

# HPV & The New Pap Guidelines

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## Objectives

- Describe the natural history of HPV infection and how it relates to recent changes in screening recommendations for cervical neoplasia
- Identify the major changes in the 2006 Consensus Guidelines for management of abnormal Pap test results
- Discuss issues in successfully incorporating these recommendations and guidelines into practice

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## Estimated Cancer Incidence in Women (US, 2006)

- Breast - 31%
- Lung – 12%
- Colon & rectum – 11%
- Endometrium – 6%
- Non-Hodgkins Lymphoma – 4%
- Melanoma – 4%
- Ovary – 3%
  
- #13 Cervix – 1.43%

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## Cervical Cancer in the US Epidemiology

- 1.43% of all cancers in US women
- 3% of all US gynecologic cancer deaths
- Median age 45-55 years

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**But Cervical Cancer is the  
second most common cause of  
cancer death in women  
worldwide**



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## Cervical Cancer Prognosis

- 5-year survival
  - CIS and Stage 1A (microinvasive) – ~100%
  - Stage IB and IIA (vagina) – 85%
  - Stage IIB – IV (pelvic wall, organs) – 40-60%
- Spreads mostly by direct extension
- Death by ureteral obstruction, renal failure

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## Cervical Cancer Risk Factors

- Early age at first intercourse
- Multiple sex partners
- Socioeconomic class, race
- Smoking

Same as risk factors as for STDs →  
now known to be caused by HPV

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## Virology of Human Papillomavirus (HPV)

- DNA virus in papovavirus family
- Epitheliotropic
- Over 100 subtypes identified
  - at least 35 attracted to genital tract
  - low risk - 6, 11, 42, 43, 44
  - high risk - 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68

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## Natural History of HPV Infection

- Sexual transmission
- Enters cell through microtrauma
- Moves to nucleus of infected cell
- Infected cell exhibits koilocytosis (HPV effect, CIN 1)
  - perinuclear halo
  - enlarged nucleus with clumped chromatin

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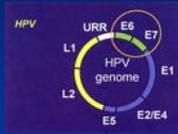
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## Activation of Oncogenes

- E6 and E7 are oncogenes
- E7 can activate synthesis of the intracellular protein p16, normally manufactured only in miniscule amounts
- Excess p16 deregulates and stimulates the cell cycle
- Cervical neoplasia (CIN 2/3) results



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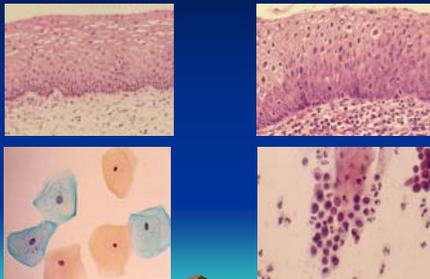
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## Progression of Cervical Neoplasia



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## HPV – Usually a Transient Infection

- In 608 college-aged women
  - 70% no longer infected at one year
  - 91% no longer infected at 2 years
  - average duration of infection - 8 months
- Manifestation of disease determined by
  - viral subtype
  - host cofactors

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## Current Pap Test Recommendations

- First test 3 years after onset of intercourse or age 21
- Test every subsequent year until age 30
- After age 30, test every 2-3 years (with negative history)
- No more testing after hysterectomy or after age 70 (with negative Pap history)
- Exceptions – immunocompromised, DES exposed

**\*Important: Pap smear ≠ annual well-woman exam**

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## Considerations for Annual Exam

- All fertile women need annual assessment of Reproductive Health Plan
- All women  $\leq 25$  and sexually active need chlamydia test and possibly other STI tests
- All women  $\geq 40$ , need clinical breast exam
- Assess other risk factors
  - Menstrual history
  - Discharge, vulvar irritation, pain, urinary symptoms
  - Risk for STI
  - Family history
  - Menopause +/- Hormone Therapy

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## The Role of High-Risk HPV Testing

- Low-risk HPV testing not meaningful, obsolete
- The only screening indication is for women  $\geq 30$  in addition to Pap
  - If both tests negative, **repeat in 3 years**
- Primarily used for triage
  - ASC-US Paps (reflex testing)
  - **LSIL or ASC-US after menopause**
- Allows for less frequent follow-up (up to 1 yr)
  - Untreated colposcopically diagnosed CIN 1
  - Post treatment

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## Guidelines for Colposcopy

- Recommended for
  - Repeat ASC-US, ASC-US with + HPV, LSIL
    - \* Exception – adolescents
  - ASC-H (consider as HSIL), AGC, HSIL
  - Cervical lesions
- Goal is to identify precancerous lesions (CIN2/3)
  - Notoriously inaccurate
    - Even “the experts” miss 18-36%
  - The more cervical biopsies the better!

1. Obstet Gynecol 2006;108:264-72.

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## Guidelines for Adolescents ( $\leq$ age 20)

- High rate of colonization with HPV
- High rate of resolution of both CIN 1 and CIN 2
- Aggressive treatment can interfere with fertility
- For ASC-US or LSIL
  - Repeat Pap in 12 months
  - Colposcopy only if
    - HSIL or
    - LSIL or ASC-US persists for 24 mos.
  - Do not perform HPV test!



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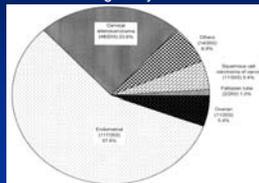
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## The Ominous AGC Pap

Recent review of 3,890 AGC Paps<sup>1</sup>  
– 5.2% had a malignancy



- Another 23% had a significant finding
  - 8.5% LSIL
  - 11.1% HSIL
  - 2.9% AIS
  - 1.4% endometrial hyperplasia

1. Obstet Gynecol 2006;107:701-8.



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## Manage AGC Pap Aggressively!

- Colposcopy with biopsies and ECC, HPV test
- Endometrial biopsy if  $\geq 35$  or high risk for endometrial disease
- If no findings, consider
  - Colposcopy of vagina
  - Pelvic ultrasound
- If “favor neoplasia”, concurrent ASCUS, or repeat AGC
  - Cone biopsy
  - CT
  - Abdominal ultrasound
  - Colonoscopy
  - Breast evaluation

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## Management of Colposcopically-Biopsied CIN

- CIN 1
  - In adolescent, follow with yearly Pap X 2
  - In adult, Pap q 6 mos X 2 or HPV test at 6-12 mos
    - Colposcope if positive
    - If persists for 2 years, consider treatment
  - If diagnosis preceded by AGC or HSIL Pap
    - Excisional procedure or
    - Pap and colposcopy q 6 mos X 2
- CIN 2,3
  - Treat both in adult, treat CIN 3 in adolescent
  - Can follow CIN 2 in adolescent with Pap and colposcopy q 6 mos X 2 years

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## Treatments for CIN

- Ablative
  - Cryotherapy
  - Laser vaporization
- Excisional
  - Loop electrosurgical excision procedure (LEEP)
  - Laser excision/conization
  - Cold knife cone
- All 90% effective<sup>1</sup>
- Follow-up important
  - Pap q 6 mos x 2 or HPV test at 6-12 mos
    - If negative, Pap every year for  $\geq 25$  years<sup>2</sup>
    - If positive, re-colposcope

1. Obstet Gynecol 1998;92:737 2. BMJ 2007;335:1077

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## Risks of Treatment

- LEEP
  - PPROM: RR 2.69, preterm delivery: RR 1.7, birthweight < 2500gm: RR 1.82<sup>1</sup>
  - Highest risk of complications in comparative study (8% bleeding > 24 hrs post treatment)
- Laser conization
  - Preterm delivery: RR 1.7<sup>1</sup>
- No significant risks for laser ablation<sup>1</sup>

→ Individualize therapy

1. Lancet 2006;367:489-498.

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## Individualized Therapy

- Avoid treating adolescents whenever possible, and minimize treatment for CIN I in all age groups
- Ablative therapy may be preferred in women with plans for future childbearing
- Always use excisional therapy if unsatisfactory colposcopy, lesion in endocervical canal, or positive ECC

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## Importance of Meticulous Follow-up

- Abnormal Pap smears
- Abnormal colposcopies
- After treatment

\*\*\*Good tickler system more important than ever now that we are treating less and following more\*\*\*

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## Cervical Cancer Prevention

- Safer sexual practices
  - Condoms 70% effective in preventing transmission<sup>1</sup>
- Avoid smoking
- Healthier lifestyle

1. N Engl J Med 2006;354:2645-2654.

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## VACCINES!

- Gardasil<sup>®</sup>
  - Prevents infection with HPV 16 & 18 (70% of CIN/CA) and 6 & 11 (90% of genital warts)
  - 3-dose regimen indicated for
    - All girls age 11-12
    - All females aged 13-26 who have not been vaccinated
- Cervarix<sup>®</sup>
  - Prevents infection with HPV 16 & 18
  - Lipopolysaccharide adjuvant
    - May be more immunogenic (confer longer-lasting immunity)
- Both also offer some cross-protection against
  - Types structurally related to HPV 16 – 31, 33, 52, 58
  - Types structurally related to HPV 18 – 39, 45, 59
- Do not accelerate clearance of the virus<sup>1</sup>

1. JAMA 2007;298:743-53.

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## Questions that Remain

- Will the vaccine be efficacious for women over age 26?
- What about men?
- What is the duration of protection?
- How will vaccination affect cervical screening?
- Will the vaccine change cancer rates in countries with good screening programs?



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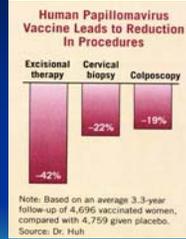
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## Results So Far

- 16% ↓ ASCUS
- 23% ↓ ASCUS + HPV
- 35% ↓ ASCUS r/o HSIL
- 14% ↓ LSIL
- 43% ↓ HSIL



Presented at Society of Gynecologic Oncologists 2008

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## The Promise of Global Cervical Cancer Prevention

N Engl J Med 2005;353:2101-4

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