

# Bioengineering and World Health

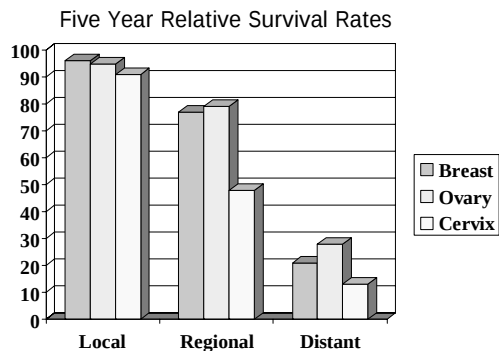
## Lecture Thirteen



## Outline

- The burden of cancer
- How does cancer develop?
- Why is early detection so important?
- Strategies for early detection
- Example cancers/technologies
  - Cervical cancer
  - Ovarian cancer
  - Prostate cancer

## Importance of Early Detection



## Screening

- Use of simple tests in a healthy population
- Goal:
  - Identify individuals who have disease, but do not yet have symptoms
- Should be undertaken only when:
  - Effectiveness has been demonstrated
  - Resources are sufficient to cover target group
  - Facilities exist for confirming diagnoses
  - Facilities exist for treatment and follow-up
  - When disease prevalence is high enough to justify effort and costs of screening

## How do we judge efficacy of a screening test?

Sensitivity/Specificity  
Positive/Negative Predictive Value

## Bioengineering and Cervical Cancer

## Statistics on cervical cancer

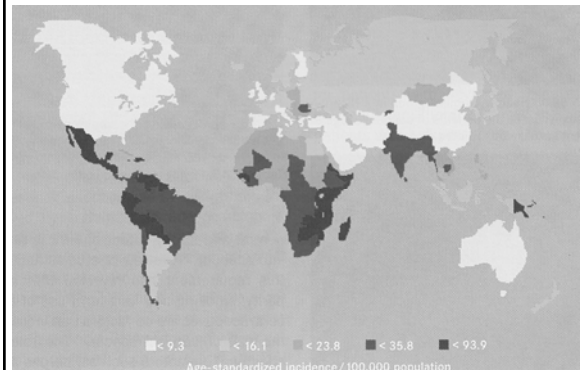
US data (2007)

- Incidence: 11,150
- Mortality: 3,670

World data (2004)

- Incidence: 510,000 (80% developing world)
- Mortality
  - 288,000 deaths per year worldwide

## Global Burden of Cervical Cancer

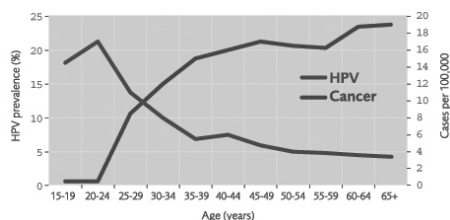
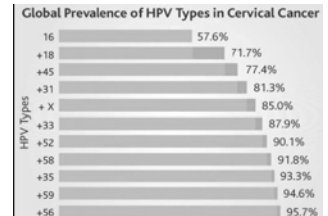
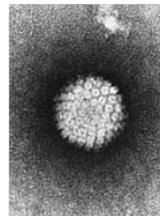


## Risk factors

- HPV infection
  - HPV infection is the central causative factor in squamous cell carcinoma of the cervix
- Sexual behaviors
  - Sex at an early age
  - Multiple sexual partners
- Cigarette smoking

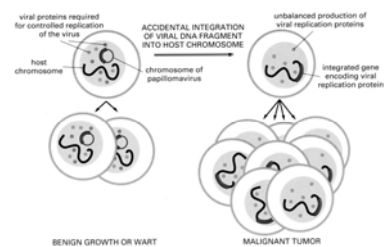
## Human papilloma virus (HPV)

- Most common STD
- >70 subtypes
- Asymptomatic infections in 5-40% of women of reproductive age
- HPV infections are transient

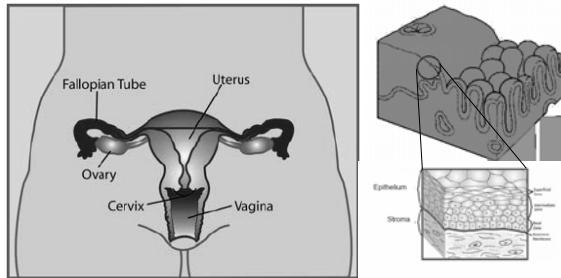


## HPV and cervical cancer

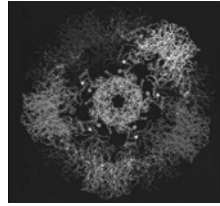
## What Initiates Transformation?



## Pathophysiology



## HPV vaccine

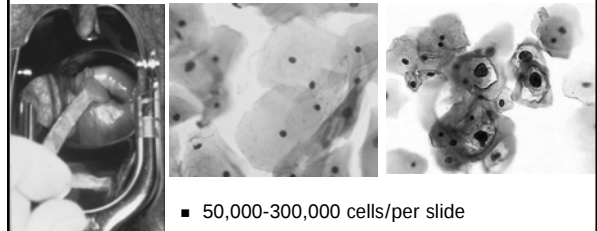


Virus-like particles (VLP) made from the L1 protein of HPV 16

- approved for use in girls and women aged 9 to 26 years in the US
- not effective to women already exposed to HPV
- Effective on 4 HPV isotypes
- Recombinant technology
- Alternative prevention technique to screening?

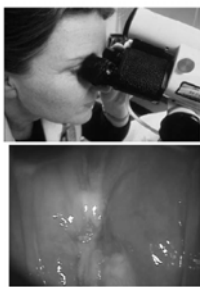
## How Do We Detect Early Cervical Cancer?

## Pap Smear

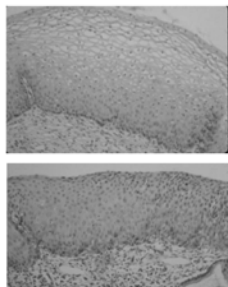


- 50,000-300,000 cells/per slide
- Cytotechnologists review slides (<100/day)
- Se = 62% —→ 3%
- Sp = 78% —→ \$6B

## Colposcopy and Biopsy

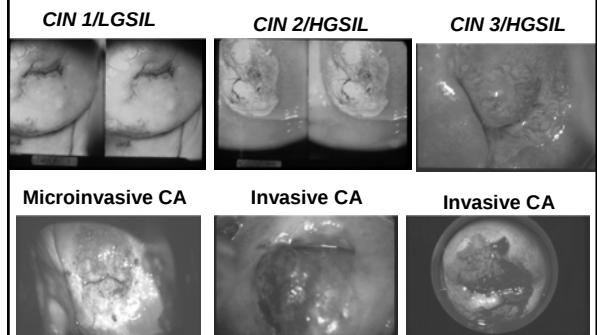


Colposcope  
Se = 95%  
Sp = 44%



Biopsy sections

## Colposcopy and Treatment



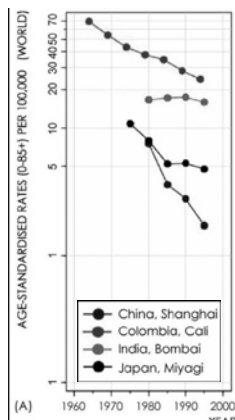
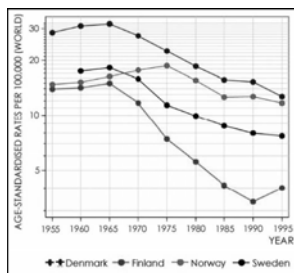
## Detection and Treatment

- Screening:
  - Pap smear
- Diagnosis:
  - Colposcopy + biopsy
- Treatment:
  - Surgery, radiotherapy, chemotherapy
- 5 year survival
  - Localized disease: 92% (56% diagnosed at this stage)

## Screening Guidelines, ACS

- All women should begin cervical cancer screening about 3 years after they begin having vaginal intercourse, but no later than when they are 21 years old. Screening should be done every year with the regular Pap test or every 2 years using the newer liquid-based Pap test.
- Beginning at age 30, women who have had 3 normal Pap test results in a row may get screened every 2 to 3 years with either the conventional (regular) or liquid-based Pap test.
- Option for women over 30 is to get screened every 3 years with either the conventional or liquid-based Pap test, *plus* the HPV DNA test.

### Trends in Screening Cervical Cancer



## Challenge

- Developed and developing world
- Cost and infrastructure requirements for screening
- Need for appropriate technologies

## New Detection Technologies

### Aims:

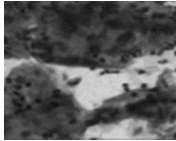
- Reduce the false positive and false negative rates
- Give instantaneous results
- Reduce the costs

## New Technologies for Cervical Cancer

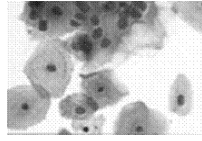
- Liquid Based Pap testing
- Automated Pap smear screening
- HPV Testing
- VIA
- HPV Vaccine

## Liquid Based Pap Smear

- Rinse collection device in preservative fluid
- Process suspension of cells to deposit a monolayer of cells on a microscope slide



Conventional Pap



Liquid Based Pap

<http://www.prlnet.com/ThinPrep.htm>

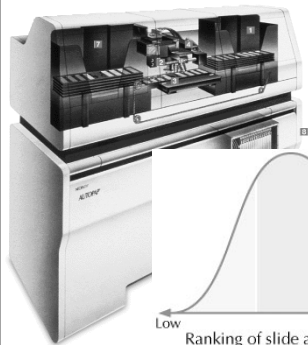
## Liquid Based Pap Smear

- Gentle dispersion breaks up blood, mucous, non-diagnostic debris, and mixes sample
- Negative pressure pulse draws fluid through filter to collect a thin, even layer of cells
- Monitor flow through filter during collection to prevent cells from being too scant or too dense
- Cells then transferred to a glass slide



## Automated Pap Smear Screening

<http://www.tripathimaging.com/images/cutaway.gif>



- TriPath Care Technologies
  - <http://www.tripathimaging.com/usproducts/index.htm>

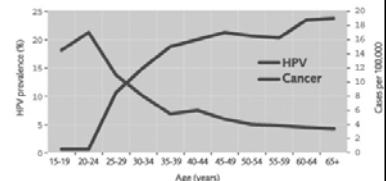
- FocalPoint Archive 25%
- Ranked cytotechnologist review 75%
- Ranked QC review 15%

Low Ranking of slide abnormality High

## HPV Testing

- The DNAwithPap Test is FDA-approved for routine adjunctive screening with a Pap test for women age 30 and older.
- Digene
  - <http://www.digene.com>

<http://www.digene.com/PapX/YLC-5301-30%20VER%20X.mpg>



### 1. Release Nucleic Acids

Cervical specimens are combined with a lysis solution which disrupts the cells and releases target DNA. No special specimen preparation is necessary.



### 2. Hybridize RNA Probe with Target DNA

Target DNA hybridizes with specific RNA probes binding the HPV sequence.



### 3. Capture Hybrids

Multiple DNA-DNA hybrids are captured onto a solid phase coated with sequence capture antibodies specific for RNA-DNA hybrids.



### 4. Label for Detection

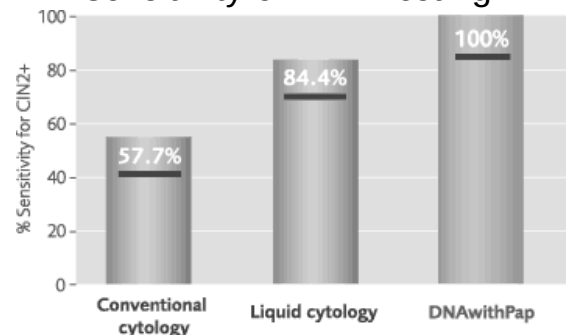
Captured RNA-DNA hybrids are detected with multiple antibodies conjugated to enzyme preparations. Resulting signal can be amplified to as few as 2000-fold.



### 5. Detect, Read and Interpret Results

HPV DNA is detected by a colorimetric assay. The colorimetric signal is read by a microplate reader. The resulting signal is compared to a threshold for HPV detection. HPV is measured in a multiplexed format using Light Units (LU).

## Sensitivity of HPV Testing



<http://www.digene.com/images/sens.gif>

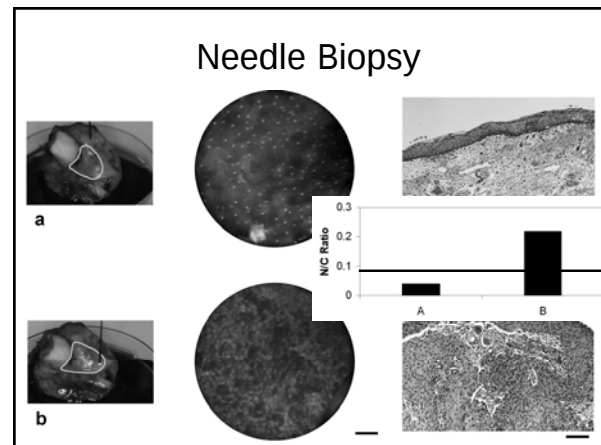
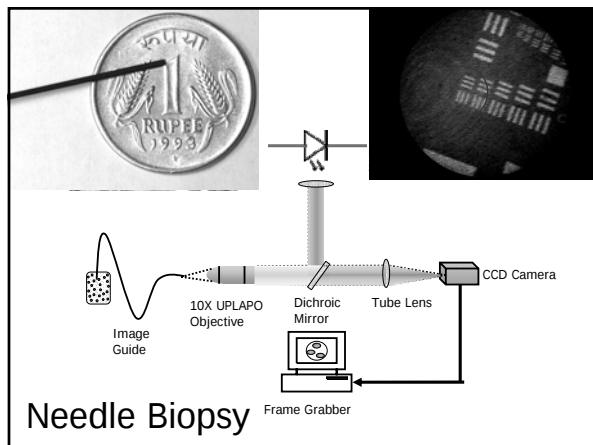
Study of 5,671 women age >30 years

## Comparison of Various Techniques

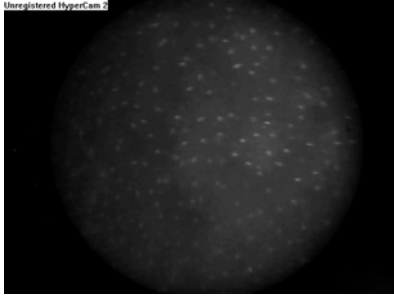
|                 | Sensitivity | Specificity |
|-----------------|-------------|-------------|
| Pap smear       | 60-80%      | 45-70%      |
| Colposcopy      | 90-100%     | 20-50%      |
| Digene HPV Test | 80-90%      | 57-89%      |
| VIA             | 67-79%      | 49-86%      |

## Costs

|                               |         |
|-------------------------------|---------|
| Pap Test                      | \$10-20 |
| Liquid-based Pap              | \$50    |
| Automated Pap Smear Screening | \$20-60 |
| HPV DNA test                  | \$90    |
| HPV vaccine                   | \$360   |



## Needle Biopsy



## Summary of Cancer

- The burden of cancer
  - Contrasts between developed/developing world
- How does cancer develop?
  - Cell transformation → Angiogenesis → Motility  
→ Microinvasion → Embolism → Extravasation
- Why is early detection so important?
  - Treat before cancer develops → Prevention
- Accuracy of screening/detection tests
  - Se, Sp, PPV, NPV

## Summary of Cervical Cancer

- Cervical cancer
  - 2<sup>nd</sup> Leading cause of cancer death in women in world
  - Caused by infection with HPV
  - Precancer → cancer sequence
  - Precancer is very common
- Screening & Detection
  - Pap smear; colposcopy + biopsy
  - Reduces incidence and mortality of cervical cancer
  - Insufficient resources to screen in developing countries
- New technologies
  - Automated reading of Pap smears → reduce FN rate
  - HPV testing
  - VIA

## Global Inequities in Cancer Prevention