Human Papillomavirus (HPV), Cervical Dysplasia and HPV Vaccination

Christopher P. DeSimone, MD
Assistant professor
Division of Gynecologic Oncology
Department of Obstetrics and Gynecology
University of Kentucky Medical Center

Consultant for:
- Merck
- Orthobiotech

Disclosures
• Developed by Drs. Papanicolaou and Traut in the 1940s
• Consists of collecting cervical cytology from the cervix and depositing them onto a slide for microscopic evaluation
• Easy to collect and objectively interpret results
• Initially used to detect cervical cancer

The Papanicolaou Test

The Papanicolaou Test has dramatically decreased the incidence and mortality rate of cervical cancer in the United States

- US - 11,150 new cases each year
  - 3,700 deaths annually from cervical cancer
- Worldwide 493,000 new cases
  - 293,000 deaths annually worldwide

Jemal et al. CA, 2007
The Papanicolaou Test

Estimated 50 million Pap tests performed in the US
5% will be diagnosed as abnormal
2-3 million ASC-US Pap tests
1.5 million LSIL Pap tests
300,000 HSIL Pap tests

Abnormal Pap Tests

- 50% of women diagnosed with cervical cancer have not had a pap test in 5 years
- 25% of all cervical cancers are diagnosed in women older than 65
- In women older than 65, it is estimated that over 50% have not had a pap test in the past 10 years
- Bottom Line – the majority of women with cervical cancer fail to get annual pap tests

Who Develops Cervical Cancer?
• Bethesda 2001 nomenclature
  • Human papillomavirus (HPV)
    ◦ Types of HPV
    ◦ Incidence of HPV
    ◦ Incidence of HPV in cervical cancer
    ◦ Mechanism for oncogenesis
    ◦ Associated risk of cervical cancer with smoking
  • Screening guidelines for cervical cancer
  • 2006 ASCCP consensus guidelines for the management of abnormal Pap tests
  • 2006 ASCCP consensus guidelines for the treatment of cervical dysplasia
  • Types of treatment
  • Screening intervals after treatment
  • HPV vaccines

**Overview**

• Mild dysplasia
  ◦ HPV effect
  ◦ ASC-US (Atypical Squamous Cells of Unknown Significance)
  ◦ LSIL (Low Grade Squamous Intraepithelial Lesion)

• Severe dysplasia
  ◦ ASC-H (Cannot rule out HGSIL)
  ◦ HSIL (High Grade Squamous Intraepithelial Lesion)
  ◦ CIS (Squamous Carcinoma In-Situ)

2001 Bethesda Nomenclature, squamous cells

Solomon et al. JAMA, 2002.
• Glandular abnormalities
  ◦ Benign appearing endometrial cells in a woman >40
  ◦ AGC (Atypical Glandular Cells of Unknown Significance)
  ◦ AIS (Adenocarcinoma In-Situ)
  ◦ Adenocarcinoma

• AGC and AIS should be handled with utmost caution

2001 Bethesda Nomenclature, glandular cells

Solomon et al. JAMA, 2002.

• Cytology pertains to a sample of cells
  ◦ Pap test

• Histology pertains to a tissue sample
  ◦ Colposcopic biopsy

• Cervical intraepithelial neoplasia (CIN) is the nomenclature used for colposcopic/cervical biopsies

• Cervical intraepithelial neoplasia (CIN) and dysplasia are synonymous

Cytology vs. Histology
Dysplasia is the pathologic term for preinvasive disease

- Dysplasia represents the **POTENTIAL** for abnormal cells to progress to invasive cancer

- This potential is subdivided
  - CIN 1 = mild dysplasia
  - CIN 2 = moderate dysplasia
  - CIN 3 = severe dysplasia
  - Carcinoma in situ and CIN 3 are the same

### Anatomy of Dysplasia

![Images of dysplasia stages]

- **Moderate Dysplasia (CIN II)**
- **Severe Dysplasia, or Carcinoma-in-situ (CIN III)**
- **Invasive Cancer**
Human Papillomavirus

- Member of the Papovaviridae family
- Double Stranded DNA tumor virus
- 45-55 nm icosohedral capsid
- More than 100 types
- Specific for target epithelium
- Epitheliotrophic and causes proliferation

- **Mucocutaneous**
  - Verruca plantaris 1,2,4
  - Verruca vulgaris 2,4,29,38
  - Verruca plana 3,10,28

- **Anogenital**
  - Condyloma 6,11
  - Dysplasia and Cancer 16,18,31,33,35,45,51,56

HPV and types of infection
• 608 college-aged women studied from 1992-1994
• Followed 3 years at 6 month intervals
• Incidence of infection 43%
• Median duration of any HPV infection, 8 months
• 70% cleared in one year, 90% in two years

Incidence of HPV

Ho et al. NEJM 1998

• African American and Hispanic races (RR 4.4 and 2.1)
• Alcohol consumption >4 times a month (RR 2)
• >2-3 sexual partners in one year (RR 3)
• >6 sexual partners of main regular partner (RR 10.1)

Risk Factors for HPV

Ho et al. NEJM 1998
• Most common types are high risk types 51,66,16,18
  ◦ Type 16 found in 7% of 514 women
  ◦ Type 18 found in 4% of 525 women

**Incidence of HPV Types**

Ho et al. NEJM 1998

• Persistent HPV more likely to progress to dysplasia

• High risk types take longer to clear (Median of 12 month)

• Women infected with high risk types documented at two 6 month visits were 38 times more likely to develop dysplasia

**HPV and Cervical Dysplasia**

Ho et al. NEJM 1998
• HPV 16 most common
  ◦ Ho, et al. 7%
  ◦ Kuhn, et al. 6%
  ◦ Winer, et al. 10%
  ◦ Richardson, et al. 8%
• HPV 18
  ◦ Roughly 3-4%
• HPV 33, 39
  ◦ Roughly 3-4%

**Incidence of HPV types**

• Bosch, et al., in 1995, accrued 932 cases of cervical cancer from around the world
• Using polymerase chain reactions (PCR), his group amplified HPV DNA from the tumor and recorded their findings
• 93% of cervical carcinoma had HPV DNA
• Common types included 16, 18, 31, 33, 35, 39, 45, 51 (high risk HPV subtypes)

**HPV and cervical cancer**

• Walboomers, et al., repeated Bosch’s experiment using new PCR primers
• Those cancers that failed to test positive for HPV DNA were retested with these new primers
• Results showed that 99.7% of Bosch’s original cases tested positive for HPV DNA

**HPV and cervical cancer**

Walboomers et al. J Pathol, 1999

**HPV and oncogenesis**
• Viral DNA E6 and E7 believed to be crucial in stimulating cellular proliferation
• E6 acts by inhibiting p53 which is a crucial cell protein involved in programmed cell death (apoptosis)
• E7 acts by binding the retinoblastoma (Rb) protein
• Once bound, Rb releases E2F transcription factor which causes cellular proliferation
• Combined they inhibit the regulatory mechanism for apoptosis while stimulating the cell to proliferate
Prior to understanding the role of HPV in cervical cancer, studies which focused on smoking as a risk factor were often contradictory.

Once stratified for HPV status, many recent studies have shown that smokers with HPV are more likely to develop cervical cancer and CIN 3.
Two probable causes for oncogenesis
  ◦ Accumulation of carcinogens from tobacco smoke in cervical mucous
  ◦ Decreased host immune system
    • Decreased T cells more likely to lead to uncontrolled cell growth

Smoking and Oncogenesis

Plummer, et al., and the IARC performed a case-control study to determine if smoking was a cofactor for progression of HPV to cancer

• Included
  ◦ 1463 squamous cell carcinomas
  ◦ 124 adenocarcinomas
  ◦ 211 CIN 3 cases
  ◦ 254 control women

• Only women positive for HPV DNA were included

Smoking and cervical cancer
Results

• Ever smoking and HPV had an OR 2.17 (95% CI 1.46-3.22)
• Stronger risk for squamous cell carcinomas OR 2.3 (95% CI 1.31-4.04)
• Ex-smokers also had an increased risk for developing squamous cell carcinoma, OR 1.8 (95% CI 0.95-3.44)
• No increased risk for smoking and adenocarcinoma

Smoking and cervical cancer

The ALTS group examined smoking as a risk factor for developing CIN 3 or cervical cancer

Included

• 5,060 women with ASC-US or LSIL Pap tests
• 3,133 women with high risk HPV
• 506 women with CIN 3 or cancer

Smoking and CIN 3

McIntyre-Seltman et al. Cancer Epidemiol Biomarkers Prev, 2005
Concluded

- Current smokers (OR 1.7) and ex-smokers (OR 1.7) had a mildly increased risk for developing >CIN 3
- Women who smoked more cigarettes and who smoked for a longer duration were at a higher risk for developing >CIN 3
- Smoked more than 2 packs per day OR 3.3 (95% CI 1.5-7.5)
- Smoked greater than 11 years OR 2.1 (95% CI 1.5-2.9)
- Both the smoking duration and smoking intensity trended towards significance (Ptrend <0.0005)

Smoking and CIN 3

<table>
<thead>
<tr>
<th>Source</th>
<th>Commencement</th>
<th>Interval &lt; 30</th>
<th>High risk factors</th>
<th>Interval &gt; 30 (3 consecutive negative Pap tests)</th>
<th>Cease</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Cancer Society (2002)</td>
<td>3 years after coitarche or no later than age 21</td>
<td>Every 2 years (liquid cytology) Annually (conventional)</td>
<td>Any abnormal Pap test HPV HIV GC or Chlamydia</td>
<td>Every 3 years Women &gt; 70 with normal Pap tests Hysterectomy for benign gynecologic reasons</td>
<td></td>
</tr>
<tr>
<td>American College of Obstetrics and Gynecology (2003)</td>
<td>3 years after coitarche or no later than age 21</td>
<td>Annually</td>
<td>Prior diagnosis of CIN 2 or 3 Immunocompromised HIV DES exposure</td>
<td>Every 2-3 years Physician discretion</td>
<td></td>
</tr>
</tbody>
</table>
Women who have had a hysterectomy for CIN 2 or 3
- Need Pap test every year until three consecutive normal Pap tests
- Incidence of vaginal dysplasia is 20% following a hysterectomy for CIN 2-3

Screening guidelines

HPV testing can be used alone or in conjunction with cervical cytology for screening in women >30
- Pooled sensitivity and specificity in women in North America and Europe for CIN 2 or greater
  - HPV testing: 95% and 93%
  - Cytology (ASC-US): 60% and 97%
  - Both: 99% and 99% (negative predictive value 99-100%)

Screening guidelines

Cuzick et al. Int J Cancer. 2006
• Clinical implications for combined screening in women >30
  • Both cytology and HPV testing are negative
    ◦ Rescreen in no less than 3 years
    ◦ 1/1000 risk of developing CIN 2 or greater
      • Wright et al. Obstet Gynecol. 2004
      • Kjaer et al. Cancer Res. 2006
      • Khan et al. J Natl Cancer Inst. 2005
  • Negative cytology but positive HPV testing
    ◦ Rescreen with cytology and HPV in 1 year
    ◦ Risk of undetected CIN 2 or greater is 2.4-5.1%
      • Ronco et al. J Natl Cancer Inst. 2006
      • Bigras et al. Br J Cancer. 2005
      • Cuzick et al. Lancet. 2003
      • Clavel et al. Br J Cancer. 2001

Screening guidelines

Atypical Squamous Cells of Unknown Significance (ASC-US)

• COMMON
• 5% of all Pap tests
• 2-3 million/year
• CIN 1, 2, 3: 20-30%
• CIN 2, 3: 5-17%
• Carcinoma: 0.1-0.2%

Multicenter, prospective, randomized controlled study
Took 3488 ASC-US referrals
Each patient had thin prep and HPV typing prior to randomly being assigned a study arm
Placed into three arms
Colposcopy
Colposcopy for positive HPV test
Colposcopy for HSIL cytology

ALTS Trial
Solomon et al. JNCI 2001

HPV is obtained with a cytobrush
Hybrid capture II® (Digene®) is the commercial test
Detects 13 high risk strains (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68)
Positive test > 1pg/ml of DNA content

Testing for HPV
• All referral Pap tests brought before pathology review board for quality control
• 3,389 Pap tests analyzed by this board
  ◦ 55% concurred ASC-US
  ◦ 45% changed !!!
    • 31% NORMAL
    • 14% LSIL

Colposcopy
• Normal 539 (62.9%)
• CIN 1 167 (19.5%)
• CIN 2 72 (7.4%)
• CIN 3 59 (6.9%)
• N 857
  • 35% are CIN

HPV screening
• Normal 237 (48%)
• CIN 1 111 (22.5%)
• CIN 2 59 (11.9%)
• CIN 3 77 (15.6%)
• N 494
  • 50% are CIN

ALTS
Solomon et al. JNCI 2001
• 136 patients with CIN 3 in both arms
  ◦ 125 women were HPV positive
  ◦ Sensitivity 96.3%
  ◦ PPV 10%
  ◦ NPV 99.5%

**ALTS**

Solomon et al. JNCI 2001

• Benefit is NPV 99.5%
• Clinical Implications: If a patient is negative for high risk HPV then it is highly unlikely she will have CIN 3
• Therefore: colposcopy and biopsies are unlikely to yield CIN3

**ASC-US**
1) Repeat Pap test in 6 months
   ◦ If ASC-US or greater - Colposcopy
   ◦ If normal repeat in 6 months; continue until two normal Pap tests are achieved then place patient on yearly Pap tests

2) Reflex HPV testing
   ◦ If HPV positive – Colposcopy
   ◦ If HPV negative – repeat Pap test in one year

3) Colposcopy

**ASC-US management**

- Adolescents (<20)
  ◦ Repeat cytology in 1 year
  ◦ No HPV testing (high prevalence would send most to colposcopy)

- Immunosuppressed
  ◦ Follow general guidelines

- Pregnant woman
  ◦ Follow general guidelines
  ◦ Colposcopy can be performed 6 weeks post-partum

**ASC-US: special populations**
• Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion

• **NOT ASC-US!!!!**

• Pap test lacks conclusive cytology to be labeled as HSIL

• Significant rate of CIN 2-3 diagnosed on colposcopic biopsies (40%)

• High Risk HPV 85%

**ASC-H**

---

**COLPOSCOPY**

- If colposcopy and biopsies are normal...
- Repeat Pap test in 6 and 12 months
- Or HPV testing in 12 months

**ASC-H management**
• 1.5 million/year
• Usually histology confirms CIN 1
• 76% of LSIL Pap tests are positive for high risk HPV
  - Metaanalysis: Arbyn et al. Vaccine. 2006
• Colposcopy is the initial management

**Low Grade Squamous Intraepithelial Lesion (LSIL)**

• Colposcopy

• Prevalence of CIN 2 or greater 12-16%
  - Alvarez et al. Gynecol Oncol. 2007
  - Chute et al. Diagn Cytopathol. 2006
  - Solomon et al. JNCI. 2001

**LSIL management**
• Adolescents (<20)
  ◦ Repeat cytology in 1 year
  ◦ No HPV testing
  ◦ At 12 months colposcopy for HSIL
  ◦ At 24 months colposcopy for ASC-US or greater

• Postmenopausal women
  ◦ HPV testing
  ◦ Or Pap testing at 6 and 12 months

• Pregnant woman
  ◦ Colposcopy
  ◦ If no evidence of CIN 2,3 or cancer then follow-up cytology post partum

LSIL: special populations

High Grade Squamous Intraepithelial Lesion (HSIL)

• The most aggressive type of squamous cell dysplasia before invasive cancer
• HSIL rate 0.7%
• Colposcopy identifies 53-66% of women with CIN 2 or greater
• Loop electrosurgical excision procedure (LEEP) identifies 84-97% of women with CIN 2 or greater
1. Colposcopy

2. LEEP

**HSIL management**

- Adolescents (<20)
  - Colposcopy
  - If no CIN 2,3 is identified histologically... observe with colposcopy and cytology (q 6 months) for 24 months
  - If HSIL persists and biopsies reveal no evidence of CIN 2 or greater after 24 months...LEEP

- Pregnant woman
  - Colposcopy
  - No excisional therapy unless cancer
  - Follow-up cytology and colposcopy 6 weeks post partum

**HSIL: special populations**
• Rate 0.5-1.8%
• Rarely associated with significant pathology
• Follow clinical history
  ◦ If obese and having abnormal bleeding consider an endometrial biopsy
  ◦ If no symptoms...observe
• Caveat - benign appearing endometrial cells in a woman >40 in a postmenopausal woman ARE associated with significant endometrial pathology i.e. CANCER

Benign appearing endometrial cells in a woman >40

Old Bethesda system AGC was known as AGUS
• AGC was created to clear confusion between ASC-US and AGUS
• THE TWO ARE NOT THE SAME !!!
• Incidence is 0.1 to 1.5% of all Pap tests
• High risk HPV correlated with 38% of AGC Pap tests
• HPV testing not recommended

Atypical Glandular Cells (AGC)
AGC is worrisome for several pathologies: CIN, adenocarcinoma in situ, cervical adenocarcinoma and endometrial adenocarcinoma.

Many studies have documented the incidence of these disease processes:

AGUS system:
- Eddy et al. 36%, 1997 Am J Obstet Gynecol
- Duska et al. 34%, 1998 Obstet Gynecol
- Veljovich et al. 32%, 1998 Am J Obstet Gynecol
- Manetta et al. 45%, 1999 Gynecol Oncol
- Tam et al. 31%, 2003 Gynecol Oncol

AGC system:
- DeSimone et al. 38%, 2006 Obstet Gynecol

1) Colposcopy with or without biopsies
2) An endocervical curettage (ECC)
3) Endometrial biopsy in women with menorrhagia or age greater than 35
Does every patient need an endometrial biopsy?

- Age is important
- Premenopausal women more likely to have HSIL vs. postmenopausal women (30.4% vs. 7.4%) \( p=0.04 \)  Duska et al. Obstet Gynecol, 1998.
- Women over the age of 40 were more likely to have adenocarcinoma than dysplasia (31% vs. 6%) \( p=0.002 \)  DeSimone et al. Obstet Gynecol, 2006

**AGC management**

- Aggressive form of dysplasia for columnar cells
- AIS cytology associated with
  - AIS histology (48-69%)
  - Cervical adenocarcinoma (38%)

**Adenocarcinoma in-situ (AIS)**

• AIS cytology mandates colposcopic biopsies and an ECC
• AIS histology is managed with a cold knife cone (CKC)
• Numerous studies support CKC over loop electrosurgical excision procedure (LEEP) because of margin status
• CKC has fewer positive margins than LEEP
• Women with positive margins have 40-70% risk of residual AIS
• Women with negative margins have a 20 to 40% risk of residual AIS

Recommend referral to GYN or GYN oncologist
• Nulliparous women are difficult to manage secondary to a high risk of residual disease
• Don’t underestimate the risk of invasive adenocarcinoma with an AIS Pap test
CIN 1 often corresponds with ASC-US or LSIL Pap tests

- High rate of regression to normal
  - 90% regression among Brazilian women within 24 months Schlecht et al. J Natl Cancer Inst. 2003
  - 70% regression among Dutch women within 48 months Nobbenhuis et al. Lancet. 2003
  - 91% regression rate among adolescents within 36 months Moscicki et al. Lancet. 2004

- Low rate of progression to CIN 2,3

CIN 1 progressing to invasive cervical carcinoma

- 0.1% in 2 years
- 0.3% in 5 years
- 1.6% in 10 years
CIN 1 Colposcopic Findings

- Acetyl white plaques
- Bright white
- Clearly demarcated
- Fine punctations
- Acetic Acid - more is better

LSIL Pap and Colposcopy
LSIL Pap with Colposcopy

- CIN 1 preceded with ASC-US, ASC-H or LSIL

**OBSERVATION**
- Cervical cytology at 6 and 12 months
- Or HPV testing in 12 months
- If repeat cytology is ASC-US or greater or HPV is positive...repeat colposcopy

- Persistence of CIN 1 for 24 months...LEEP
- Podophyllin for treatment is unacceptable
- Hysterectomy as primary and principle treatment is unacceptable

CIN 1 management
• CIN 1 preceded by HSIL
  • 1) LEEP

• 2) Colposcopy and cytology at 6 month intervals
  ◦ If repeat cytology is still HSIL...LEEP

CIN 1 management

• Adolescents (<20)
  ◦ Observation
    • Repeat cytology in 12 months
    • At 12 months colposcopy for HSIL
    • At 24 months colposcopy for ASC-US or greater
  ◦ No HPV testing

• Pregnant Women
  ◦ Follow-up with cytology 6 weeks post partum

CIN 1 special populations
• CIN 2, 3 often corresponds with ASC-H and HSIL Pap tests

• CIN 3 will progress to carcinoma if left untreated
  ◦ 12% in 2 years
  ◦ 70% in 8 years

CIN 2, 3

Dull acetyl white plaques
Cobblestoning
Coarse punctations
Atypical vessels
Mosaicism

CIN 2, 3 Colposcopic Findings
HSIL Pap and Colposcopy

HSIL Pap and Colposcopy
LEEP
- Hysterectomy is unacceptable for primary treatment
- Positive margins follow LEEP should be observed with repeat cytology in 6 months
- Hysterectomy is an acceptable treatment for recurrent CIN 2, 3

CIN 2, 3 management

Adolescents (<20)
- 1) Colposcopy and cytology at 6 month intervals for up to 24 months or..
- 2) LEEP

Pregnant Women
- Colposcopy during pregnancy is acceptable to ensure lesion does not progress to carcinoma
- 6 weeks post partum repeat colposcopy and cytology

CIN 2, 3 special populations
Treatment Modalities

- Cryosurgery
- Loop Electrosurgical Excision Procedure (LEEP)
- Laser Ablation
- Cold Knife Conization
- Hysterectomy

Cryosurgery

- Inexpensive, easy to perform, tolerated well by patients
- Cells are destroyed by (cold) thermal damage
- 3 minute freeze/1 minute thaw/3 minute freeze well documented technique
- Does cause 2 -3 weeks of malodorous discharge
- Does hinder repeat colposcopy (SCJ often obscured)
Procedure of choice for most OB/GYN’s
- Easy to perform, well tolerated and provides specimen for pathologic evaluation (Margins)
- Concern that multiple excisions or one large excision will increase rate of preterm labor/incompetent cervix

LEEP

- Meta-analysis of 27 studies
- The studies chosen had to have a control group
- Evaluation of CKC, LEEP and laser for
  - Preterm delivery (<37 weeks gestation)
  - Low birth weight (<2500 g)
  - Cesarean delivery
- **CKC**
  - Preterm delivery- RR 2.59 (95% CI 1.80-3.72)
  - Low birth weight- RR 2.53 (95% CI 1.19-5.36)
  - Cesarean section- RR 3.17 (95% CI 1.07-9.40)

- **LEEP**
  - Preterm delivery- RR 1.70 (95% CI 1.24-2.35)
  - Low birth weight- RR 1.82 (95% CI 1.09-3.06)
  - Cesarean section- RR 2.69 (95% CI 1.62-4.46)

- **Laser**
  - NS for Preterm delivery- RR 1.71 (95% CI 0.93-3.14)

**Summary**

- CKC patients are 2.5 times more likely to have a preterm delivery, low birth weight infant and/or cesarean section
- LEEP 1.5 times more likely
- Incidence of preterm delivery is 2-3%
  - CKC ~ 7.5% (1 in 15 women)
  - LEEP ~ 4.5% (1 in 20 women)
• Margin status helpful in predicting recurrence of cervical dysplasia
• Negative margins ~15%
• Positive margins ~ 30-60%
• Re-excision not needed. Follow patient with serial Pap tests and treat accordingly if patient recurs

Margins and LEEP

Dietrich, Obstet Gynecol 2002

• CO2 laser works by vaporizing cervical cells
• Very precise method; only need 5-7 mm of vaporization for treatment
• Heals great, spares cervical excisions
• COST major problem
• No pathology specimen

Laser
- Used to be the treatment of choice before LEEP
- Surgically excises dysplasia with scalpel/scissors
- Large cost to patient from physician, anesthesia and hospital charges
- Incompetent cervix an issue
- Indications to perform are few

**Cold Knife Conization (CKC)**

- The final treatment for cervical dysplasia
- Comes with significant morbidity/mortality and lengthy recovery (6 weeks)
- Complications include: hemorrhage, infections, bowel & bladder injuries, MI, pulmonary embolus, stroke, death
- 10-20% of patients will continue to have abnormal pap tests: vaginal dysplasia

**Hysterectomy**
Randomized controlled trial between cryosurgery, LEEP and laser showed no statistical difference in efficacy.

Recurrences were measured from 6-37 months:
- Cryosurgery: 19%
- LEEP: 13%
- Laser: 13%

**Efficacy of treatment**

Several factors to consider: age, desire for fertility, size of lesion, size of the cervix, severity of dysplasia, and prior therapies.

**Generalizations**
- Cryosurgery: best for young women with few finances and CIN 1 or 2
- LEEP: the majority of women with CIN 2 or 3. Women with endocervical lesions also suited for LEEP.

**Which method to choose?**
Laser - women who have had multiple recurrences of CIN 2 or 3 and who want to retain fertility. Example: a 19 year old G0 who has CIN 3, prior LEEP and a small cervix.

CKC - glandular abnormalities (AIS) or early invasive cancer

Hysterectomy - women finished with childbearing and who have persistent CIN. Often best utilized with other gynecologic problems like pelvic pain or abnormal uterine bleeding

**Which method to chose?**

- Repeat Pap testing at 6 and 12 months
  - ASC-US or greater = colposcopy (referral 63%)
  - 2 normal Pap tests = annual cytology screening

- High risk HPV testing at 12 months
  - Positive test = colposcopy
  - HPV 92% sensitive for detecting CIN 2-3 (referral 55%)

- Bottom line - more cost effective/less colposcopy with HPV testing

**Post Procedure Surveillance**

• HPV testing for post procedure surveillance is superior to cytology
  ◦ Paraskevaidis et al. Cancer Treat Rev. 2004
  ◦ Zielinski et al. Obstet Gynecol Surv. 2004
  ◦ Cytology pooled sensitivity 70%
  ◦ HPV pooled sensitivity 90%

Post Procedure Surveillance

• Quadrivalent HPV 6/11/16/18 L1 virus-like particle (VLP) vaccine.
  • VLPs are produced in *Saccharomyces cerevisiae.*
    ◦ The L1 proteins self-assemble into VLPs
    ◦ Purified VLPs are adsorbed on aluminum-containing adjuvant
    ◦ The adjuvant is amorphous aluminum hydroxyphosphate sulfate (225 μg per dose)
  • Each 0.5-mL dose contains HPV Types 6/11/16/18 (20/40/40/20 μg L1 protein, respectively)

GARDASIL®: A Quadrivalent HPV Vaccine
Based on prespecified combined efficacy analysis of 4 phase 2/3 clinical trials\(^1\)–\(^4\)

- More than 20,000 women (15–26 years) from the Americas, Europe and Asia were enrolled\(^1\)–\(^4\)
- In one trial, subjects were randomized to either a monovalent HPV 16 L1 VLP vaccine or placebo\(^1\)
- In three trials, subjects were randomized to either GARDASIL\(^\circledR\) or placebo\(^2\)–\(^4\)
- Vaccine or placebo was administered at day 1, month 2 and month 6\(^1\)–\(^4\)
- Central pathology review\(^1\)–\(^4\)

### End-of-Study Analysis for GARDASIL\(^\circledR\)


### GARDASIL\(^\circledR\): Efficacy Against HPV 16– or 18–Related CIN\(^a\) 2/3 or AIS\(^b\)

<table>
<thead>
<tr>
<th>Related Cases</th>
<th>HPV 16/18–Related</th>
<th>HPV 16–Related</th>
<th>HPV 18–Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>GARDASIL(^\circledR)</td>
<td>98% Efficacy (94, 100)</td>
<td>98% Efficacy (92, 100)</td>
<td>100% Efficacy (87, 100)</td>
</tr>
<tr>
<td>Placebo</td>
<td>2(^c)</td>
<td>2(^c)</td>
<td>29</td>
</tr>
</tbody>
</table>

\(^a\) CIN = cervical intraepithelial neoplasia. \(^b\) AIS = adenocarcinoma in situ.

One case was a coinfection with HPV 51, the other was a coinfection with HPV 51 and 56.
GARDASIL®: Efficacy Against HPV 6/11/16/18 Related External Genital Lesions

Per-Protocol Efficacy Population

<table>
<thead>
<tr>
<th>Related Cause</th>
<th>GARDASIL®</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 6/11/16/18-Related Genital Warts</td>
<td>193</td>
<td>99% Efficacy (96, 100)</td>
</tr>
<tr>
<td>VINa 2/3</td>
<td>10</td>
<td>100% Efficacy (56, 100)</td>
</tr>
<tr>
<td>VaINb 2/3</td>
<td>9</td>
<td>100% Efficacy (50, 100)</td>
</tr>
</tbody>
</table>

n=7,900 n=7,902

VINa = vulvar intraepithelial neoplasia.  VaINb = vaginal intraepithelial neoplasia.

- Study of 3,276 sexually active women evaluated the use of risk factors to determine a young adult patient’s appropriateness for HPV vaccination

- Identified risk factors that (1) could be assessed during an outpatient clinical encounter, and (2) were previously associated with either HPV-related cervical disease or HPV infection
  - Sex partner >2 years older
  - >3 lifetime sex partners
  - New sex partner in last 12 months
  - Illegal drug use in last 12 months
  - Sex while impaired by drinking
  - Never married

Risk-Based Vaccination Strategies

Of the estimated 2.5 million women with >3 sex partners:
- 12% would already be currently infected with one or more HPV vaccine types.
  - 88% would not be currently infected with 6, 11, 16, and/or 18.
- The population-level impact of not vaccinating women with >3 lifetime sex partners means an estimated 2.2 million women who could potentially benefit would not be vaccinated.

**Estimated Population-Level Impact of Not Vaccinating Women With >3 Lifetime Sex Partners**

Risk-factor–based vaccination would cause HPV vaccines to be withheld from a large number of women without evidence of current infection.

Identification of individuals based on either the presence or absence of risk factors does not appear to be a viable strategy for HPV catch-up vaccination of young adults.

The ACIP does not recommend a risk-based immunization strategy for HPV vaccination.

**Risk-Based Vaccination Strategies: Study Conclusion**
### Injection Site (1 to 5 Days Postvaccination)

<table>
<thead>
<tr>
<th></th>
<th>GARDASIL® (N=5,088)</th>
<th>Placebo (Aluminum) (N=3,470)</th>
<th>Placebo (Saline) (N=320)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>83.9%</td>
<td>75.4%</td>
<td>48.6%</td>
</tr>
<tr>
<td>Swelling</td>
<td>25.4%</td>
<td>15.8%</td>
<td>7.3%</td>
</tr>
<tr>
<td>Erythema</td>
<td>24.6%</td>
<td>18.4%</td>
<td>12.1%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3.1%</td>
<td>2.8%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

### Systemic (1 to 15 Days Postvaccination)

<table>
<thead>
<tr>
<th></th>
<th>GARDASIL® (N=5,088)</th>
<th>Placebo (N=3,790)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>10.3%</td>
<td>8.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.2%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.8%</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

- Few subjects (0.1%) discontinued due to adverse experiences.
- The table shows the vaccine-related adverse experiences that were observed among recipients of GARDASIL® at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients.

### Vaccine-Related Adverse Experiences

- Females age 11-12
- Females as young as 9 may receive HPV vaccination
- Vaccination is also recommended to females age 13-18 to catch up missed vaccine or to complete the series
- Vaccination is not currently recommended for women over the age of 26 or for males
- Screening for cervical cancer should continue in both vaccinated and unvaccinated women

### American Cancer Society recommendations for HPV vaccination

### Summary of US Vaccine Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>ACIP&lt;sup&gt;1,a&lt;/sup&gt;</th>
<th>ACOG&lt;sup&gt;2,b&lt;/sup&gt;</th>
<th>AAFP&lt;sup&gt;3,c&lt;/sup&gt;</th>
<th>AAP&lt;sup&gt;4,d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine vaccination in females 11–12 years old and catch-up vaccination in 13- to 26-year-olds</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Females 9–10 years old can be vaccinated</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Vaccinate regardless of previous HPV infection or abnormal Pap test results</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Continue Pap testing after vaccination</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

<sup>1</sup>ACIP = Advisory Committee on Immunization Practices.  
<sup>2</sup>ACOG = American College of Obstetricians and Gynecologists.  
<sup>3</sup>AAFP = American Academy of Family Physicians.  
<sup>4</sup>AAP = American Academy of Pediatrics.

---

**If it is best to administer HPV vaccination prior to coitarche, when are adolescents engaging in sexual activity?**

  - 24% of females are sexually active by 15  
  - 40% by age 16  
  - 70% by age 18

- Grunbaum et al. Surveill Summ. 2004  
  - 7% of high school students (males and females) reported coitarche before 13  
  - 10% of 9th graders (14-15) reported having more than 4 partners
• Harper et al. Lancet. 2006
  ◦ Bivalent vaccine HPV 16/18
  ◦ 98% seropositivity for 4.5 years
  ◦ 96.9% reduction in HPV 16/18

• Villa et al. Br J Cancer. 2006
  ◦ Quadrivalent HPV 6/11/16/18
  ◦ 100% seropositivity for 5 years
  ◦ 96% reduction in HPV 6/11/16/18
  • (2 vaccine/ 46 placebo)

### Duration of Protection

• Efficacy trials are ongoing with males 9-15 (Gardasil®)

• If efficacious the vaccine would prevent
  ◦ Anogenital warts in males and indirect transmission to women
  ◦ Penile, anal, oral and head and neck cancers
  ◦ Juvenile respiratory papillomatosis

• Data should be released next month

### HPV Vaccination of Males
HPV is **THE** cause of cervical cancer and dysplasia

- Majority of men and women will have been exposed to HPV before the age of 50
- Smoking is an important co-factor in oncogenesis
- Vaccinations are effective in preventing HPV infections and histologic abnormalities

**Summary**

- **ASC-US**
  - Repeat cytology in 6 months
  - HPV testing
  - Colposcopy

- **LSIL/ASC-H**
  - Colposcopy

- **HSIL**
  - Colposcopy
  - LEEP

**Summary of Abnormal Squamous Pap Tests**
• AGC Pap tests
  ◦ Colposcopy
  ◦ ECC
  ◦ Endometrial biopsy (women >35 or with menorrhagia)

• AIS
  ◦ Referral to a gynecologist or a gynecologic oncologist

**Summary of Abnormal Glandular Pap Tests**

• CIN 1
  • Serial cytology at 6 and 12 months
  • HPV testing in 12 months

• CIN 2-3
  • LEEP

**Summary of CIN**