

BIOE 301

Lecture Fourteen



Your CONFIDENTIAL Test Results

- First Chance...
- Possible Results:
 - Instant freebies
 - Lose 10 points on Exam 2
 - Lose 1 point on Exam 2
 - No effect on Exam 2 score
- You can open now, or you can wait and learn more...

Central dogma of molecular biology → Molecular basis of cancer

DNA → RNA → Protein

Mutation

- Good or bad
- Single or multiple
- Duration
- Causes

Alterations in cell physiology:

- (1) Develop self-sufficiency in growth signals
- (2) Become insensitive to signals of growth inhibition,
- (3) Evade programmed cell death,
- (4) Develop limitless replicative potential
- (5) Sustain angiogenesis
- (6) Acquire the ability to invade tissue and metastasize.

Case Studies

- Cervical Cancer
- Prostate Cancer
- Ovarian Cancer
- American Cancer Society (cancer.org)
- National Cancer Institute (cancer.gov)

Dr. Koop



Bioengineering and Cervical Cancer

Statistics on cervical cancer

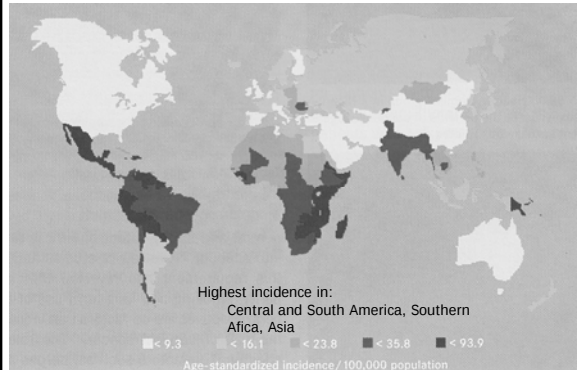
US data (2007)

- 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

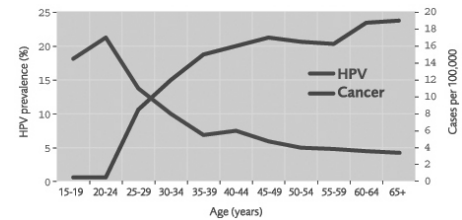
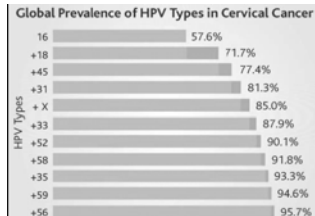
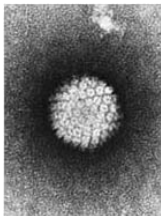


Risk factors

- 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

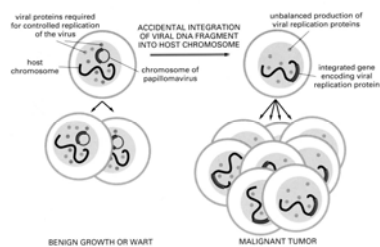
Human papilloma virus (HPV)

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

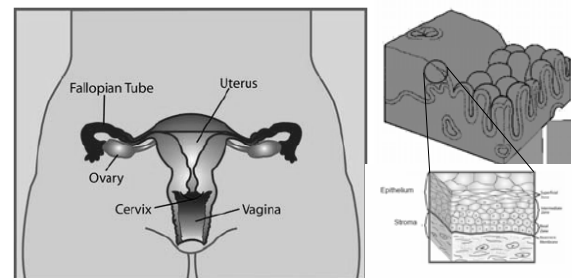


HPV and cervical cancer

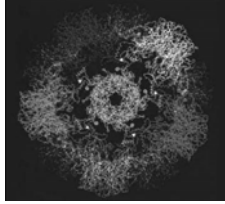
What Initiates Transformation?



Pathophysiology



HPV vaccine

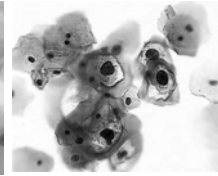
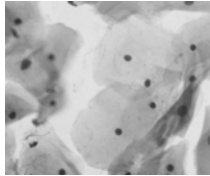
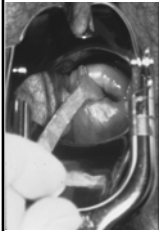


Virus-like particles (VLP) made from the L1 protein of HPV 16

- approved for use in 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?

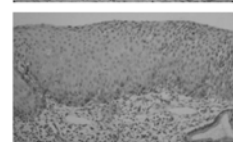
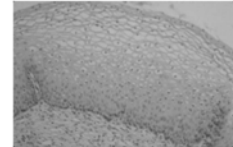
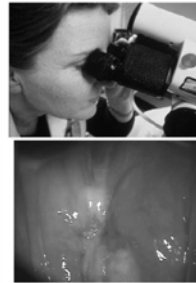
How Do We Detect Early Cervical Cancer?

Pap Smear



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

Colposcopy and Biopsy



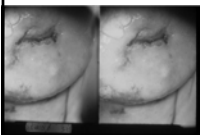
Colposcope

Se = 95%
Sp = 44%

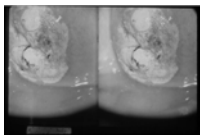
Biopsy sections

Colposcopy and Treatment

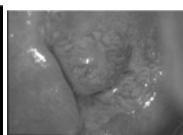
CIN 1/LGSIL



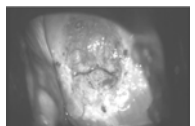
CIN 2/HGSIL



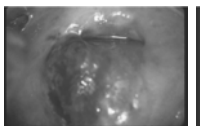
CIN 3/HGSIL



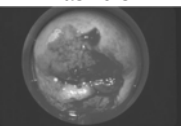
Microinvasive CA



Invasive CA



Invasive CA



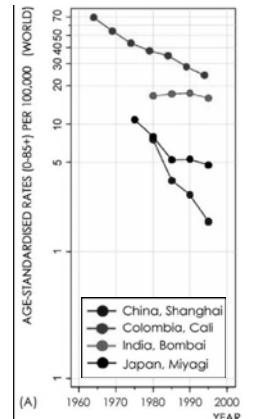
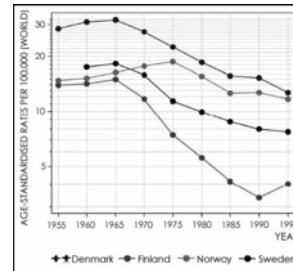
Detection and Treatment

- 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

Access to technology

- Developed and developing world
- Cost and infrastructure requirements for screening

Need for appropriate technologies

New Detection Technologies

Aims:

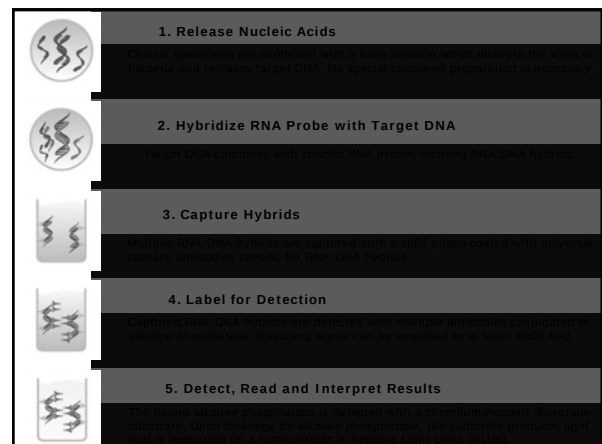
- Reduce the false positive and false negative rates
- Give instantaneous results
- Reduce the costs

HPV DNA Test

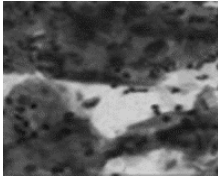
- The DNA with Pap Test is FDA-approved for routine adjunctive screening with a Pap test for women age 30 and older.



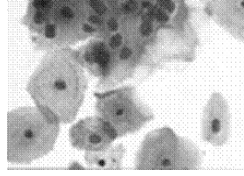
Se= 80-90%
Sp= 57-89%



Liquid Based Pap Smear



Conventional Pap



Liquid Based Pap

Automated Pap Smear Screening

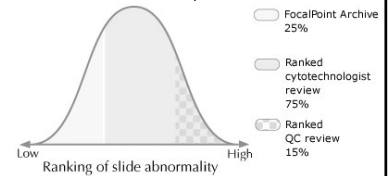


Technology

- High-speed video microscope collects images
- Algorithms interpret images and classify slides

Performance

- 33% to 44% reduction of false negatives
- 16% reduction in false positives



Optical technologies

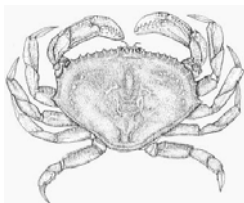
Visual Inspection with acetic acid (VIA)

Digital Image Analysis (DIA)

Costs

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

Bioengineering and Cervical Cancer



Risk factors
Detection
Treatment
Challenges
New technologies

Your CONFIDENTIAL Test Results

■ Second chance

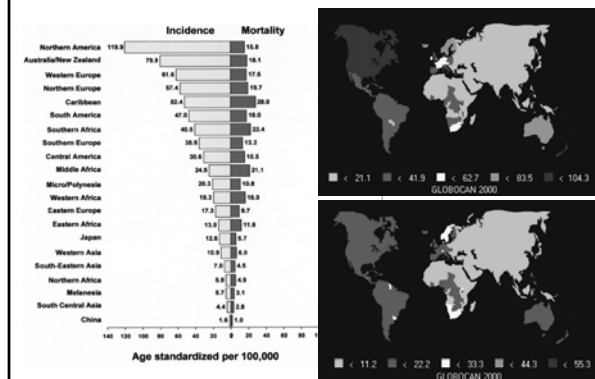
Possible Outcome	Cancer Diagnosis
Freebies	True Positive: You have cancer and the test correctly identified your condition. You will receive treatment.
Lose 10 points on Exam 2	False Negative: You have cancer, but the test did not identify your condition. You will not receive treatment.
Lose 1 point on Exam 2	False Positive: You do not have cancer, but the test says you do. You will undergo unnecessary, painful tests.
No effect on Exam 2 score	True Negative: You do not have cancer and the test correctly identified that you do not have cancer.

Bioengineering and Prostate Cancer

Statistics on Prostate Cancer

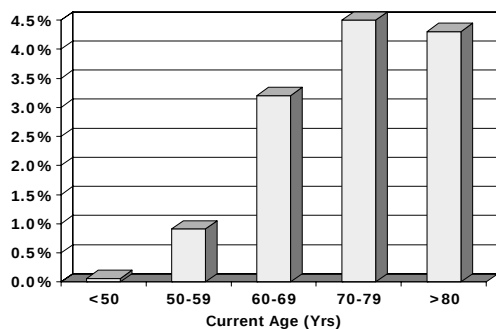
- United States:
 - 218,890 new cases in US
 - 27,050 deaths in US
 - 2nd leading cause of cancer death in men
- Worldwide:
 - Third most common cancer in men
 - 679,000 new cases each year

Global Burden of Prostate Cancer

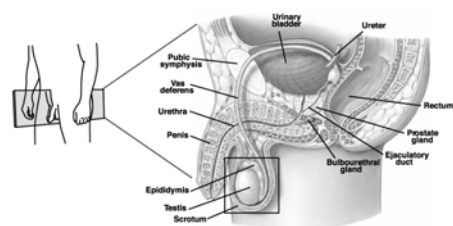


Risk factors

- Age
 - chance of having prostate cancer rises rapidly after age 50
 - about 2 out of 3 prostate cancers are found in men over the age of 65.
- Race
 - incidence 3x higher in African Americans
 - occurs less often in Asian-American and Hispanic/Latino men than in non-Hispanic whites.
- Family History
 - Having a father or brother with prostate cancer more than doubles a man's risk of developing prostate cancer

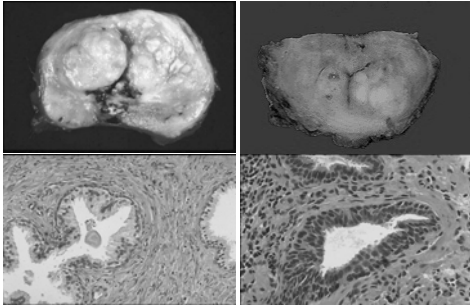


Pathophysiology



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Development of Prostate Cancer

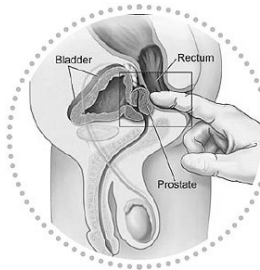


Normal

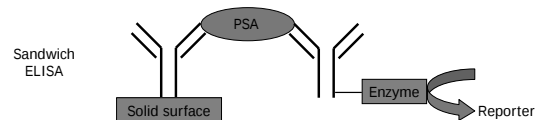
Invasive cancer

How Do We Detect Prostate Cancer?

Digital Rectal Examination



PSA Test



Normal PSA Levels: < 4 ng/ml

Cancer Patients:

20-25% have PSA < 4 ng/ml

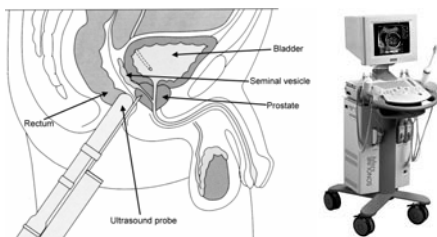
20-25% have 4 ng/ml < PSA < 10 ng/ml

50-60% have PSA > 10 ng/ml

Sensitivity = 63-83%

Specificity = 90%

Prostate biopsy



Treatment for Localized Prostate Cancer

- Radical prostatectomy (remove prostate)
 - Usually curative
 - Serious side effects:
 - Incontinence (2-30%),
 - Impotence (30-90%)
 - Infertility
- Conservative management
 - Just watch until symptoms develop

Cancer Grade	Surgery 10-yr survival	Conservative 10-yr survival
Grade I	94%	93%
Grade II	87%	77%
Grade III	67%	45%

Detection and Treatment

- Screening
 - PSA test
 - Digital rectal exam
- Diagnosis
 - Biopsy
- Treatment:
 - Surgery, radiation therapy, hormone therapy, chemotherapy
- 5 year survival
 - All stages: 98%
 - Localized disease: 100%
 - Distant metastases: 31%

New Screening Technologies

- Additional serum markers → Improve Sp
 - Free PSA
 - PSA density
 - PSA velocity
- Predict those cancers which will progress to advanced disease
 - Gene chips

Your CONFIDENTIAL Test Results

- Last chance

Possible Outcome	Cancer Diagnosis
Freebies	True Positive: You have cancer and the test correctly identified your condition. You will receive treatment.
Lose 10 points on Exam 2	False Negative: You have cancer, but the test did not identify your condition. You will not receive treatment.
Lose 1 point on Exam 2	False Positive: You do not have cancer, but the test says you do. You will undergo unnecessary, painful tests.
No effect on Exam 2 score	True Negative: You do not have cancer and the test correctly identified that you do not have cancer.

Challenge: Should we screen?

- Costs
- Efficacy of screening

DRE/PSA test	\$30-100
Prostate biopsy	\$700-1500

Cost of screening

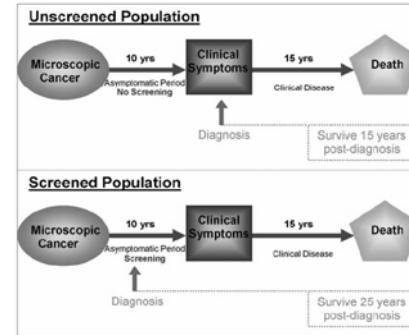
- Screening Performance:
 - Se = 73%; Sp = 90%
- Number Tested:
 - N=1,000,000; Prevalence = 2%
- Costs:
 - Screening = \$30; Follow up biopsy = \$1500
- What is detection cost?
- What is cost/cancer found?

	Test Positive	Test Negative	
Disease Present	14,600	5,400	# with Disease = 20,000
Disease Absent	98,000	882,000	#without Disease = 980,000
	# Test Pos = 112,600	# Test Neg = 887,400	Total Tested = 1,000,000

Cost to Detect = $\$30 \times 1,000,000 + \$1500 \times 112,600 = \$168,900,000$
 Cost/Cancer = $\$168,900,000 / 14,600 = \$11,568.49$

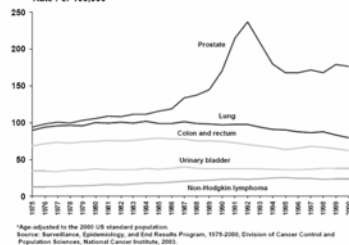
Efficacy of screening

- DRE Case studies
 - Mixed results
- PSA test
 - Mortality decreased 42% since 1993 in Tyrol, Austria
- RCT's
 - ERSPC
 - PLCO



Why are RCTs so Important?
Lead Time Bias

Cancer Incidence Rates* for Men, US, 1975-2000
Rate Per 100,000



5-Year Survival, % Absolute Increase in 5-Year Survival, % % Change (1950-1996)

	1950-1954	1989-1995	Absolute Increase in 5-Year Survival, %	Mortality	Incidence
Prostate	43%	93%	50%	+10%	+190%
Cervix	59%	71%	12%	-76%	-79%
Ovary	30%	50%	20%	-2%	+3%

Should we screen?

- Yes:
 - Localized prostate cancer is curable
 - Advanced prostate cancer is fatal
 - Some studies (not RCTs) show decreased mortality in screened patients
- No:
 - False-positives lead to unnecessary biopsies
 - Over-detection of latent cancers
 - We will detect many cancers that may never have produced symptoms before patients died of other causes (slow growing cancer of old age)
 - No RCTs showing decreased mortality

Screening guidelines

Organization	Recommendation
American Academy of Family Medicine	Physicians should counsel men between ages of 50 and 65 about known risks and uncertain benefits of screening so they may make an informed choice.
American Cancer Society	Offer the PSA and DRE tests annually beginning at age 50 to men who have a 10 year life expectancy and to younger men at higher risk
American College of Physicians	Physicians should describe potential benefits and known harms of screening, diagnosis and treatment, listen to patient's concerns and individualize the decision of whether to screen
American Urological Association	Men over 5 should consider testing. Men at high risk should begin testing at age 45.
CDC	Routine screening is not recommended because there is not consensus on whether screening and early treatment reduces mortality.
US Preventive Services Task Force	Evidence is insufficient to determine whether the benefits of screening outweigh the harms.

Do All Countries Screen with PSA?

- United States:
 - Conflicting recommendations
- Europe:
 - No
 - Not enough evidence that screening reduces mortality

Next Time

- Exam 2: March 13th