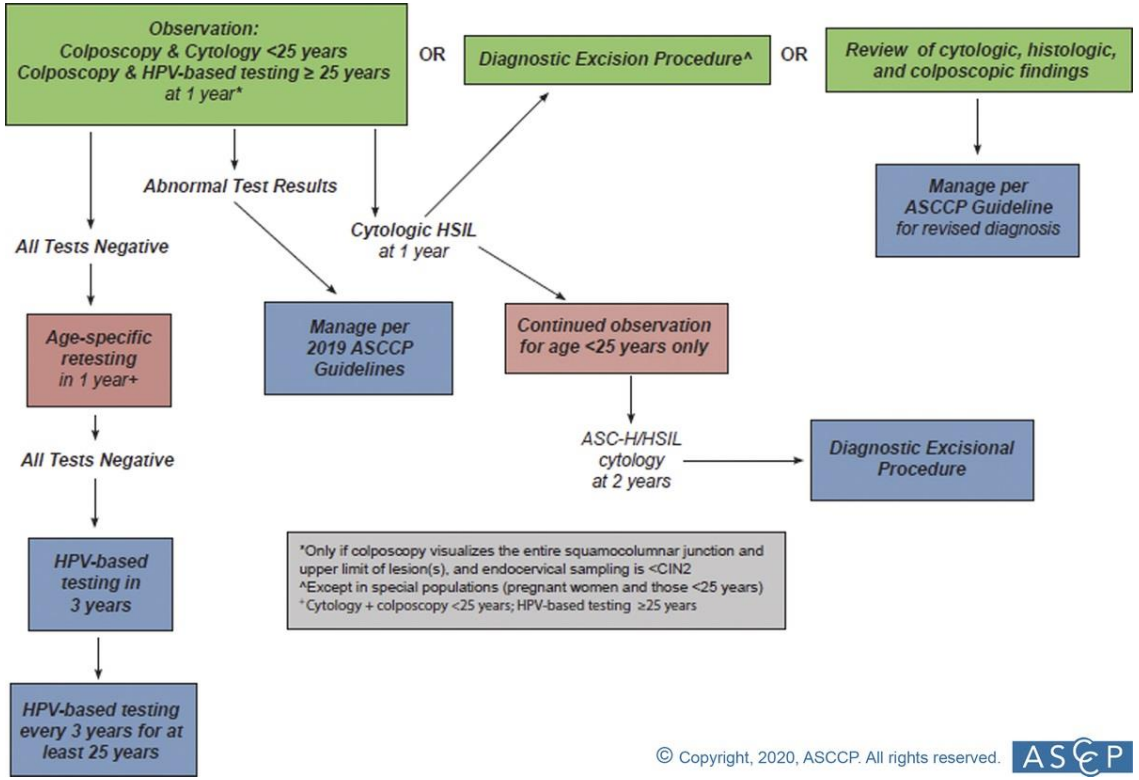
Management of Patients under 25 with Cytologic Abnormalities



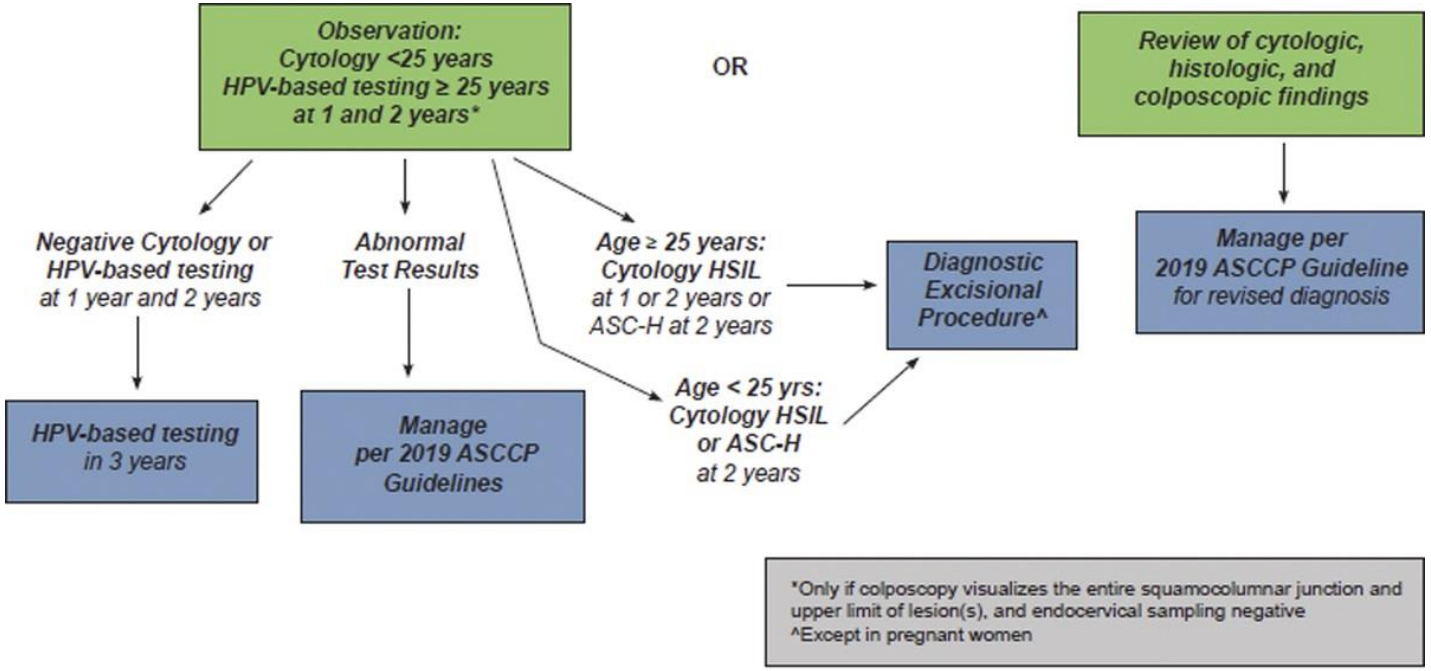
Management of Patients under 25 with CIN1 on Colposcopy



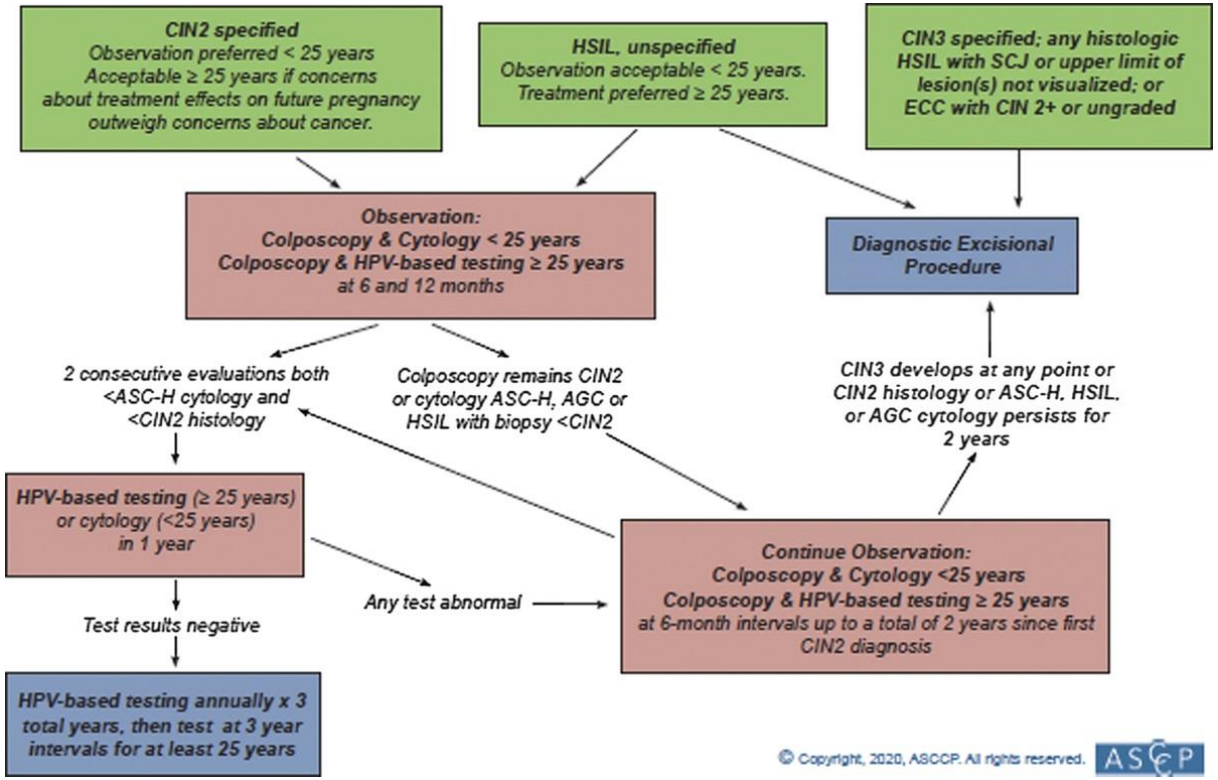
Management of Patients with CIN1 on Colposcopy after HSIL



Management of Patients with CIN1 on Colposcopy after ASC-H



Management of Patients with CIN2 on Colposcopy



Women 30-65 years old

SCREEN WITH CYTOLOGY EVERY 3 YEARS or SCREEN EVERY 5 YEARS WITH hrHPV COTESTING

- Cervical cancer prevalence increases to 24/100,000 after age 30. The goal is to catch people before they get to CIN3.
- A European cohort study demonstrated that the chance of developing CIN3 was the same (0.16-0.17%) 3 years after normal cytology, 5 years after a negative hrHPV test, and 5 years after normal cytology with a negative hrHPV test.
- A Kaiser Permanente cohort study found that CIN3 rates were higher 5 years after normal cytology alone than they were 5 years after normal cytology with a negative hrHPV test.
- The conclusion is that it is safe to wait 5 years to screen again if we have normal cytology and negative HPV, but if we only have cytology results, we need to screen again in 3 years.

30-65: hrHPV testing

negative

- Goal: minimize unnecessary testing
- After 30 years old, new infection is less likely
- Positive tests are more likely to be false positives (lower positive predictive value)

NILM/hrHPV negative:

NEXT SCREEN IN 5 YEARS

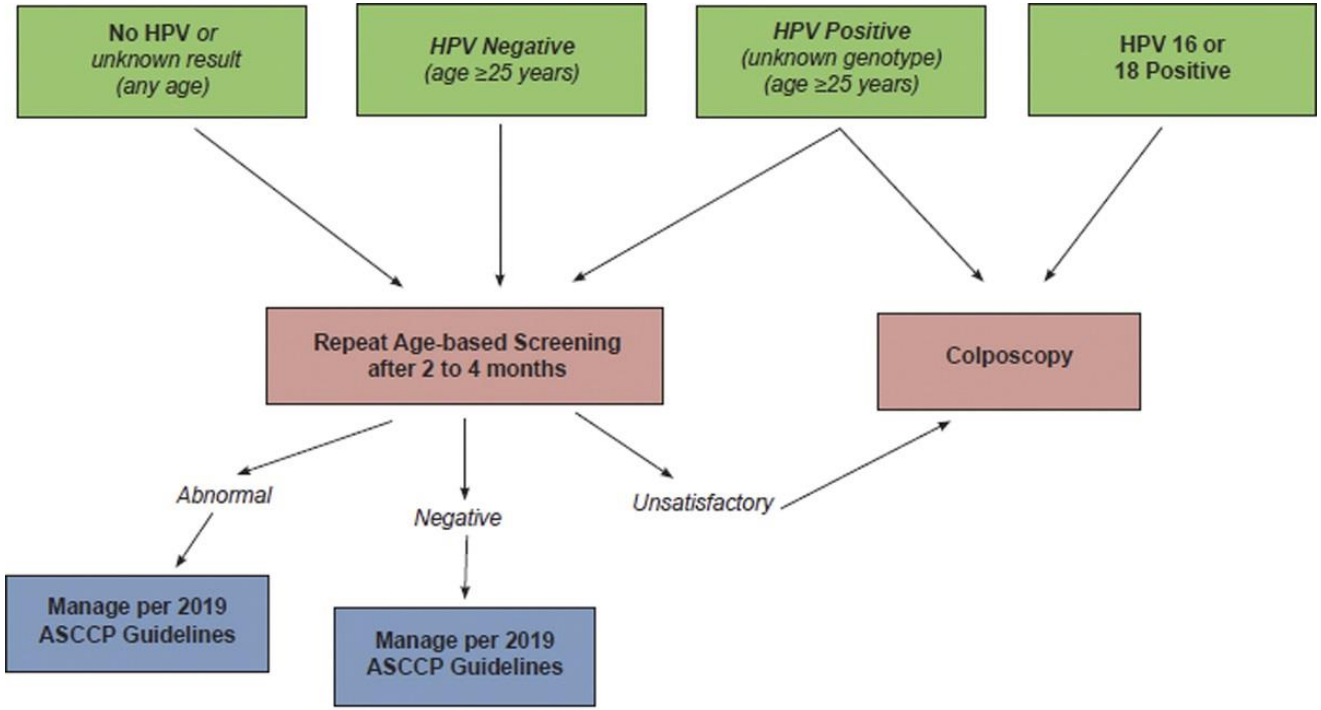
positive

- Goal: detect persistent HPV infection
- Highest rates of cervical cancer

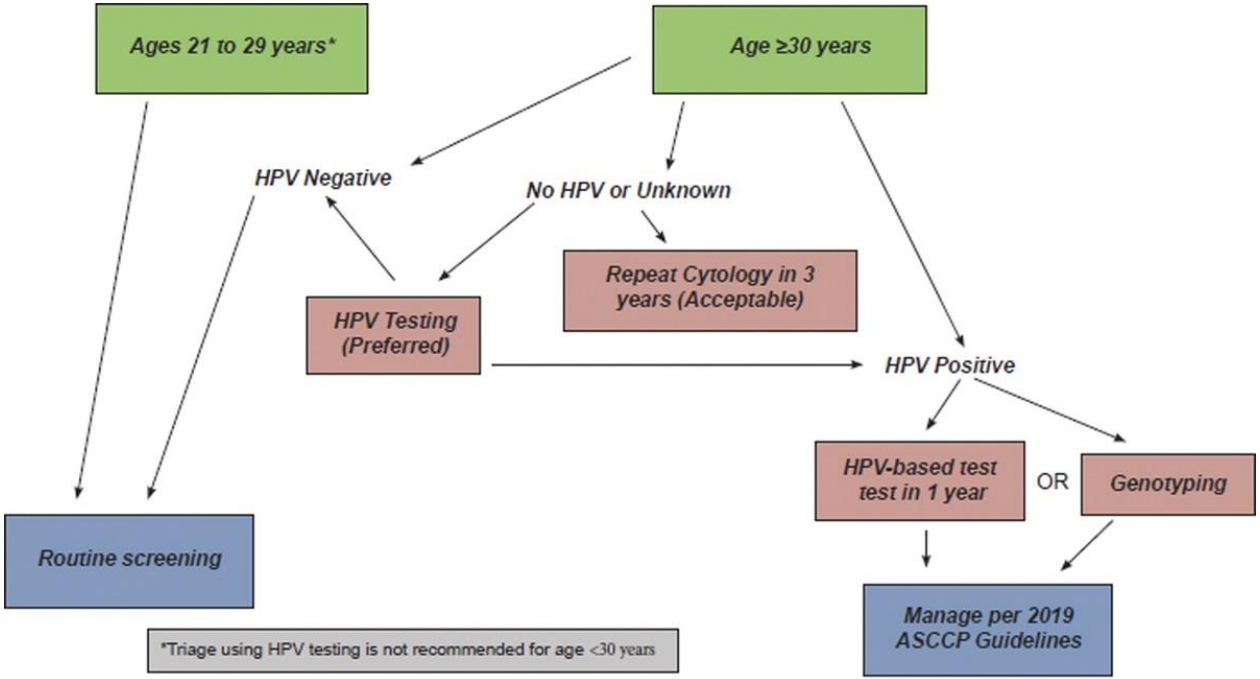
hrHPV positive, abnormal cytology:

COLPOSCOPY

Management of Patients with Unsatisfactory Cytology



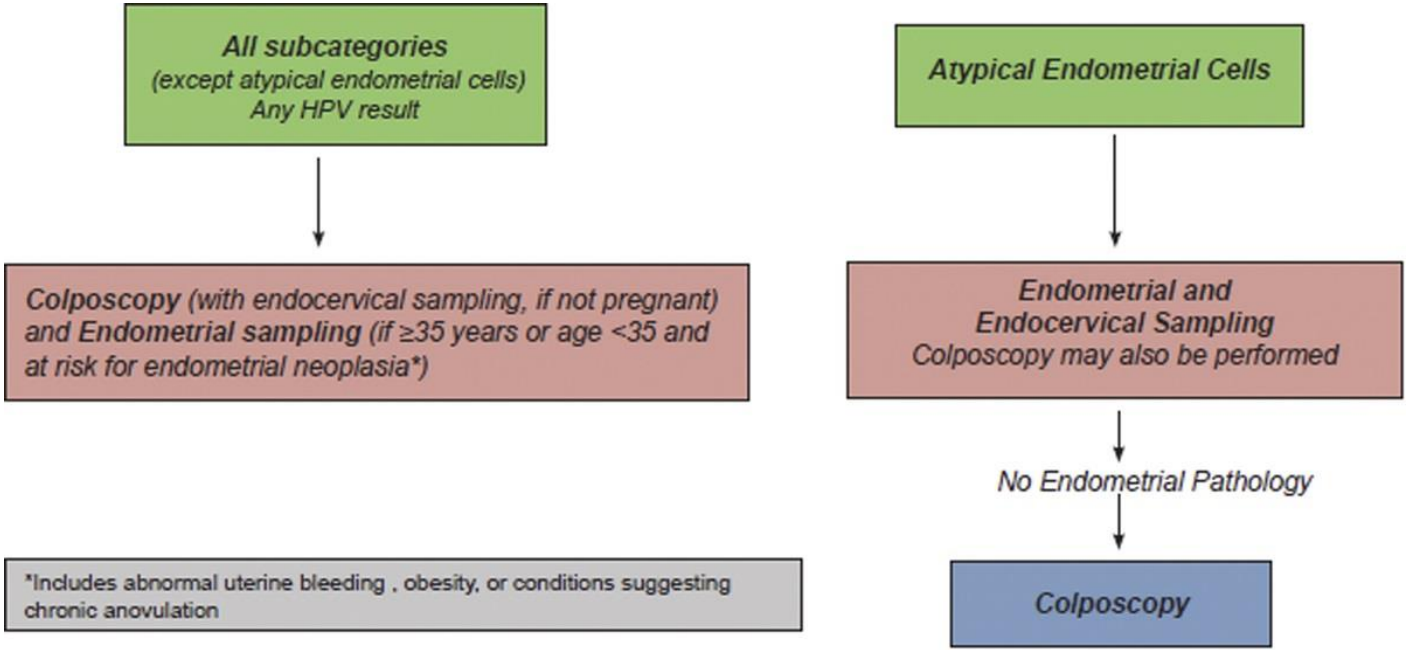
Management of Patients with Normal Cytology but Absent Transformation Zone or Endocervical Cell Component



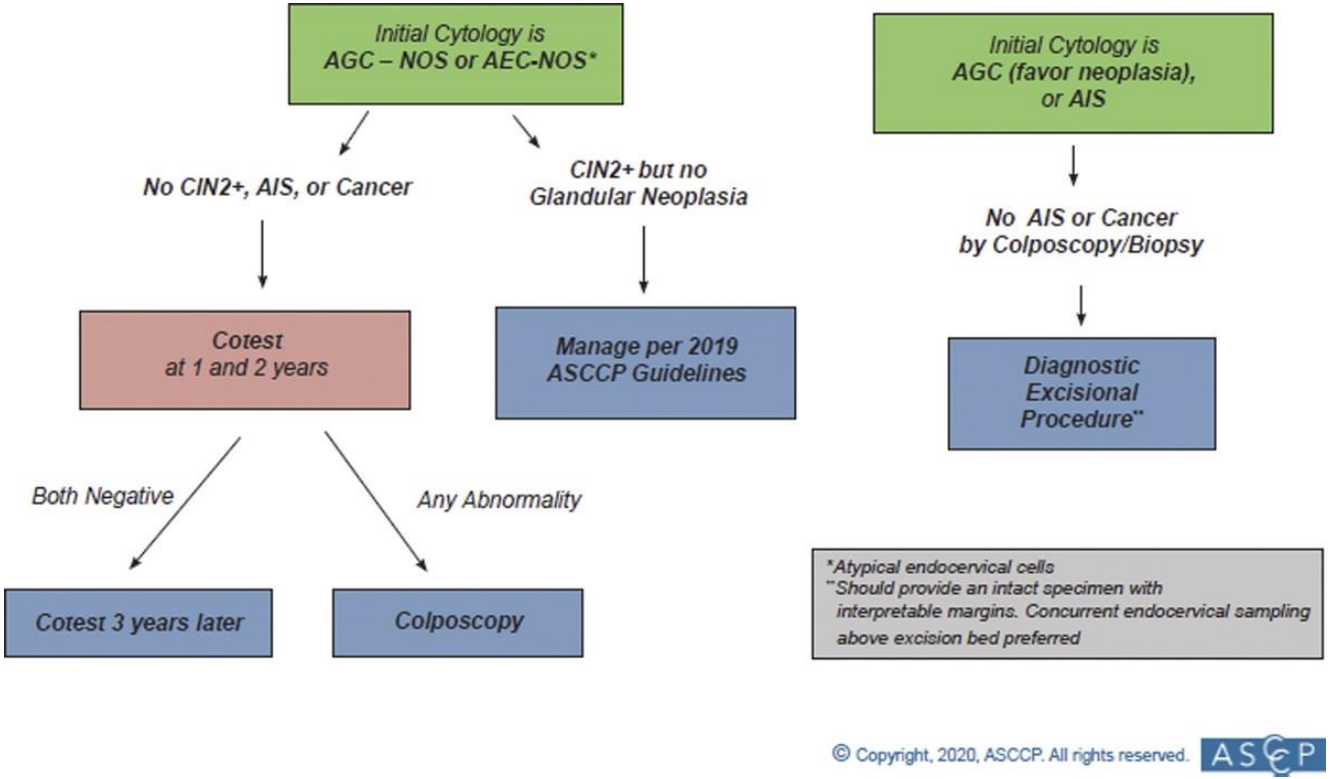
Adenocarcinoma/Adenocarcinoma *in situ*

- This is a cancer of columnar cells rather than squamous cells.
- Because columnar cells line the endocervix, adenocarcinoma can be harder to detect with cytology.
- hrHPV testing improves detection.

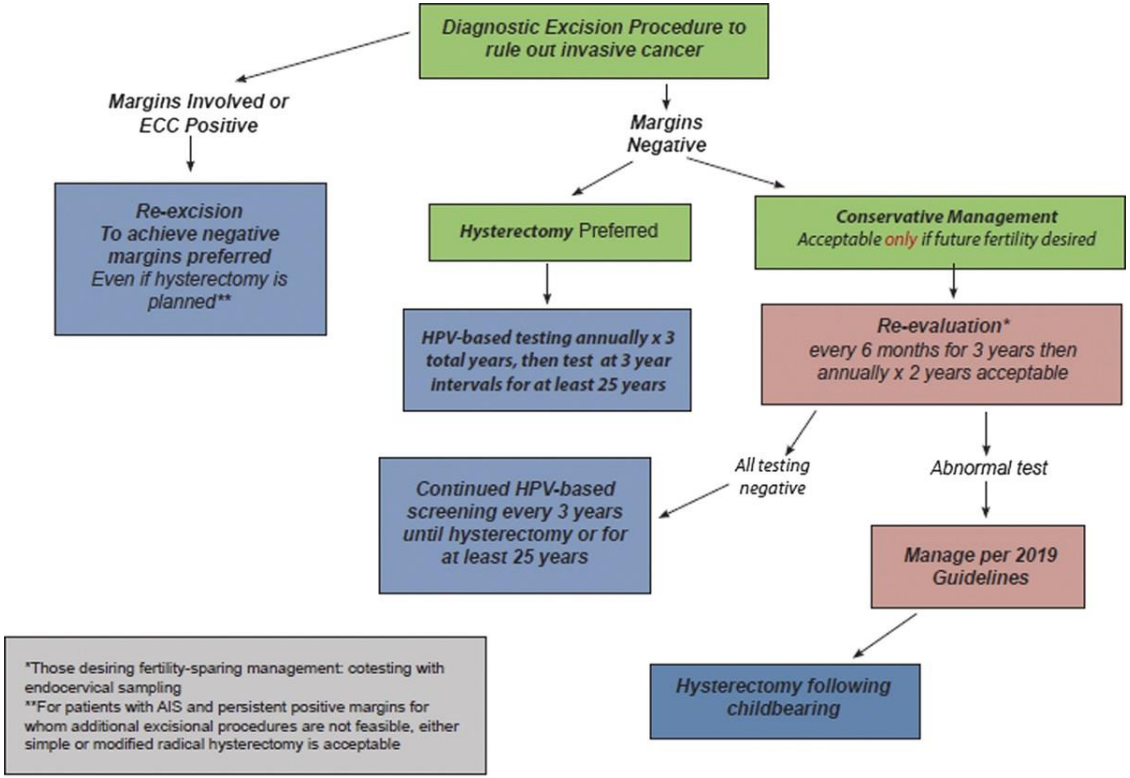
Management of Patients with Atypical Glandular Cells on Cytology



Management of Patients after Evaluation for AGC



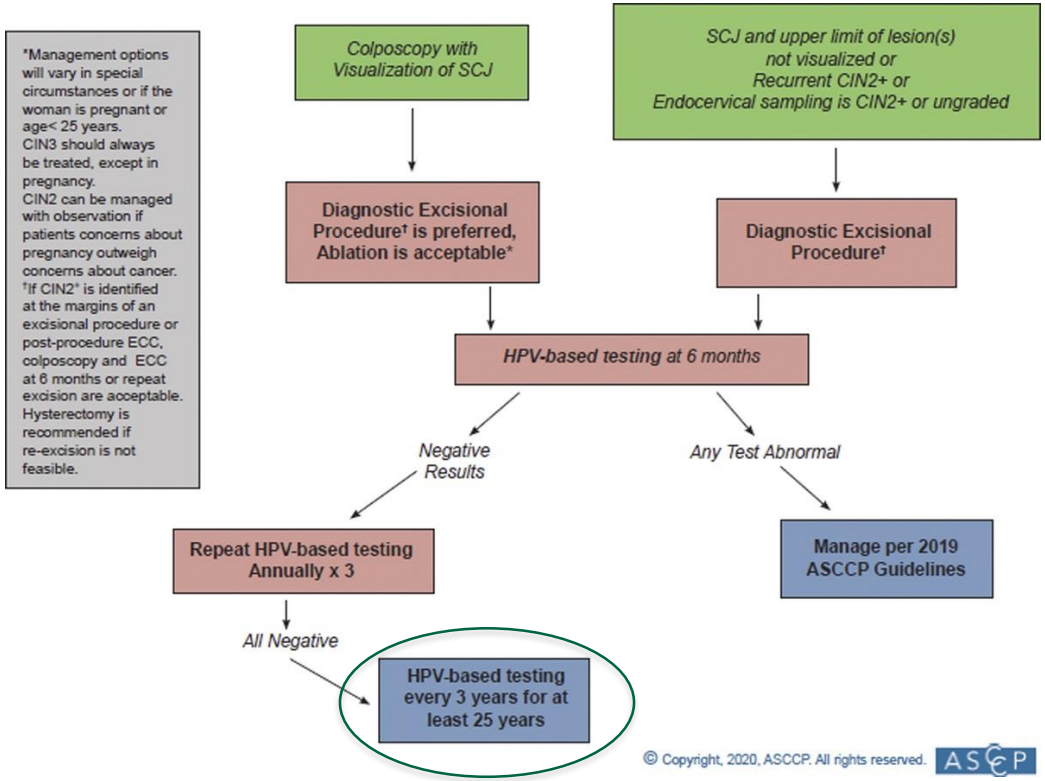
Management of Patients with Adenocarcinoma *in situ*



Women over 65 years old:
DO NOT SCREEN

- The transformation zone is smaller with less exposure to HPV.
- Continuing screening to age 90 prevents only 0.5 deaths per 1000 women, with 127 more colposcopies per 1000 women.
- Stop only if adequate screening is documented.
  - cytology: 3 consecutive NILM in past 10 yr
  - cotesting: 2 consecutive negative hrHPV tests in past 10 yr
  - most recent screen < 5 years ago
- CIN2+: screen every 3 years until 25 years after diagnosis.

Management of Patients with CIN2 or CIN3



cobas HPV test

- This test allows genotyping of hrHPV.
- Three results reported
  - Type 16
  - Type 18
  - Pooled result for high risk types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68
- This can be useful in directing toward immediate colposcopy for HPV16 (most common) or HPV18 (most aggressive) in certain situations.

Primary HPV screening

ATHENA trial

- cytology alone:
  - lowest sensitivity for CIN2+
- 1° HPV testing then HPV typing:
  - highest sensitivity for CIN2+
  - more colposcopy
- cytology and hrHPV cotesting:
  - similar sensitivity to 1° HPV
  - more screening (two tests)

- As a screening test is meant to be highly sensitive, it makes sense to use primary HPV screening rather than cytology.
- Maybe you are already doing this at your institution?

Screening in the vaccinated patient

- Vaccination will decrease the prevalence of HPV infection, decreasing the positive predictive value of the test.
  - This results in more false positive tests and more unnecessary interventions.
- Primary hrHPV testing may be the best approach.
- Consider starting at 25 years old, as the prevalence of cancer will be even lower in patients under 25.

Consider delaying screening until 25 years old

Suggested prerequisites for this option:

- Documented completion of vaccination series
- No sexual activity prior to vaccination
  - Frank discussion of activity that leads to HPV exposure – it's not just penile-vaginal intercourse!
- Confidence that patient will return at 25 yo for screening
- Initial screening must have high sensitivity
  - Detection of lesions from types other than 16 and 18
  - Cytology alone is not adequate

American Cancer Society Screening Guidelines

- **Cervical cancer screening should start at age 25.** People under age 25 should not be tested because cervical cancer is rare in this age group.
- **People between the ages of 25 and 65** should get a primary HPV (human papillomavirus) test done every 5 years. If a primary HPV test is not available, a co-test (an HPV test with a Pap test) every 5 years or a Pap test every 3 years are still good options.

Agenda

- Human papillomavirus (HPV)
  - Natural history
- Cervical cancer screening
  - Past, present, future
- **Vaccination**
  - **Efficacy**
  - **Strategies to increase uptake**

The HPV Vaccine

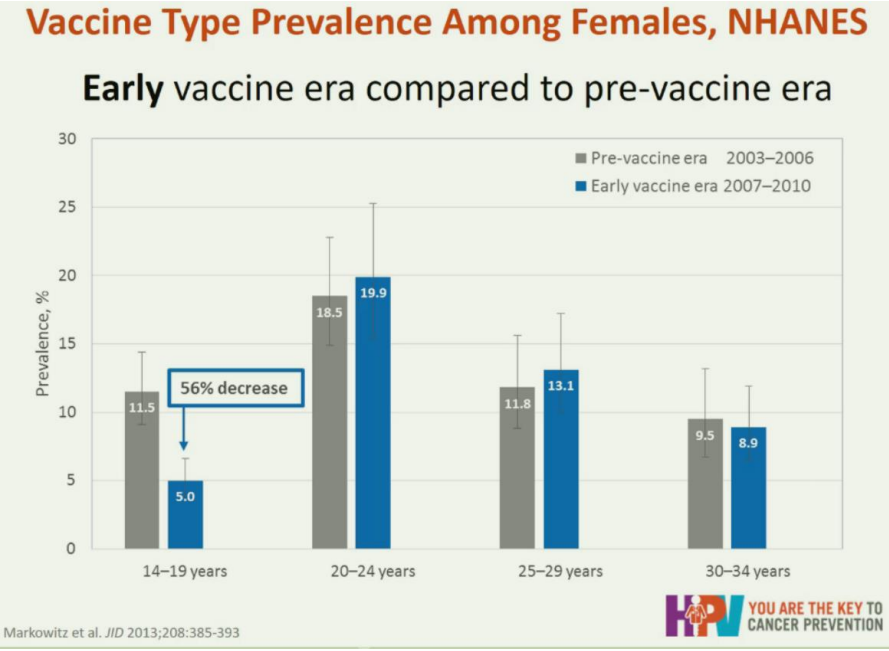
- Vaccination is effective.
- Vaccination is safe.
  - We have data from 2006-2018 indicating that most adverse effects are mild. Also, serious adverse effects do not cluster, suggesting that they are not due to the vaccine.
- Early vaccination is more effective than later vaccination.

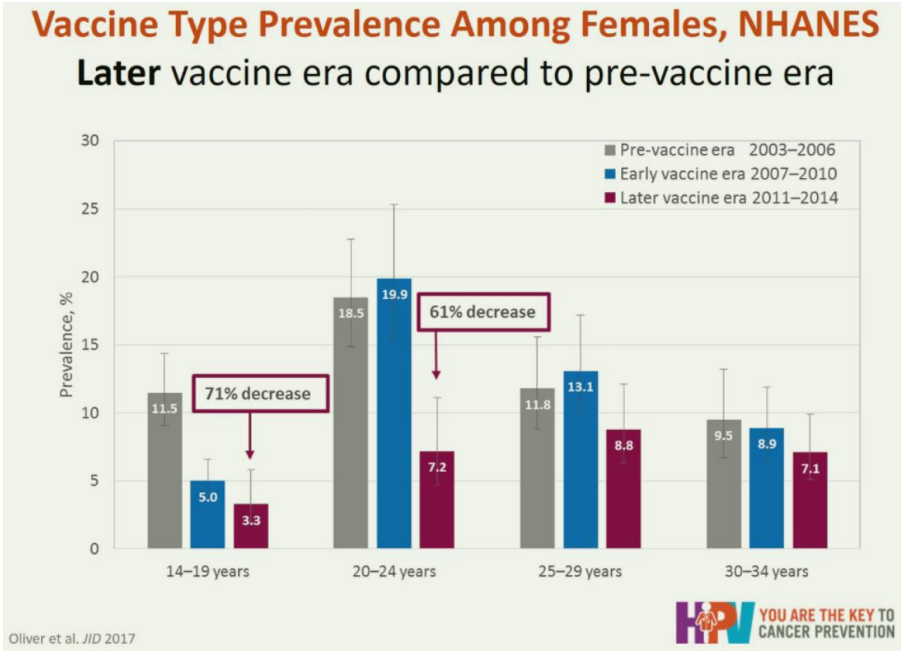
Initial Efficacy Data

- In Australia, once 70% of girls were vaccinated, incidence of anogenital warts decreased by 85% in girls and 71% in boys, even though the boys were not vaccinated.
- In the US, even with only 32% of girls vaccinated, efficacy was demonstrated:
  - HPV prevalence down 56% (11.5% to 5.1%)
  - HSIL down from 834 to 688 cases per 100K
  - decrease in AG warts in military patients

ALI H. BMC INFECT DIS 2013; GARLAND SM. PREV MED 2011; MARKOWITZ LE. J INFECT DIS 2013;
NICCOLAI LM. CANCER EPIDEMIOL BIOMARKERS PREV 2013; NSOULI-MAKTABI H. MSMR 2013

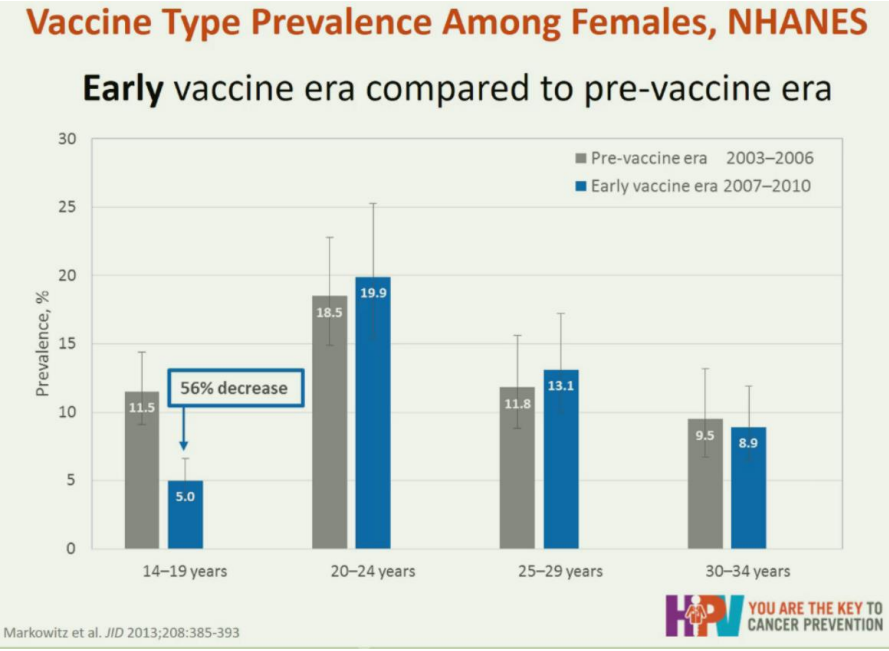
Vaccination is effective

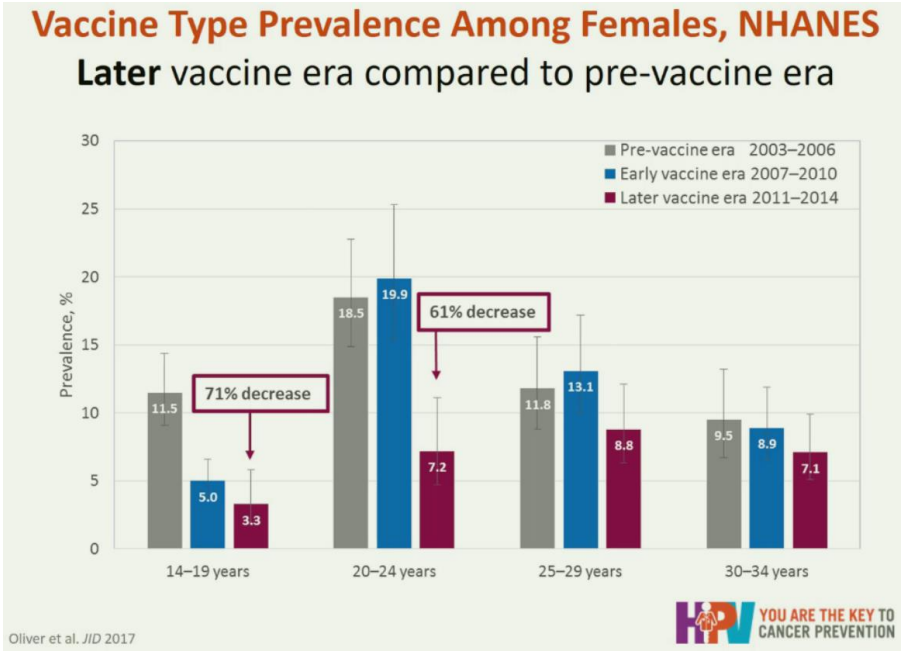




Grey bars represent prevalence of HPV types 6, 11, 16, and 18 in cervicovaginal samples collected between 2003 and 2006, before HPV vaccination was available.

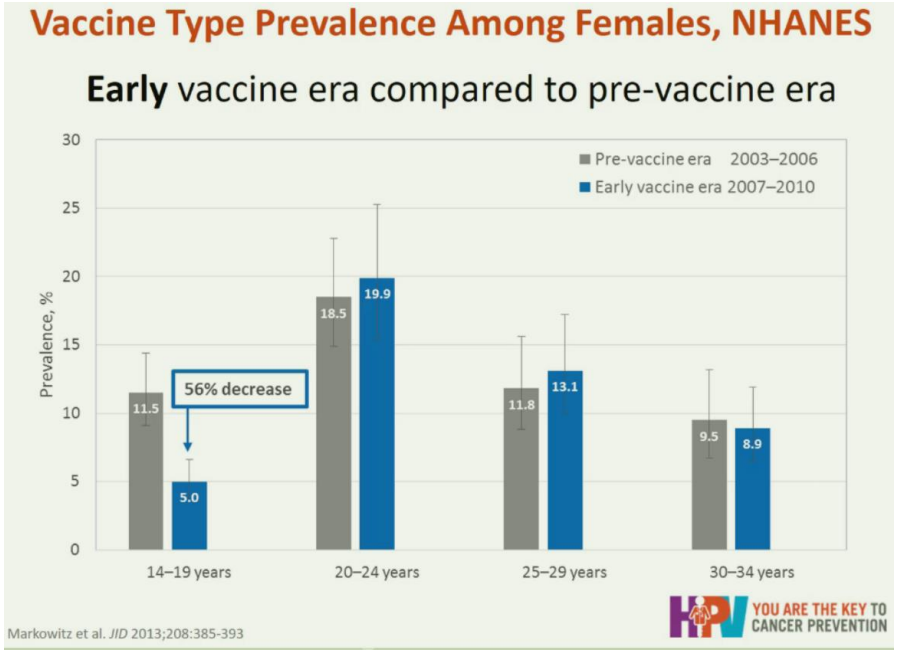
Vaccination is effective

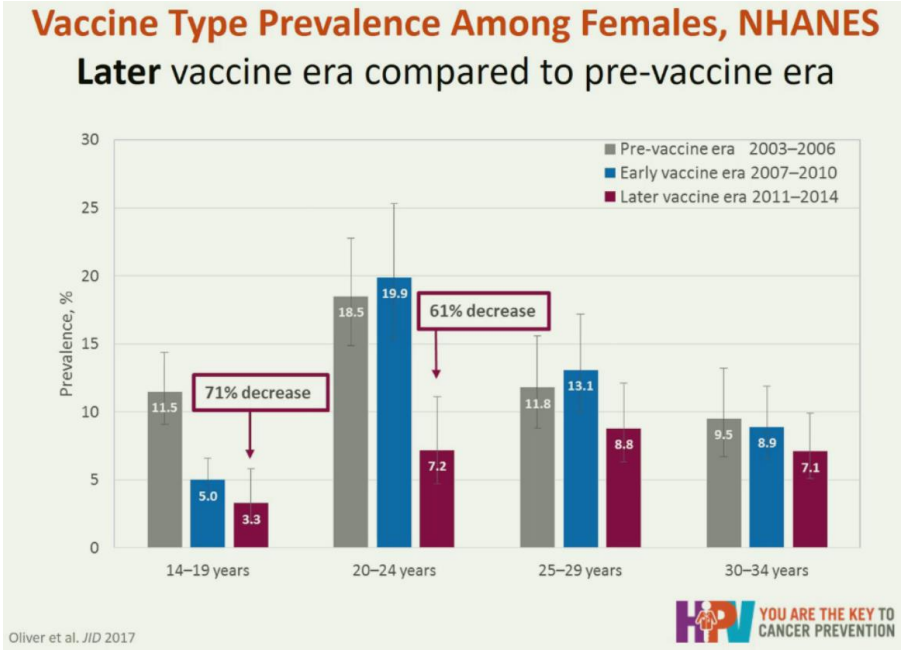




Blue bars represent prevalence of these HPV types in samples collected between 2007 and 2010.
Despite vaccination rates of about 32% in the 14-19yo group, the prevalence of HPV decreased.

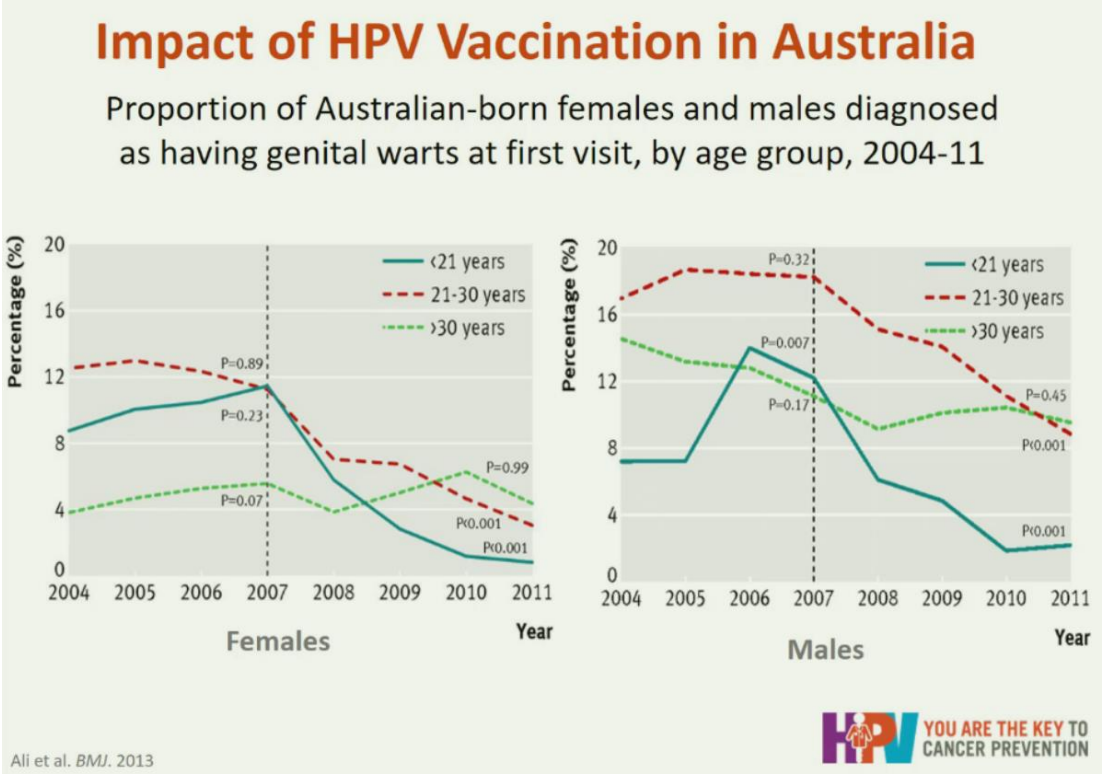
Vaccination is effective





Red bars represent prevalence of these HPV types in samples collected between 2011 and 2014. The prevalence of HPV decreased in the groups who had been vaccinated.

Vaccination is effective



The prevalence of genital warts in Australia decreased after vaccination.

Younger people make a stronger immune response

- Vaccine is more effective when given at 11-17 yo than when it is given at 18 yo or older.
  - 46% vs 35% reduction in HSIL
  - 35% vs 0% reduction in LSIL
- There is no protection in patients with a history of abnormal Pap before vaccination.

Younger people make a stronger immune response

- The next slide presents raw data on Geometric Mean Titers, a measurement of response to vaccine.
- Data were collected at different time points for response to each strain of HPV covered in the quadrivalent vaccine in people who received 2 doses at age 9-13, 3 doses at age 9-13, and 3 doses at 16-26.
- People aged 9-13 were called “girls” and people aged 16-26 were called “women.”
- The GMT Ratio compares the response between groups.
- We’ll zoom in on the bottom line on the slide after next …

Table 2. Summary of Month 7, 18, 24, and 36 Anti–Human Papillomavirus Competitive Immunoassay Geometric Mean Titers in the Intention-to-Treat Population[a]

	Girls, 9-13 y				Women, 16-26 y		GMT Ratio (95% CI), mMU/mL		
	2 Doses		3 Doses		3 Doses				
Antibodies	No. of Patients	GMT (95% CI), mMU/mL	No. of Patients	GMT (95% CI), mMU/mL	No. of Patients	GMT (95% CI), mMU/mL	Girls (2 Doses)/ Women (3 Doses)	Girls (2 Doses)/ Girls (3 Doses)	Girls (3 Doses)/ Women (3 Doses)
Month 7									
HPV-16	254	7344 (6310-8547)	256	7736 (6651-8999)	300	3545 (3083-4076)	2.07 (1.62-2.65)[b]	0.95 (0.73-1.23)	2.18 (1.71-2.79)
HPV-18	254	1169 (1021-1338)	256	1730 (1512-1980)	300	664 (586-752)	1.76 (1.41-2.19)[b]	0.68 (0.54-0.85)	2.61 (2.09-3.25)
HPV-6	253	2117 (1787-2508)	254	1876 (1585-2221)	300	943 (807-1101)	2.25 (1.71-2.96)	1.13 (0.85-1.50)	1.99 (1.51-2.62)
HPV-11	254	2339 (2088-2619)	256	2117 (1891-2370)	300	1268 (1143-1408)	1.84 (1.53-2.22)	1.10 (0.91-1.34)	1.67 (1.39-2.01)
Month 18									
HPV-16	100	1579 (1322-1885)	100	1806 (1512-2156)	104	840 (706-999)	1.88 (1.40-2.53)	0.87 (0.65-1.18)	2.15 (1.60-2.89)
HPV-18	100	137 (107-176)	100	238 (186-305)	104	77 (61-98)	1.78 (1.17-2.69)	0.58 (0.38-0.88)	3.08 (2.03-4.66)
HPV-6	100	346 (291-411)	100	351 (295-417)	104	203 (171-241)	1.70 (1.27-2.28)	0.99 (0.74-1.32)	1.73 (1.29-2.31)
HPV-11	100	451 (381-532)	100	429 (363-507)	104	286 (242-336)	1.58 (1.19-2.09)	1.05 (0.79-1.39)	1.50 (1.14-1.99)
Month 24									
HPV-16	201	1407 (1234-1606)	188	1726 (1506-1978)	230	844 (746-954)	1.67 (1.34-2.07)	0.82 (0.65-1.02)	2.05 (1.64-2.55)
HPV-18	201	131 (108-158)	188	264 (218-321)	230	96 (81-114)	1.36 (1.00-1.85)	0.49 (0.36-0.68)	2.75 (2.01-3.77)
HPV-6	201	278 (244-315)	188	357 (313-407)	230	217 (193-244)	1.28 (1.04-1.58)	0.78 (0.62-0.97)	1.65 (1.33-2.04)
HPV-11	201	370 (326-420)	188	423 (371-482)	230	272 (242-306)	1.36 (1.11-1.67)	0.87 (0.70-1.09)	1.56 (1.26-1.92)
Month 36									
HPV-16	86	1151 (919-1441)	85	1407 (1122-1764)	111	719 (590-876)	1.60 (1.12-2.29)	0.82 (0.56-1.20)	1.96 (1.37-2.80)
HPV-18	86	104 (76-141)	85	237 (174-322)	111	74 (57-97)	1.40 (0.86-2.29)	0.44 (0.26-0.74)	3.19 (1.95-5.21)
HPV-6	86	243 (199-296)	85	376 (308-460)	111	189 (159-225)	1.28 (0.94-1.76)	0.65 (0.46-0.90)	1.99 (1.45-2.74)
HPV-11	86	298 (245-363)	85	404 (332-493)	111	215 (181-255)	1.39 (1.01-1.90)	0.74 (0.53-1.03)	1.88 (1.37-2.58)

Abbreviations: GMT, geometric mean titer; HPV, human papillomavirus; mMU/mL, milli-Merck units per milliliter.
[a]This table excludes missing values from the recipients of the 2-dose and 3-dose vaccine.
[b]Results corresponding to the primary objective.

We'll zoom in on this data on the next slide.

Summary of month 36 Geometric Mean Titer (GMT) Ratios

Antibody	Girls (2 doses) / Women (3 doses)	Girls (2 doses) / Girls (3 doses)	Girls (3 doses) / Women (3 doses)
HPV-16	1.60	0.82	1.96
HPV-18	1.40	0.44	3.19
HPV-6	1.28	0.65	1.99
HPV-11	1.39	0.74	1.88

GMT Ratios greater than 1 mean that girls who received 3 doses made a stronger response than women who received 3 doses.

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HPV-18	1.40	0.44	3.19
HPV-6	1.28	0.65	1.99
HPV-11	1.39	0.74	1.88

GMT Ratios less than 1 mean that girls who received 2 doses made a weaker response than girls who received 3 doses (which makes sense).

Summary of month 36 Geometric Mean Titer (GMT) Ratios

Antibody	Girls (2 doses) / Women (3 doses)	Girls (2 doses) / Girls (3 doses)	Girls (3 doses) / Women (3 doses)
HPV-16	1.60	0.82	1.96
HPV-18	1.40	0.44	3.19
HPV-6	1.28	0.65	1.99
HPV-11	1.39	0.74	1.88

Even so, GMT Ratios greater than 1 mean that girls who received 2 doses made a stronger response than women who received 3 doses!

Three HPV vaccines have been available The 9-valent vaccine has been the only one available since 2016

	Bivalent/2vHPV (Cervarix)	Quadrivalent/4vHPV (Gardasil)	9-valent/9vHPV (Gardasil 9)
Manufacturer	GlaxoSmithKline	Merck	Merck
Year Licensed	October 2009 - females	June 2006 - females; October 2009 - males	December 2014 - males and females
HPV types in vaccine	16 and 18	6, 11, 16, and 18	6, 11, 16, 18, 31, 33, 45, 52, and 58
Adjuvant in vaccine	AS04: 500 µg aluminum hydroxide 50 µg 3-*O*-desacyl-4′-monophosphoryl lipid A	AAHS: 225 µg amorphous aluminum hydroxyphosphate sulfate	AAHS: 500 µg amorphous aluminum hydroxyphosphate sulfate
Recommended for…	• Females ages 11-12 • Females ages 13 through 26 who have not been previously vaccinated	• Females and males ages 11-12 • Females ages 13 through 26 and males ages 13 through 21 who have not been previously vaccinated • Unvaccinated males ages 22 through 26 who have sex with men or who are immunocompromised	• Females and males ages 11-12 • Females ages 13 through 26 and males ages 13 through 21 who have not been previously vaccinated • Unvaccinated males ages 22 through 26 who have sex with men or who are immunocompromised
Contraindicated for…	• People with hypersensitivity to latex	• People with hypersensitivity to yeast	• People with hypersensitivity to yeast

The bivalent vaccine covers HPV16 (associated with over half of cervical cancers) and HPV18 (associated with the most aggressive cervical cancers).

Three HPV vaccines have been available The 9-valent vaccine has been the only one available since 2016

	Bivalent/2vHPV (Cervarix)	Quadrivalent/4vHPV (Gardasil)	9-valent/9vHPV (Gardasil 9)
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HPV types in vaccine	16 and 18	6, 11, 16, and 18	6, 11, 16, 18, 31, 33, 45, 52, and 58
Adjuvant in vaccine	AS04: 500 µg aluminum hydroxide 50 µg 3-*O*-desacyl-4′-monophosphoryl lipid A	AAHS: 225 µg amorphous aluminum hydroxyphosphate sulfate	AAHS: 500 µg amorphous aluminum hydroxyphosphate sulfate
Recommended for…	• Females ages 11-12 • Females ages 13 through 26 who have not been previously vaccinated	• Females and males ages 11-12 • Females ages 13 through 26 and males ages 13 through 21 who have not been previously vaccinated • Unvaccinated males ages 22 through 26 who have sex with men or who are immunocompromised	• Females and males ages 11-12 • Females ages 13 through 26 and males ages 13 through 21 who have not been previously vaccinated • Unvaccinated males ages 22 through 26 who have sex with men or who are immunocompromised
Contraindicated for…	• People with hypersensitivity to latex	• People with hypersensitivity to yeast	• People with hypersensitivity to yeast

The quadrivalent vaccine adds HPV6 and HPV11 (associated with most anogenital warts).

Three HPV vaccines have been available The 9-valent vaccine has been the only one available since 2016

	Bivalent/2vHPV (Cervarix)	Quadrivalent/4vHPV (Gardasil)	9-valent/9vHPV (Gardasil 9)
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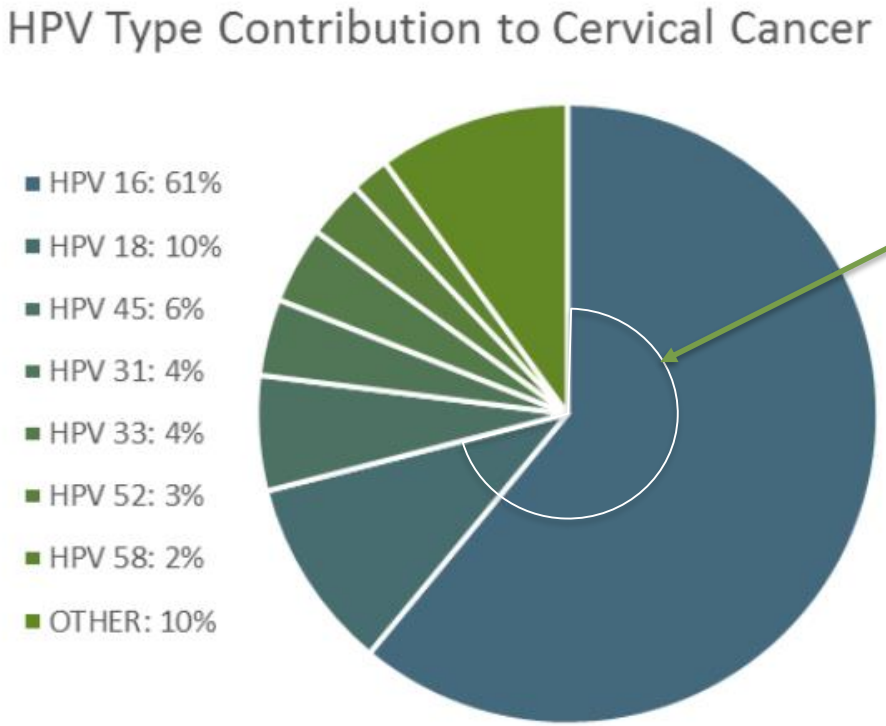
Contraindicated for…	• People with hypersensitivity to latex	• People with hypersensitivity to yeast	• People with hypersensitivity to yeast

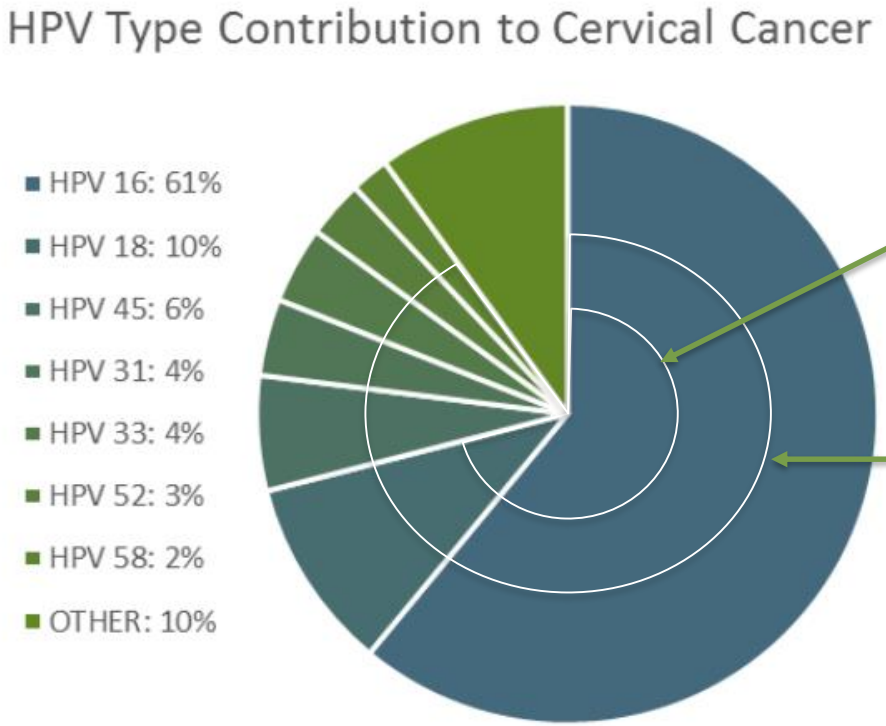
The nonovalent vaccine adds five more hrHPV strains. Remember that pie chart from slide 13?

HPV types 16 & 18 cause most cases of cervical cancer



The bivalent and quadrivalent vaccines should prevent 71% of cervical cancers.

HPV types 16 & 18 cause most cases of cervical cancer



The bivalent and quadrivalent vaccines should prevent 71% of cervical cancers.

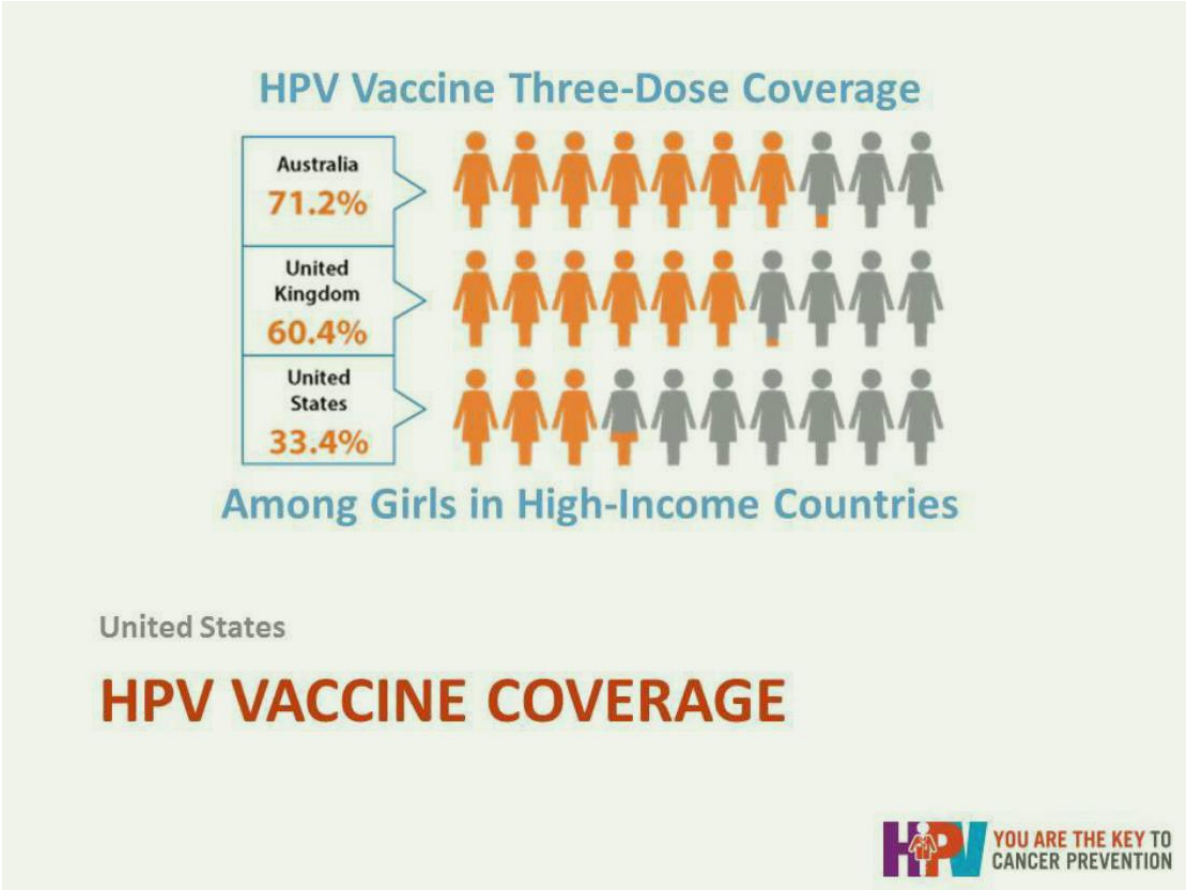
The nonovalent vaccine should prevent 90% of cervical cancers.

Recommended Vaccination Schedule

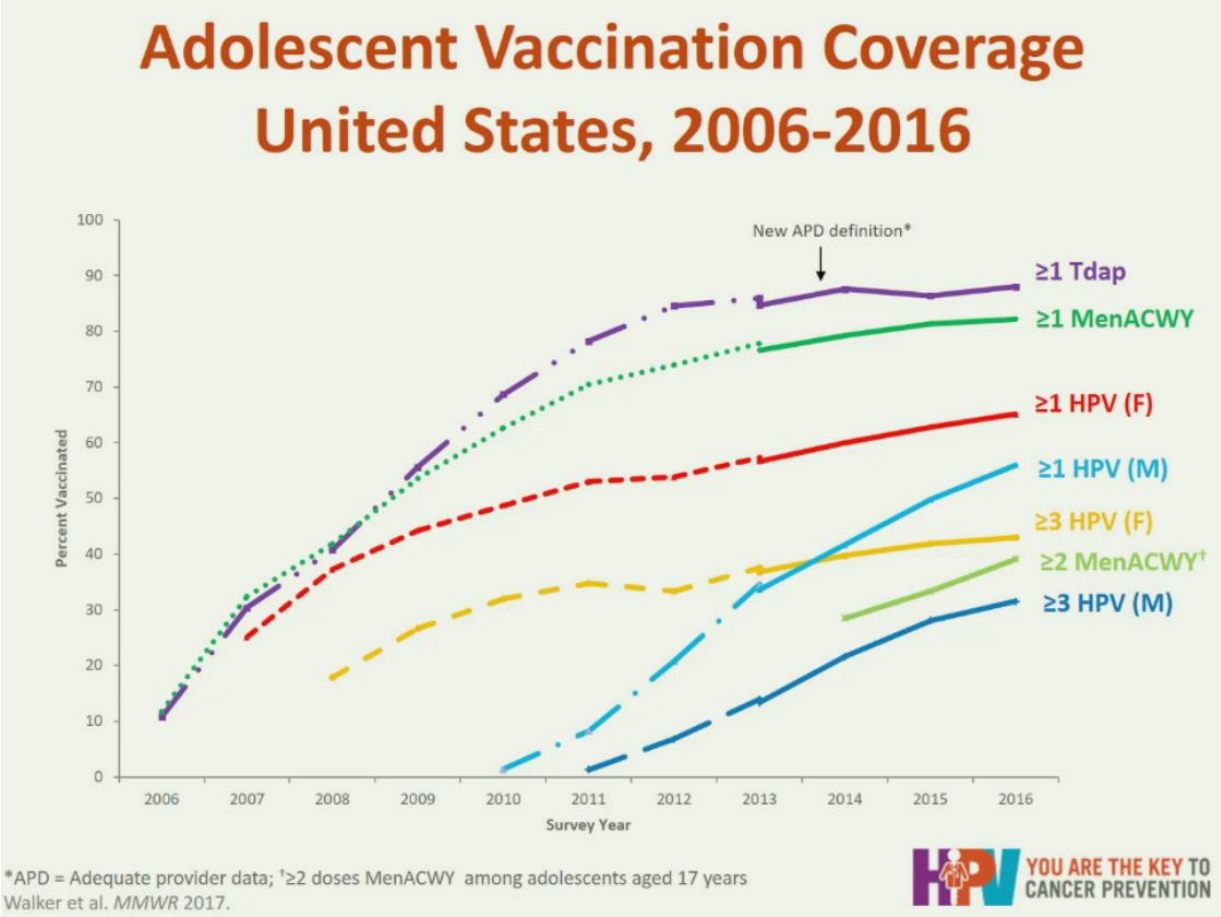
- Routine vaccination is recommended at 11-12 years old.
  - If the first dose is given before age 15, only 2 doses are needed, with at least 5 months between doses.
  - If the first dose is given at 15 or older, 3 doses are needed at 0 months, 1-2 months, and 6 months.
- Completion of the series is recommended by age 26.
  - There is no benefit to giving HPV9 to patients who already received the HPV4 series.
  - Vaccination between age 27 to 45 can be given based on shared-decision making.

We can improve HPV vaccination rates in the United States

- CDC resources: https://www.cdc.gov/hpv/hcp/index.html
  - continuing education, including 1 hr CME self-study
  - tools for providers
  - patient/parent handouts



Australia and the United Kingdom had much more robust uptake of immunization in the first few years after the vaccine was released in 2006.



Vaccination rates have increased over time in the United States, but immunization with even one dose lags behind rates of immunization against tetanus/diphtheria/pertussis and meningitis. These vaccines are recommended at the same age.

Five Ways to Increase HPV Vaccination Rates

❶ Bundle the recommendation for all adolescent vaccines to be given on the same day.

> "Now that your child is 11, he/she needs three vaccines to help protect against meningitis, HPV cancers, and whooping cough. We'll give these shots during today's visit. Do you have any questions about these vaccines?"

If parents are concerned about the number of shots in one day, I recommend giving HPV9 and a meningitis vaccine at this visit, as both require a second dose. Tdap can be given with the second dose of HPV9.

Five Ways to Increase HPV Vaccination Rates

❷ Train staff throughout the office to answer questions about vaccination and to give a consistent message, so parents do not hear doubts about the HPV vaccine from front office or nursing staff.

❸ Check immunization status at every visit, to catch up on any vaccines that may have been missed.

Five Ways to Increase HPV Vaccination Rates

4 The CDC suggests providing personal examples. Talk about how you have vaccinated your own children against HPV, or recommended it for other family members.

5 Be prepared to answer parents' questions with empathy and using understandable language. Motivational interviewing techniques can be helpful.

Summary: Natural History of HPV

- Infection with HPV is almost universal over the lifespan.
- Acquisition is highest during adolescence and young adulthood.
- Most infections are cleared before they become clinically significant.
- Persistent infection can lead to dysplasia, which can progress to cancer.

Summary: Cervical Cancer Screening

- Current guidelines for cervical cancer screening are based on the natural history of HPV.
- Goals:
  - Avoid excess testing and treatment in patients less likely to have high-grade dysplasia.
  - Screen and monitor at appropriate intervals to detect dysplasia before it progresses to cancer.
- Use the web application available at www.asccp.org to determine appropriate management plans.

Summary: HPV Vaccination

- The HPV vaccine is effective at reducing prevalence of HPV infection and related diseases.
- The vaccine is more effective when given at younger ages, so only two doses are needed if the series starts before age 15.
- Many resources are available at https://www.cdc.gov/hpv/hcp/index.html to help providers increase vaccination rates within their practices.

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