HPV and Cervical Cancer, Screening and Prevention

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CME Lecture Series
Trends in incidence rates, 1975-2014
by sex, for cervix
Per 100,000, age adjusted to the 2000 US standard population.

We have come a long Way...
Prevalence HPV in Young Adults in U.S

NOTE: Error bars indicate 95% confidence interval.

HPV genotypes

- 55-60% of all cancers
- 90-95% of warts
- 20% of all adeno-carcinomas
- 25% of all cervical cancers

16

18

6,11

The rest
Percentage of adolescent boys and girls who have received one or more doses of HPV vaccine*

NATIONWIDE 6 OUT OF 10 parents are choosing to get the human papillomavirus vaccine for their children.

CDC RECOMMENDS THE HPV VACCINE AT AGES 11-12
Talk to your child’s doctor about HPV cancer prevention

*Estimated coverage with ≥ 1 dose of human papillomavirus (HPV) vaccine among adolescents aged 13-17 years, National Immunization Survey-Teen (NIS-Teen), United States, 2016. Source: MMWR August 25, 2017
HPV Vaccines

- **Gardisil 9**: 6, 11, 16, 18, 31, 33, 45, 52, and 58
- **Gardisil**: 6, 11, 16, and 18
- **Cervarix**: 16 & 18
  - For girls only

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**5 reasons why the HPV vaccination is recommended for pre-teens**

1. **More effective**
   - Early vaccination prevents substantially more pre-cancer than late vaccination.

2. **Long lasting**
   - Current evidence shows that the HPV vaccination does not wear off!

3. **Low risk of exposure**
   - HPV vaccine only works if the series is complete before a person is infected. Almost no 9-12 year olds have HPV.

4. **More chances to vaccinate**
   - Every visit on or after the 9th birthday is an opportunity to provide the vaccine.

5. **Better immunity**
   - After receiving HPV vaccine pre-teens make more infection fighting antibodies than older teens. That is why they need only 2 doses of the vaccine are recommended at this age, instead of 3.
How Effective is the HPV vaccine?

• Answer – very!!!

• Large RCT of 2392 women ages 16-23 split into two groups. All women were tested for HPV virus at enrollment
  – One group was placebo
    • Rate of persistent HPV infection 3.8%
  – One group got series of 3 HPV 16 vaccines at 0,2,and 6 months
    • Rate of persistent infection 0%

A controlled trial of a human papillomavirus type 16 vaccine.
Koutsky LA1, Ault KA, Wheeler CM, Brown DR, Barr E, Alvarez FB, Chiacchierini LM, Jansen KU; Department of Epidemiology, University of Washington, Seattle, USA. kouts@u.washington.edu
HPV vaccine: efficacy

- HPV Cancers U.S. 2008-12:
  - 38,793 HPV-associated cancers (11.7 per 100,000 persons)
    - 23,000 (13.5) among females
    - 15,793 (9.7) among males.
  - 30,700/38,793 = HPV attributed
  - 28,500/38793 = Preventable

74% Preventable

Human Papillomavirus–Associated Cancers — United States, 2008–2012 MMRW Weekly / July 8, 2016 / 65(26);661–666
Risk Factors
Cervical Cancer Screening

Being rarely or never screened is **THE major contributing factor** to the **MOST** cervical cancer deaths today.
Cervical Anatomy

- Squamous epithelium
- Transformation zone
- Columnar epithelium
- SC Junction
- OS
CE: columnar epithelium

SCJ: squamo-columnar junction

SE: squamous epithelium

TZ: transformation zone
Review of Pap Nomenclature & Results
A bit of Context....

• **Bethesda system**
  - **System** for reporting cervical or vaginal cytologic diagnoses, used for reporting Pap smear results. It was introduced in 1988 and revised in 1991, 2001, and 2014.

• **ASCCP:**
  - Governing body
  - Devised rationale cytological definitions then correlated with pathologic definitions
  - Established Guidelines:
    • Based on data from 1.4 million women followed from Jan 2003 – December 31st 2010 at Kaiser
Reflecting our evolving understanding HPV pathology

The ASCCP will no longer be referenced as the American Society for Colposcopy and Cervical Pathology — but rather now simply as the ASCCP, with a mission to improve lives through the prevention and treatment of ano-genital and other HPV-related diseases.
HPV testing: a game changer

An increased detection of CIN3 → Concomitant decrease in CIN3+ or cancer detected in subsequent screening → increased diagnostic lead time → Longer screening intervals
HPV testing: a game changer

• Enhanced detection of women with adenocarcinoma of the cervix and its precursors
<table>
<thead>
<tr>
<th>Bethesda System</th>
<th>CIN System</th>
<th>Dysplasia</th>
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<tbody>
<tr>
<td>ASCUS</td>
<td>Cellular Atypia</td>
<td>Unspecified Changes</td>
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<tr>
<td>ASC-H</td>
<td>Cannot r/o high grade</td>
<td>Variable</td>
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<tr>
<td>LGSIL</td>
<td>CIN 1</td>
<td>Mild Dysplasia</td>
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<tr>
<td>HGSIL</td>
<td>CIN 2</td>
<td>Moderate Dysplasia/Severe Dysplasia</td>
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<td>CIN 3</td>
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Cytologic Pathologic Phenotypic

ASCCP
nuclear enlargement in Pap tests is due to reactive change

About 4% of total pap results

Not a cancer equivalent but evidence of infection

First exclude moderate/severe cervical intraepithelial neoplasia or carcinoma in-situ (CIN3/HSIL)

A rare but significant finding of a cancer equivalent

2% have cancer at time of pap

20% will go on to get cancer without proper care
What % of low grade pap smears progress to CIN2 or greater?

A) 12-16%
B) Less than 3%
C) 18-22%

Mildly increase nuclear/cytoplasmic ratio
Mild/moderate staining
What happens to LGSIL?

- 60% of CIN 1 regresses
- 30% of CIN 1 persists
- 10% progress to CIN 3
- 1% may ultimately go on to invasive cancer
HGSIL

- Increased nucleoplasm to cytoplasm ratio
- Moderately to severely abnormal morphology
- Chromatin is more granular
- Nuclear notches and folds
- Nucleus is more hyper chromic
Cervical cancer Screening: Adolescents

- Care for contraception of STI screening / treatment is paramount
- NO pap test
- NO speculum exam for asymptomatic women
- STI screening can be done using urine
Treatment Saves Lives, but there is a cost….

• After LEEP women are more likely to have
  – Preterm birth (O.R 1.7)
  – Low birth weight (O.R. 1..8)
  – PPROM (O.R. 2.7)
• Increased risk (small) with perinatal death from incompetent cervix
• Risk rises with depth and number of LEEPs
• Conization vs. laser treatment risks essentially the same
• Absolute risk is quite small

Bruinsma et al BJOG 2007;114:70-80
Case 1
CASE 1

A 21 year-old G0P0 presents to your office for her first gynecologic examination.

She has no symptoms or complaints and does not report chronic medical conditions.

She does not smoke or use illicit drugs.

She has had two male sexual partners in her lifetime and has been using combination oral contraceptive pills for the past 14 months.

She has completed her HPV immunization series
What is the screening interval for a 21 year old female?

- Pap and co-testing every three years
- Pap only every three years
- Pap only every 5 years
- Annual pap smear
Cervical Cancer Screening for Women under 30

- HPV testing should not be used to screen
- NOT as a function of co-testing
- NOT as a primary stand-alone screen

Cytology *Alone* every three years

Why???

- 20-30% prevalence of HPV in early 20s
- Vast majority of cancer causing HPV infections resolve
- Call backs, anxiety, interventions
When is this ever going to clear???

- Most cervical HPV infections are transient
- Typically 12-24 months to clear most infections
- Who clears and why not fully understood
- 16-18 genotypes more likely to persist
- Younger women more likely to resolve
A gynecologic exam is performed and cervical cytology is collected. Results of the cytology are as follows:

- Interpretation: Atypical squamous cells Cannot rule out high grade SIL (ASC-H)
- Adequacy: Satisfactory for evaluation.
- Transformation zone present.
What is the next step?

- Colposcopy
- Repeat pap in 6 months
- Repeat pap and co-testing in 6 months
- Diagnostic excisional procedure (LEEP)
3-5% Acetic Acid has been applied. Which one of the following describes the colposcopic findings?

- Squamocolumnar junction (SCJ) not fully visualized. Dense acetowhite epithelium with vessel changes.
- SCJ not fully visualized. Dense acetowhite epithelium without vessel changes.
- SCJ fully visualized. Dense acetowhite epithelium with vessel changes.
- SCJ fully visualized. Dense acetowhite epithelium without vessel changes.
Management of women aged 21-24 years with biopsy confirmed HSIL (CIN 2) and inadequate colposcopy includes which one of the following?

- Diagnostic excisional procedure.
- Ablative procedure.
- Cotesting in 1 year.
- Colposcopy and cytology at 6 month intervals for the next 24 months.

• **Histology results**
  - Cervix, 12:00 and 6:00, biopsy: (HSIL (CIN 2))
  - A p16 immunostain is positive
  - Endocervical curettage: Minute fragment of low-grade squamous intraepithelial lesion LSIL (CIN 1)
Pathology Results

Cervix, loop electrosurgical excision procedure (LEEP):
- Transformation zone with HSIL (CIN 2)
- Ectocervical surgical margin negative
- Endocervical margin negative

What’s the follow up for CIN 2?

Answer
- Colposcopy and cytology in 6 months.
- Cytology in 3 years.
- Cervical cotesting in 3 years.
- Cervical cotesting in 12 months.
Case 2
32 year old woman has her first co-test which returns as cytology negative & HPV positive.

- She asks about her chances of testing HPV negative at her next visit and you respond
  - About 25%
  - About 50%
  - About 75%
  - About 100%
Follow Up pap in one year shows

• Persistent HPV infection with normal cytology

• Next Steps?
• Colposcopy
Your colposcopic impression is:

1. Normal
2. Low grade lesion 12 o’clock
3. High grade lesion at os
4. Cancer
She is concerned and wants more information about possible outcomes. You tell her:

1. If cytology negative /HPV positive next year, she will need LEEP
2. If cytology negative /HPV positive next year, you will repeat colposcopy
3. If cytology ASC-US /HPV negative next year, she may return to routine screening in 5 years
4. If cytology negative /HPV negative next year, she may return to routine screening in 5 years
Case 3
A 58 year-old G0 postmenopausal woman comes to your office for follow-up. She had a first co-test two years ago showing negative cytology, but HR-HPV positive.

She was referred for colposcopy and had 2 cervical biopsies and ECC were all negative for dysplasia. Co-testing was be repeated in 12 months.

Due to her move, it was 18 months before she was seen by her new PCP, who performed cytology only.

The result returned as Atypical Squamous Cells, Cannot Exclude High-Grade Intraepithelial Lesion (ASC-H).

What is the appropriate next step?
She is referred for colposcopy. There are no atypical vessels under the green filter. 3-5% acetic acid is applied. The squamo-columnar junction (SCJ) is not fully visualized in this static image and manipulation to visualize it should be attempted.

Colposcopy impression is:
- Normal with atrophic changes
- Low grade
- High grade
- Cancer
Biopsies are performed at 6:00 and 12:00 and an ECC is done. Biopsies and ECC return as negative for dysplasia, with atrophic changes.

Which one of the following options is recommended?

• Cotesting at 6 month intervals for 2 years
• Cotesting at 12 and 24 months and if negative, cotesting in 3 years
• Diagnostic excisional procedure
• Hysterectomy
Case 4
A 54 yo G0P0 presents to your office to establish care because of an insurance change. She received care from her former gynecologist for the past 15 years. She received annual cervical cancer screening showing no history of cervical abnormalities or gynecologic procedures. She has never had an HPV test. Today, she expects her “annual exam” including a PAP test.
Pap test results: AGUS
What are the next steps?

- **Interpretation**: Atypical glandular cells, not otherwise specified (AGC-NOS).
- **Adequacy**: Satisfactory for evaluation. Transformation zone present.
- **HPV testing**: Negative for high-risk HPV.
AGCUS

- Colposcopy
- Endocervical Curettage
- Endometrial biopsy
Aggregate Result of AGUS colposcopy

- 8% of patients have: low-grade squamous intraepithelial lesions (LSIL).
- 11% of patients have: high-grade squamous intraepithelial lesions (HSIL).
- 3% of patients have: adenocarcinoma in situ..
- 1% of patients have endometrial hyperplasia.
- 5% of patients have cancer.
- 72% of patients have no problem
End of Cases
Cervical Cancer

- Mostly no symptoms
- Bladder obstruction
- Pelvic or back pain
- Management
  - Stage: size, depth of invasion, distant mets and Lymph node involvement
  - Comorbidities
  - Risk factors for recurrence
- Prognosis
  - IA: 93% at 5 years
  - IVB: 15% at 5 years
Current Disease burden

- Approximately 12,000 new cases in 2017
- Approximately 4,200 deaths
When to Stop Screening

- Three consecutive negative paps
- Two consecutive negative HPV tests

(Tests within 10 years of stopping; most recent within 5 years.)
When to Stop Screening

After total hysterectomy & No history of CIN2+
When NOT to stop Screening

Who:

- History of CIN 2 or greater disease

For How Long?

- A) Until death
- B) 10 years
- C) 3 normal pap smears
- D) 20 years
Screening After Vaccination: Looking to the Future…

- May lead to later screening and less frequent intervals of screening… but not there yet
  - Vaccinating until age 26
  - Vaccination rates still quite low in the U.S. (32% vaccination rate in 2010 had received all three dosages)
Where the research is headed...

• Ways to increase vaccination rates
• Moving towards HPV testing only
• Determining duration of protection from vaccination
• Refining management of cytology negative/HPV positive women
Take home points

• Our HPV vaccination rates are low – thousands of cancers could be prevented if we improve

• The greatest risk factor for cervical cancer is lack of or insufficient screening

• HPV screening for those 30 and older

• The algorithms are complex and evolving – use ASSCP guidelines to direct screening and management
GET THE APP

Greet it.

Feed it.

Read it.
Women with this result have a 5-year CIN3+ risk of 6.8%.
Questions?