

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

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%

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

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



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

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

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

Natural History of HPV Infection

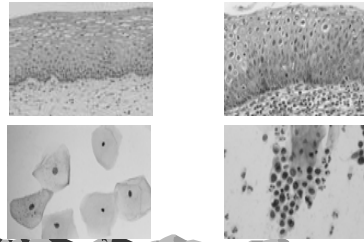
- Sexual transmission
- Enters cell through microtrauma
- Moves to nucleus of infected cell
- Infected cell exhibits koilocytosis (HPV effect, CIN 1)
 - perinuclear halo
 - enlarged nucleus with clumped chromatin

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



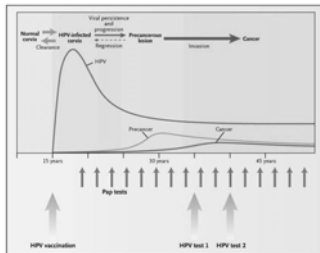
Progression of Cervical Neoplasia



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

The Natural History of HPV Infection and Cervical Cancer

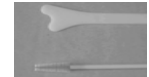


Cofactors for HPV Infection

- Nonmodifiable
 - Immunosuppression
 - Age
 - Genetic susceptibility
- Modifiable
 - Smoking
 - Genital coinfections (HSV, BV, chlamydia)
 - Vitamin deficiencies (A, C, E, folic acid)
 - Stress¹
- Others?

Pap Test – The Ideal Screening Test

- Inexpensive
- Easy to perform
- Well-accepted by women
- Cervical Ca is preceded by several years by a premalignant phase (an intraepithelial lesion)
- Treatment proven effective in reducing progression to invasive disease



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**

Considerations for Annual Exam

- All fertile women need annual assessment of Reproductive Health Plan
- All women ≤ 25 and sexually active need chlamydia test and possibly other STI tests
- All women ≥ 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

The Role of High-Risk HPV Testing

- Low-risk HPV testing not meaningful, obsolete
- The only screening indication is for women ≥ 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

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

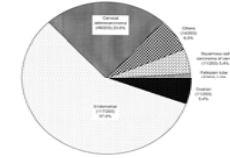
1. Journal of Clinical Oncology 2005; 23:10826A-72

Guidelines for Adolescents (≤ 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!

The Ominous AGC Pap

Recent review of 3,890 AGC Paps¹
– 5.2% had a malignancy



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

1. Journal of Clinical Oncology 2005; 23:107701-8

Manage AGC Pap Aggressively!

- Colposcopy with biopsies and ECC, HPV test
- Endometrial biopsy if ≥ 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

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

Treatments for CIN

- Ablative
 - Cryotherapy
 - Laser vaporization
- Excisional
 - Loop electrosurgical excision procedure (LEEP)
 - Laser excision/conization
 - Cold knife cone
- All 90% effective¹
- Follow-up important
 - Pap q 6 mos x 2 or HPV test at 6-12 mos
 - If negative, Pap every year for ≥ 25 years²
 - If positive, re-colposcope

1. Obstet Gynecol 1999; 93:777-81; 2. BMJ 2007; 335:1077

Risks of Treatment:

- LEEP
 - PPROM: RR 2.69, preterm delivery: RR 1.7, birthweight < 2500gm: RR 1.82¹
 - Highest risk of complications in comparative study (8% bleeding > 24 hrs post treatment)
 - Laser conization
 - Preterm delivery: RR 1.7¹
 - No significant risks for laser ablation¹
- Individualize therapy

1. Journal of Clinical Oncology 2005; 23:450-458

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

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

Cervical Cancer Prevention

- Safer sexual practices
 - Condoms 70% effective in preventing transmission¹
- Avoid smoking
- Healthier lifestyle

1. NCI/NIH/2002-0554/2045-2054.

VACCINES!

- Gardasil®
 - 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®
 - 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!

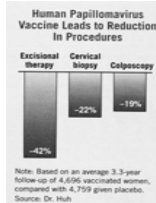
1. NCI/NIH/2002-0554/2045-2054.

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?

Results So Far

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



Presented at Society of Gynecologic Oncologists 2008

The Promise of Global Cervical Cancer Prevention

1. NCI/NIH/2002-0554/2101-4.