Human Papilloma Virus

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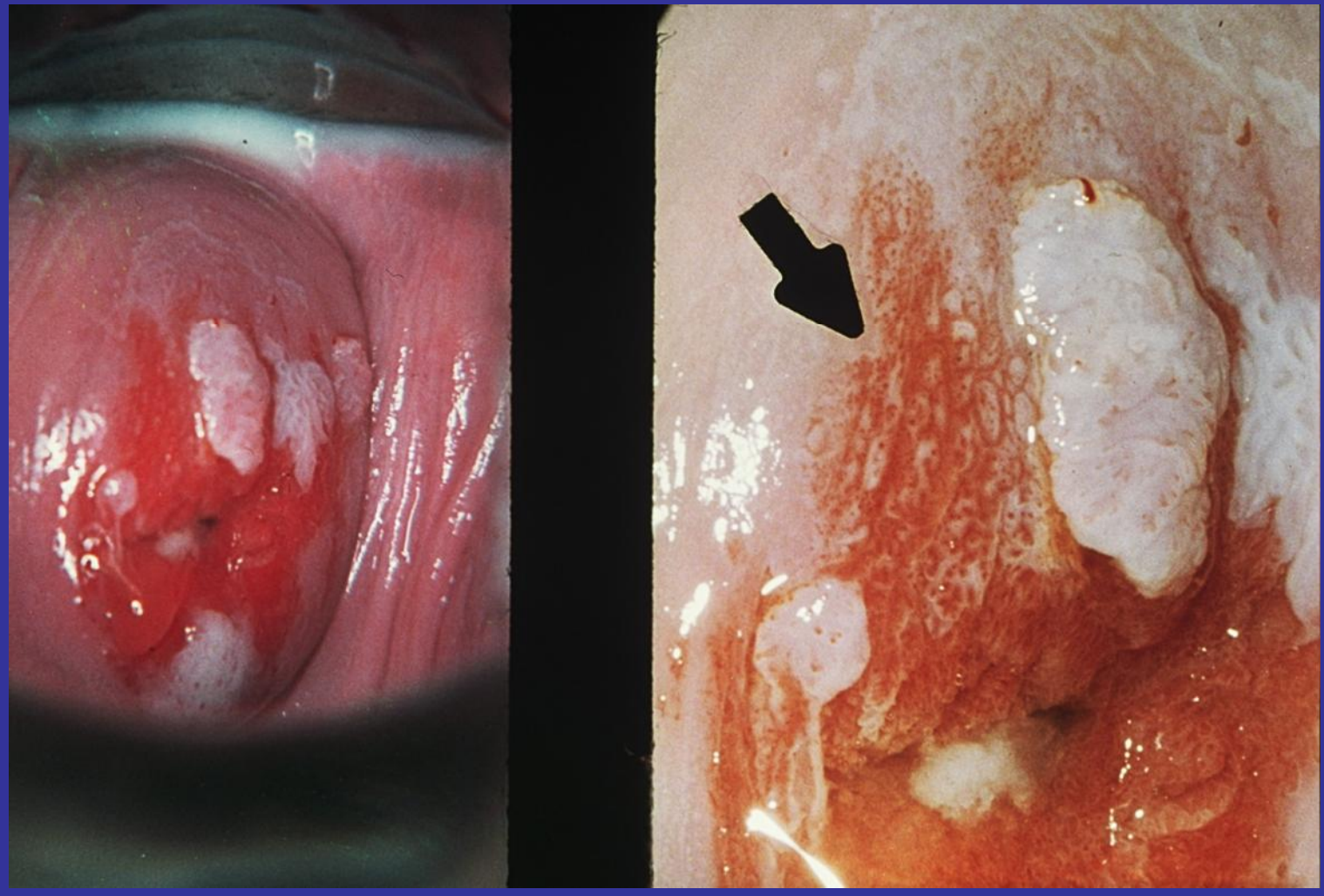
CERVICAL WARTS and HSIL



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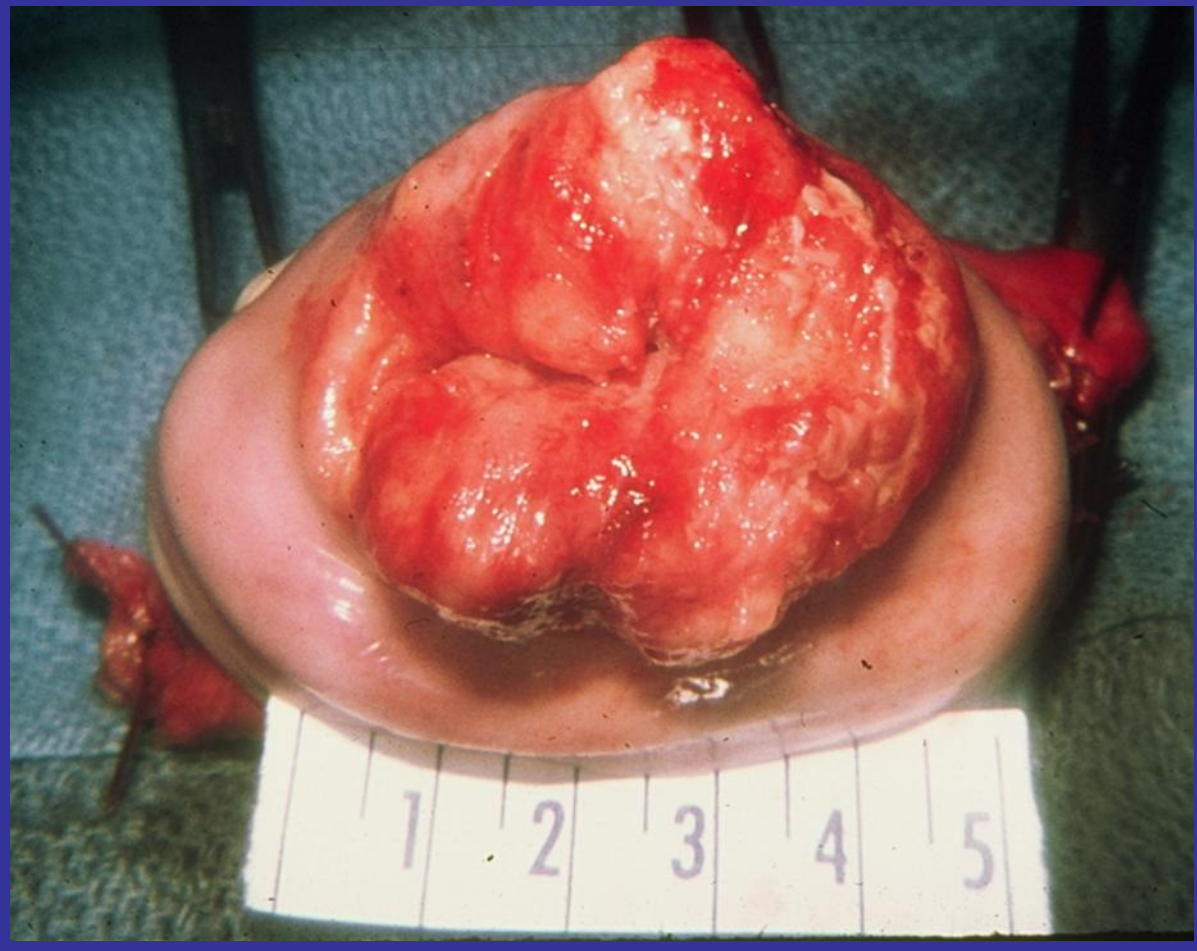
CERVICAL CANCER



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Human PapillomaVirus (HPV) (More than 100 types)

- Infects only humans
- High risk (oncogenic) types
  - 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, 82
- Low risk (non-oncogenic) types
  - 6, 11, 40, 42, 43, 44, 54, 61, 72, 81

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Human Papilloma Virus

- Anogenital Disease: cervix, vulva, vagina, anus, penis
  - Condylomata accuminatum
  - Squamous intraepithelial neoplasia
  - Cancer
- Head/Neck Disease:
  - Mouth, tongue, tonsils
  - Sinuses
  - Oropharangeal
  - Respiratory mucosa (children; type 6, 11)
  - Cancer: usually HPV 16
- Cofactors: S**moking, Alcohol**

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HPV DNA Detection

- Hybrid capture II assay by Digene Diagnostics
  - Only pos. or neg. for Hi Risk HPV: not type specific
- Research techniques
  - In-situ hybridization
  - Polymerase chain reaction
  - Dot blot
  - Filter hybridization
  - Southern transfer hybridization

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HPV Nomenclature

Cervical/ Vaginal/ Vulvar/ Anal/ Penile

Dysplasia	Mild Dysplasia	Moderate Dysplasia	Severe Dysplasia Carcinoma in-situ
Intraepithelial Neoplasia	CIN I VIN 1 VAIN 1	CIN 2 VIN 2 VAIN 2	CIN 3 VIN 3 VAIN 3
Squamous Intraepithelial Lesion (SIL)	Low Grade SIL (LSIL)	High Grade SIL (HSIL)	High Grade SIL (HSIL)

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Acute (Incident) HPV Infection

- 5 – 10 years to develop cancer from time of infection

- Infects only the epithelium – no viremia
- **Most cases** – no histologic or cytologic changes (66% - 90%)
  - Resolution of infection and cytologic changes occurs secondary to antibodies, and NKC, activated CD-4 and T lymphocytes

- HPV16, 18: **integrated into the genome**
  - LSIL: 25%
  - HSIL: 60%
  - Cancer: 70%
  - Increased chance of SIL/Cancer with persistent infection
  - Associated with tobacco use and immune deficiencies

- HPV 6/11: undergoes replication, but **not integrated into the genome**
  - Nuclear enlargement, multinucleation, peri-nuclear halo at 2 – 8 months
  - Condylomata – 90%; ASCUS and LSIL- majority

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Transmission of HPV

- Genital contact
- **Vaginal intercourse not required**
- Number of partners; partners number of partners
- New partner greater risk
- Smoking: 4 times R.R.
- **Persistence of Hi Risk HPV: increases risk of SIL**
- Viral load correlates with developing SIL
- **Immunosuppression**: HIV, Rheumatoid Arthritis, Cancer
- **Condoms**: not very good at preventing HPV
- Spermide nonoxynol-9: not protective

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HPV Epidemiology

- Worldwide prevalence:10%, (Africa 22%)
- Prevalence decreases after age 30
- More than 1 HPV type: 40%
- US Females
  - Prevalence: 20 million infected
  - Incidence: 5.5 million per year
  - **HSIL: age 25 – 35**
  - **Cervical cancer: age > 40**
  - One lifetime partner: 4-20% are HPV+
  - 30-45% of women will acquire HPV in college
  - **Age 18-40:** 40% are HPV positive by PCR
- US males
  - **Prevalence: 55%** HPV+ by PCR (1/3 high risk HPV+)
  - Shaft (circ.) or glans penis (uncirc.) 58%, urethra 10%, semen 5%, Anus 10%

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Cervical Cancer

- HPV found in almost all cases
- Worldwide: 400,000 new cases per year
- Second most common after breast ca. in low resource countries
- Cervical cancer: 11,150 cases in US in 2007 with 3670 deaths
- About 50 million paps/ year in US
  - 3.5 million: abnormal
  - 2.5 million: colposcopy
  - **HPV 16 – 50% of cancers**
  - **HPV 18 – 15-20%**
  - HPV 31 – 5%
  - HPV 45 – 5%
  - Adenocarcinoma: 50% positive for HPV 16/18

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SCREENING for CERVICAL CANCER

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Cervical Cancer Screening

- **HIGH Predictive value**
  - False negative – S**ensitivity** – probability of a positive test among patients with disease
  - False positive – S**pecificity** – probability of a negative test among patients without disease
- Cost effective
- Stage shift- hopefully resulting in decreased mortality
  - Cancer → Precancerous
  - Stage IV → Stage I

  Acceptable to women
- Enormous decrease in the incidence of cervical cancer
- 50% of women with cervical cancer have either **never been screened**, or were **not within the past 5 years**
- 20% of older US women never screened

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Screening and Diagnostic Procedures

- Clinical exam – vulva, cervix, vagina, anus
- Cervical cytology (conventional/ liquid based)- with or without HPV DNA testing
- HPV DNA testing only
- VIA: Visual Inspection with Acetic Acid 5%
- VILI: Visual Inspection with Lugol's Iodine
- Colposcopy with 5% Acetic acid / Lugol's Iodine
- Anoscopy & Cytology: for women with perianal, perineal lesions, or anal sex

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Screening: Pap Smear

- **Conventional**: Cervix (SCJ/ TZ) sampled with spatula and brush, placed on a glass slide, fixed with chemicals
  - 50% detection of LSIL, 75% detection of HSIL
- **Liquid based**: Sampled similarly and suspended in liquid medium, spun or filtered and placed on slide in thin layers
  - **Not really more accurate**
  - **Fewer unsatisfactory specimens:** air dry, blood, no ecc's
  - Thin Prep: 1996, Surepath: 2000
  - Single specimen to test for Cytology, HPV,G.C.,Chlamydia
- **Automated screening:** (thin prep screening imaging system)
  - Increased detection of LSIL and HSIL by 40%
  - More expensive
- **Large amount of interobserver variability** (esp. ASCUS/LSIL)
- Correlation between pap and biopsy is 50%

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Bethesda Classification System (2001/1988)

Diagnosis	%
ASCUS: Atypical Squamous Cells of Undetermined Significance	< 3.0
ASCH: Atypical Squamous Cells – possible HSIL	2.0
LSIL: Low Grade Squamous Intraepithelial Lesion	1.7
HSIL: High Grade Squamous Intraepithelial Lesion	1.5
AGC: Atypical Glandular Cells	1
Squamous cancer	0.3
Adenocarcinoma	0.1

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False Negative Pap Smear

- False negative rates of 10-20%
  - Clinician error
  - Too few cells: atrophy
  - No endocervical cells: transformation zone not sampled
  - Abnormal cells not plated on slide
  - Abnormal cells not fixed well with preservative
  - Blood, inflammation
  - Cytopathologist error
  - Inaccurate reporting
- Women with cervix cancer: up to 50% have dysplastic cells on review of previous paps

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HPV DNA Screening

- Primary HPV DNA Screening only
  - Inc. risk of unnecessary colposcopies and biopsies
  - Poor specificity and predictive value if used alone
  - Cost: 7.5 billion dollars per year in the US
- HPV positive: refer for cytology
  - Pap positive: colposcopy
  - Pap negative: repeat 6 – 12 mo.
- **Best use:** combined with cytology for triage to colposcopy
- Considered experimental for now

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Cytology and Reflex HPV Testing

- Cervical cytology – high specificity
- HPV DNA testing – high sensitivity
- Women with negative pap and HPV negative
  - ≥ CIN 2 – 1:1000 chance at that visit
  - Developing CIN 3 in 5 years < 1:2000 chance
  - Ok to screen every 3 years
- 5% who are HPV+ with neg. pap develop ≥ CIN 3 by 5 years
- 55% of women of who are HPV+ have neg. pap
- 5 – 10% of women who are HPV- have abnormal pap
- Women with persistently positive HPV need colpo as 21% develop ≥ CIN 2 within 30 months

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Screening: Visual Inspection with Acetic Acid (VIA) and Lugols Iodine (VILI)

- Acetowhite epithelium and/ or non-staining areas seen with naked eye or hand held magnifying lens
- **High false positive rate!**
  - Sensitivity 65-96% (VILI > VIA)
  - Specificity 50-98% (VILI = VIA)
  - Low PPV – 10% (VILI = VIA)
  - 10% - 20% of women screened are positive
- Both are easy techniques to learn
  - Train MD's/ RN's/ Midwives, etc.
- Low cost: Supplies easy to get, less testing required
- Triage: pap, HPV DNA testing, colposcopy, treatment

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Recommended Screening Frequency of US Professional Organizations

- **Start**: 3 years after beginning sexual activity (teens often lie), or age 21
- **Stop**: age 65-70 if 3 negative paps, unless new partner
- **Annual screening until 3 negative paps** for sexually active women **:** then every 2-3 years- unless a new partner
- **Screen every 3 years if both cytology and HPV negative**
- **Screen high risk yearly**

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Recommended Screening Frequency of US Professional Organizations

- **HPV vaccinated:** screen at later age, and less often (no data yet)
- **Prior hysterectomy for benign disease and** negative HPV history – do not screen
- **Hysterectomy for SIL** (VAIN 2 after – 7.5%): yearly screening
- 10% of Cervix Cancer – **inadequate F/U of an abnormal pap**.
  - Average delay 22 months

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Screening in Countries with Low Screening Rates

- **Visual Inspection with Acetic acid (VIA) and/or Lugols Iodine (VILI)**
- **HPV DNA testing only**
- Both tests in 1 or 2 visits were cost effective
  - decreased risk of cervix cancer by 33% (India)
- **Cytology –** high prevalence of precursor lesions in an unscreened population
- **Cytology only**, **may be best**, if not enough people trained in VIA and VILI, and HPV testing is expensive

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Screening in Countries with Low Screening Rates

- Active invitation of women & **same day screening** very effective
- Decrease stigmata of cancer and its prevention
- Train local health care workers
- Western forms of health education – often perceived as neocolonialism, need to involve local community committees and at risk women.

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MANAGEMENT of THE ABNORMAL PAP SMEAR

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ASCUS: Pre-menopausal Women

- Spontaneous Resolution at 5 years: 75%
- **Options:**
  - **Reflex HPV Testing**
  - **Repeat Cytology**
  - **Colposcopy**

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ASCUS: Pre-menopausal Women: Options

- **Reflex HPV testing: preferred in the US for ASCUS/ LSIL on pap smear**
  - Higher sensitivity for detecting CIN 2/3 than cytology alone
  - **Most cost effective in US**
  - **HPV positive:** colposcopy
    - 53% of ASCUS paps are HPV+
    - 15 – 25% will have CIN 2/3 on biopsy
    - 0.1 – 0.2 % have cervical cancer
    - 2 year risk of developing ≥ CIN 2 – 51%
    - Multiple HPV types: increases risk of CIN
  - **HPV negative:** repeat cytology 12 months / No colposcopy
    - Risk of developing CIN 2 (3%), CIN 3 (1.4%) in 2 years
  - False negative HPV
    - Hybrid Capture 2 negative but positive by PCR (5%)

(BJOG: 14:951.2007 ALTS Triage Study)

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ASCUS Evaluation Options: Pre-menopausal Women (Cont.)

- **Repeat cytology in 6 or 12 months**
  - 15 to 33% false negative rate/pap
  - Normal pap on repeat ~10% have SIL on biopsy
  - ASC-US on repeat (66% of patients): Colposcopy
    - 20% have SIL on biopsy
  - Disadvantage
    - Multiple visits
    - Time delay
    - No data on frequency or duration of repeat cytology
- **Immediate colposcopy: not cost effective**

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ASCUS: Adolescents, Pregnant, Post-menopausal

- **Sexually active adolescents (B. Moscieski)**
  - Transient infection common and **often resolves** (90% of cases)
  - 50% have 2 or more Hi Risk HPV types
  - 52% with HPV have normal pap
  - **No reflex testing**: risk of cancer negligible
  - **Repeat pap 12 months**
    - ASCUS/LSIL – repeat pap 1 year
    - HSIL – Colposcopy
    - 187 patients age 13-22 with ASCUS/LSIL on pap
      - 61% regressed in 1 year
      - 91% regressed in 3 years
- **Pregnant**: same evaluation as non-pregnant
  - Increased incidence of ASCUS/LSIL
- **Post-menopausal**: Eval. same as pre-menopausal women
  - Topical estrogen generally not recommended

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Atypical Squamous Cells – High grade SIL (ASCH)

- Colposcopy
- Endocervical curettage/ Biopsy
- No HPV typing necessary
- 10 – 68% will have ≥ CIN 2
- If no lesion or LSIL on Bx
  - Repeat pap 6/12 months
  - HPV testing in 12 months
  - Repeat colpo for ASCUS/ ASCH/ HPV positive
- Colposcope pregnant women

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LSIL: Pre-menopausal Women

- Adult: Colposcopy/ Biopsy
- Almost all are HPV positive
- 45%: LSIL on biopsy
- 33%: normal
- 15-25%: HSIL on biopsy

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LSIL: Pregnant Women

- Colposcopy recommended
- Can be deferred until 6 weeks postpartum.
- No Endocervical curettage
- Biopsy: HSIL; cancer
- LSIL on colposcopy – no biopsy needed
  - If biopsy shows LSIL - no F/U until post partum
- 129 women with LSIL on pap during pregnancy.
  - Persistent LSIL P.P. – 32%
  - Negative cytology – 62%
  - Progress to HSIL – 6%

(Cancer 2004: 102,228)

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LSIL: Post-menopausal Women

- LSIL on pap – risk of HSIL low on biopsy --Often HPV negative
- Immediate colpo or reflex HPV
- HPV positive: colposcopy
- HPV negative: repeat pap 6 or 12 months or repeat HPV in 12 months

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Management of Women Screened with the Combined Test (Pap/HPV)

Results of Cytology/HPV	Recommended follow-up
Negative / Negative	Routine screening in 3 years
Negative / Positive	Repeat combined test in 12 months
ASC-US / Negative	Repeat cytology in 6 or 12 months
ASC-US / Positive	Colposcopy
>ASC-US / Positive or negative	Colposcopy

(ACOG)

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Atypical Glandular Cells (AGC)

- Cytology (Bethesda 2001)
  - AGC Not Otherwise Specified (NOS); site specified
  - AGC – favor cancer; site specified (Cervix/ Endo.)
  - AIS
  - Adenocarcinoma
- Originates from cervix or endometrium
  - Can detect ovarian/ tubal/ vaginal/ colonic cancer
- Cytology less sensitive than for squamous lesions
  - Difficult for cytopathologists to distinguish between HSIL/ glandular cells
  - Lesion arises high in canal
- **Colposcopy, directed biopsies, ECC, HPV DNA**

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AGC NOS: Negative Biopsies

- Reflex HPV negative: repeat pap 12 months
- Reflex HPV positive: Repeat pap 6 months
  - If negative HPV/ Pap – routine F/U
  - If HPV positive or ≥ ASCUS:
    - Colposcopy/ Directed biopsies/ ECC
- If HPV not available: repeat paps every 6 months
- Women with 2 AGC NOS Paps:
  - Cone Bx & D+C: if colpo, Bx's and EMB negative

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AGC: Favor Neoplasia/AIS

- **Colposcopy/ biopsy/ Endocervical curettage**
- **Endometrial Biopsy if** older than 35, or younger if risk factors
- Cold Knife Cone or Leep
- Final pathology
  - HSIL – 28%
  - LSIL – 8.5%
  - AIS – 4%
  - Adenoca of cervix – 2%
  - Endo cancer – 2%
- Atypical endometrial cells only
  - EMB/ECC, No colpo., No HPV testing
  - If negative biopsy: colpo and HPV testing
- Cone biopsy, HSC; D & C negative: Sono/ CT Scan/ LSC

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Abnormal Biopsy Management

- **BIOPSY ≥ HSIL**
  - Leep/ Cryotherapy/ Laser
    Cold Knife Cone (CKC)/ Hysterectomy

- **BIOPSY ≤ LSIL and HPV positive**:
  - 10% will have CIN 2/3 on biopsy in 2 years
  - Options
    - Follow up pap – 6/12 months
    - Follow up HPV – 12 months
    - Cytology negative 2 times – routine screening
    - Colposcopy: for repeat ≥ ASCUS/HPV positive
    - Consider treating large lesions

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See and Treat

- Requires only one or two visits
- VIA / VILI
- Cryotherapy
  - cheap, no bleeding, acceptable pain
  - mild post therapy symptoms and risks
- Leep
  - Requires electricity
  - Cost more
  - Greater technical skills required than cryotherapy
  - Bleeding post therapy more common than cryotherapy

- RISK of OVER TREATMENT is HIGH!

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Cryosurgery for SIL

- Agreement between colposcopy findings, biopsies and pap
- Carbon Dioxide or Nitrous Oxide
- Large tank is preferable
- **Pressure in tank is important: > 40 kg/cm2**
- Repeat colposcopy
- Lugol's solution
- Freeze entire lesion and Transformation zone (multiple applications may be necessary)
- **Double – Freeze**
  - **Iceball with 5mm margin (should take 1.5 – 2 min.)**
  - Thaw
  - Iceball with 5mm margin
- Watery discharge for 10 – 14 days after cryotherapy
- CRYOTHERAPY is successful – about 5% failure rate
- If pap abnormal at 6 months – consider cryotherapy a failure

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Cone Biopsy (CKC) / Leep/ Laser Cone

- Procedure tailored to size and location of lesion, age of patient, and colposcopy findings
- High endocervical lesion
- Large ectocervical lesion
- Pregnant
- Lugol's – to help with size and configuration of cone
- CKC – Sultures 3:00 and 6:00; scalpel #11 blade
- Vasopressin: 0.5 U/ml (10 cc)
- Epinephrine 1:200,000
  - Lidocaine 0.5% - 2h effectiveness
  - Marcaine (Bupivicaine) 0.25%/ 0.5%
- Perform an Endocervical curettage after cone

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Hysterectomy

- HSIL with positive margins on Leep or Cone
- Adenocarcinoma in situ on Leep or Cone
- Microinvasive squamous cell cancer (stage 1A) on a Leep or Cone Bx

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HPV VACCINE

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HPV Vaccines

- HPV infection induces a time limited HPV type specific immunity
- **Vaccine needs to be effective against the HPV type prevalent in the population**
- Protective antibody levels are dependent on initial and sustained vaccine responses as well as booster shots (not clear if required)
- Antibody level required for protection not known
- **Duration of protection is unknown**

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HPV Vaccines

- Vaccine can protect against HPV types not already acquired
- **Vaccine does not "cure" already present lesions (not therapeutic)**
- **Can protect some women who are already HPV+ against development of CIN**
- Need to screen with pap at time of initial vaccine if sexually active
- Will not replace or eliminate cervical screening

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Most Frequent HPV Types in Vietnam

Type	Percentage
52	13%
51	12%
18	11%
16	11%

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Tests for Vaccine Efficiency

- Surrogate markers for effectiveness against cervix ca.
  - Prevention of incident (new) HPV infection by DNA testing
  - **Prevention of ≥ CIN 2**
  - Antibodies
- Antibodies are unique for each HPV type and not comparable across types
- Antibodies titers are different for each commercially available vaccine and are not comparable
  - Milli ELISA U/ml
  - Milli MERCK U/ML
- Titer levels above infection levels are thought to be protective
- No correlation between titer levels and protection

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Quadravalent HPV Vaccine (Gardisil)

- HPV 6/11/16/18
- Recommended age: 9 – 26
- Vaccinate: 0, 2, 6 months
- LI Capsid protein – no viral DNA
- Future I trial
  - 5455 patients, age 16 – 24
  - 100% effective in preventing CIN, AIS, and anogenital disease
  - 73% effective in preventing external anogenital disease and vaginal lesions in women HPV positive at baseline.
  - 55% effective against preventing CIN if HPV+ at baseline

(Lancet 2007, 369:693.)

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Quadravalent HPV Vaccine (Gardisil)

- Future II trial – NEJM 356: 1915, 2007.
  - Phase III multinational prospective study
  - Double blind, placebo controlled
  - 12000 patients 15 – 26 years old
  - 98% effective ≥ CIN 2
  - 91% effective who received vaccine off recommended time scheduled
  - Seroconversion 96/97/99/68%
  - Well tolerated
  - 100% effective for VAIN 2/3
  - 100% effective for VIN 2/3

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Bivalent HPV 16/18 Vaccine (Cervarix)

- 1113 patients; age 15 – 25; 5.5 years F/U
- Vaccinate: 0, 1, 6 months
- HPV 16/18: 96+% effective
- 90% effective even with off schedule vaccination
- No cases of CIN
- Protection against HPV 45 (80%) & HPV 31 (53%)

Lancet 369: 2161-70, 2007.

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HPV Vaccine Safety

- Mild injection site reaction
- Not a live virus – no oncogenic potential
- Do not give in pregnancy
- Breast feeding allowed
- No birth defects in offspring
- Rare cases of Guillan-Barre

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Cost Effectiveness HPV Vaccine

- COST in US: $360 for the 3 injections- not including administration fees
- If all 12 old girls in USA were vaccinated:
  - Prevent 200,000 HPV infections
  - Prevent 100,000 abnormal paps
  - Prevent 3,300 cases of cervix cancer
- Booster shot at 10 years not cost effective in countries with screening programs
- Vaccinate both men & women:
  - probably more effective
  - Not cost effective to prevent cervix cancer
  - Large trial planned

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