BIOE 301

Lecture Thirteen

David J. Javier
djj3872@rice.edu
Office Hours: Mon 1-4 PM

Amniocentesis Example

- Amniocentesis:
  - Procedure to detect abnormal fetal chromosomes
- Efficacy:
  - 1,000 40-year-old women given the test
  - 28 children born with chromosomal abnormalities
  - 32 amniocentesis test were positive, and of those 25 were truly positive
- Calculate:
  - Se, Sp, PPV, NPV

Possible Test Results

	Test Positive	Test Negative	
Disease Present	25	3	# with Disease = 28
Disease Absent	7	965	#without Disease = 972
	# Test Pos = 32	# Test Neg = 968	Total Tested = 1,000

Se = 25/28 = 89% Sp =965/972 = 99.3%

PPV = 25/32 = 78% NPV =965/968 = 99.7%

Dependence on Prevalence

- Prevalence – is a disease common or rare?
  - p = (# with disease)/total #
  - p = (TP+FN)/(TP+FP+TN+FN)
- Does our test accuracy depend on p?
  - Se/Sp do not depend on prevalence
  - PPV/NPV are highly dependent on prevalence

Is it Hard to Screen for Rare Disease?

- Amniocentesis:
  - Usually offered to women > 35 yrs
- Efficacy:
  - 1,000 20-year-old women given the test
  - Prevalence of chromosomal abnormalities is expected to be 2.8/1000
- Calculate:
  - Se, Sp, PPV, NPV

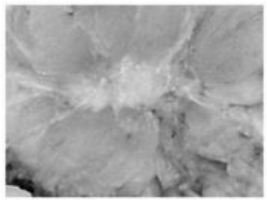
Possible Test Results

	Test Positive	Test Negative	
Disease Present	2.5	.3	# with Disease = 2.8
Disease Absent	6.98	990.2	#without Disease = 997.2
	# Test Pos = 9.48	# Test Neg = 990.5	Total Tested = 1,000

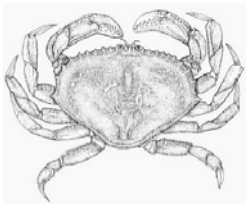
Se = 2.5/2.8 = 89.3% Sp 990.2/997.2= 99.3%

PPV = 2.5/9.48 = 26.3% NPV =990.2/990.5 = 99.97%

Cancer Overview

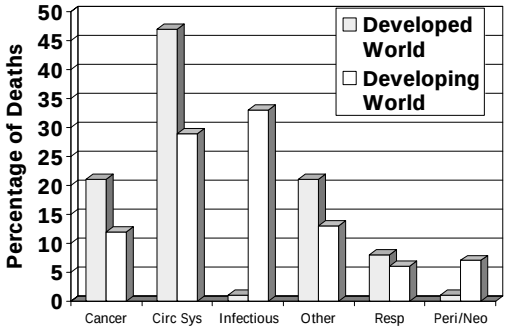


Malignant tumor

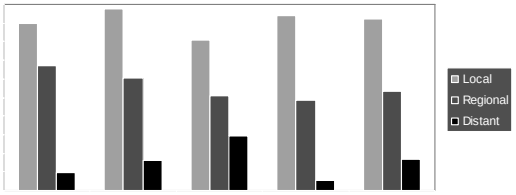


"The Crab"

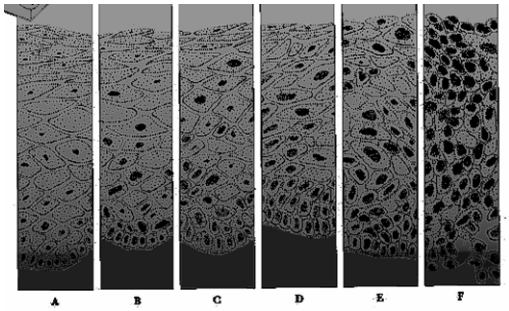
Causes of Mortality, 1996



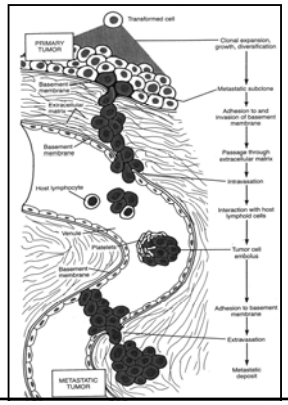
Importance of Cancer Screening



Cell transformation: precancer to cancer

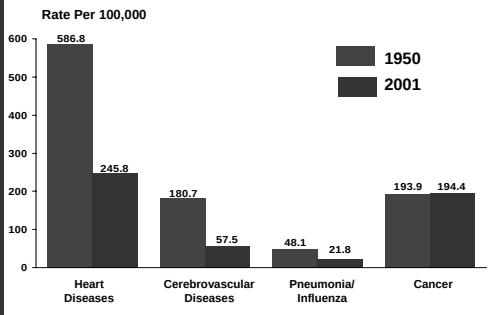


Cancer cells to metastatic tumors



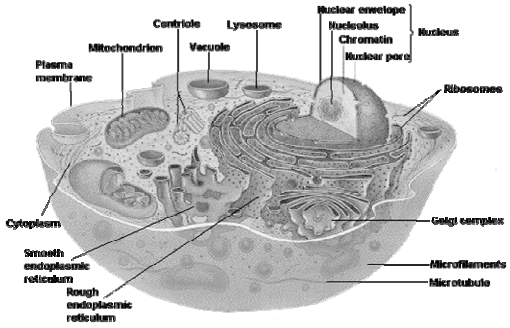
Process of Cancer Development

Change in the US Death Rates* by Cause, 1950 & 2001



* Age-adjusted to 2000 US standard population.
Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
2001 Mortality Data–NVSR-Death Final Data 2001–Volume 52, No. 3.
http://www.cdc.gov/nchs/data/nvsr/nvsr52/nvsr52_03.pdf

Molecular basis of cancer

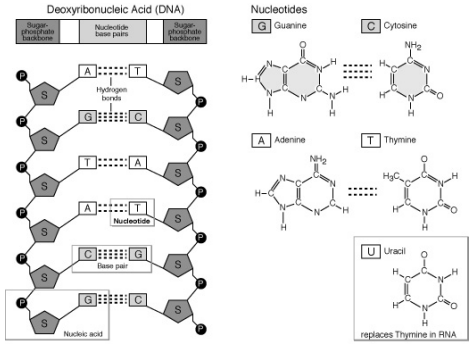


Cell physiology

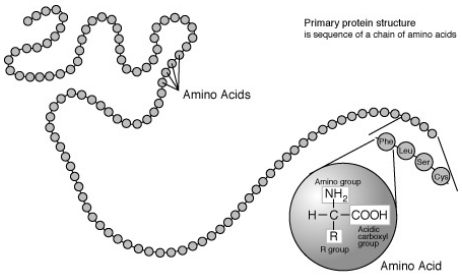
- *Francis Crick, Nobel Prize in Medicine 1962*
- *" The central dogma of molecular biology deals with the detailed residue-by-residue transfer of sequential information. It states that such information cannot be transferred back from protein to either protein or nucleic acid."*

DNA RNA Protein

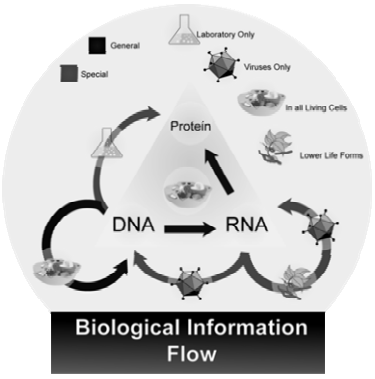
Central dogma of molecular biology



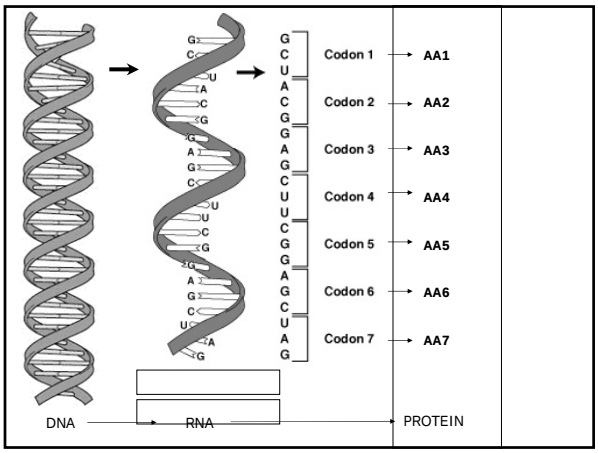
DNA and RNA



Protein



Central dogma of molecular biology



Genetic Code

1st base	2nd base U	2nd base C	2nd base A	2nd base G
U	UUU (Phe/F)Phenylalanine UUC (Phe/F)Phenylalanine UUA (Leu/L)Leucine UUG (Leu/L)Leucine	UCU (Ser/S)Serine UCC (Ser/S)Serine UCA (Ser/S)Serine UCG (Ser/S)Serine	UAU (Tyr/Y)Tyrosine UAC (Tyr/Y)Tyrosine UAA Ochre (*Stop*) UAG Amber (*Stop*)	UGU (Cys/C)Cysteine UGC (Cys/C)Cysteine UGA Opal (*Stop*) UGG (Trp/W)Tryptophan
C	CUU (Leu/L)Leucine CUC (Leu/L)Leucine CUA (Leu/L)Leucine CUG (Leu/L)Leucine	CCU (Pro/P)Proline CCC (Pro/P)Proline CCA (Pro/P)Proline CCG (Pro/P)Proline	CAU (His/H)Histidine CAC (His/H)Histidine CAA (Gln/Q)Glutamine CAG (Gln/Q)Glutamine	CGU (Arg/R)Arginine CGC (Arg/R)Arginine CGA (Arg/R)Arginine CGG (Arg/R)Arginine
A	AUU (Ile/I)Isoleucine AUC (Ile/I)Isoleucine AUA (Ile/I)Isoleucine AUG (Met/M)Methionine, *Start*[m]	ACU (Thr/T)Threonine ACC (Thr/T)Threonine ACA (Thr/T)Threonine ACG (Thr/T)Threonine	AAU (Asn/N)Asparagine AAC (Asn/N)Asparagine AAA (Lys/K)Lysine AAG (Lys/K)Lysine	AGU (Ser/S)Serine AGC (Ser/S)Serine AGA (Arg/R)Arginine AGG (Arg/R)Arginine
G	GUU (Val/V)Valine GUC (Val/V)Valine GUA (Val/V)Valine GUG (Val/V)Valine	GCU (Ala/A)Alanine GCC (Ala/A)Alanine GCA (Ala/A)Alanine GCG (Ala/A)Alanine	GAU (Asp/D)Aspartic acid GAC (Asp/D)Aspartic acid GAA (Glu/E)Glutamic acid GAG (Glu/E)Glutamic acid	GGU (Gly/G)Glycine GGC (Gly/G)Glycine GGA (Gly/G)Glycine GGG (Gly/G)Glycine

Central dogma of molecular biology ⟶ Molecular basis of cancer

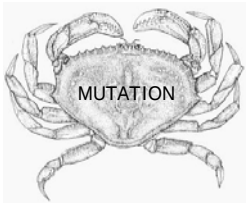
DNA ⟶ RNA ⟶ Protein

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

Alterations in cell physiology:

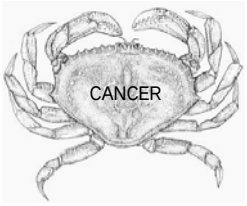
(1) Develop self-sufficiency in growth signals
(2) Become insensitive to signals of growth inhabitation,
(3) Evade programmed cell death,
(4) Develop limitless replicative potential
(5) Sustain angiogenesis
(6) Acquire the ability to invade tissue and metastasize.

Molecular basis of cancer



Multiple causes
Multiple sites
Multiple treatment
Multiple challenges

Bioengineering and Cancer



Risk factors
Detection
Treatment
Challenges
New technologies

Case Studies

- Cervical Cancer
- Prostate Cancer
- Ovarian and Lung Cancer

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

Dr. Koop

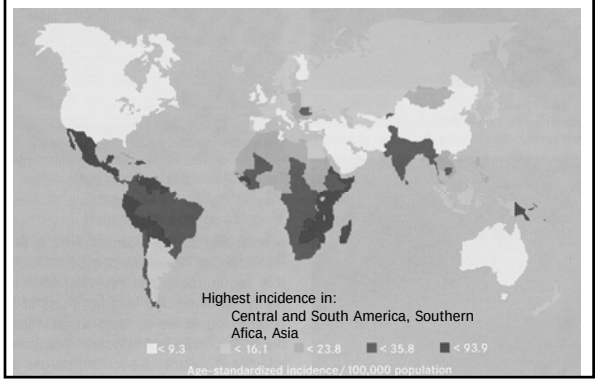
Bioengineering and Cervical Cancer

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

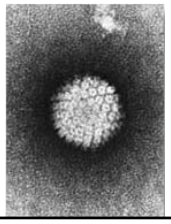


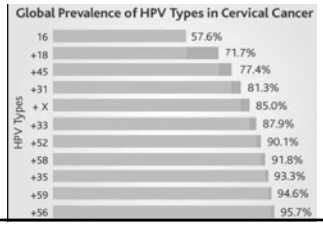
Risk factors

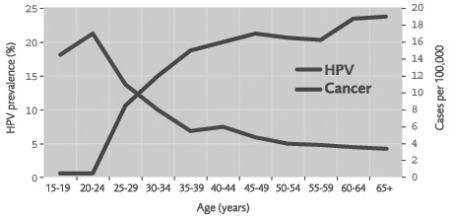
- HPV infection
  - HPV infection is the central causative factor in squamous cell carcinoma of the cervix
- Sexual behaviors
  - Sex at an early age
  - Multiple sexual partners
- Cigarette smoking

Human papilloma virus (HPV)

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

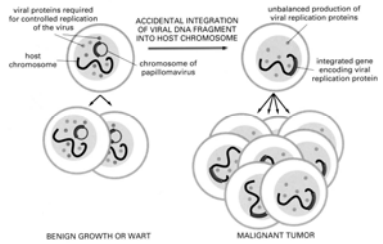




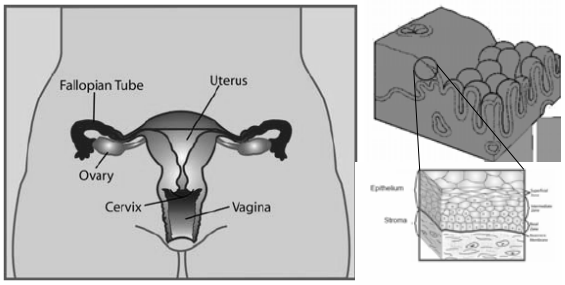


HPV and cervical cancer

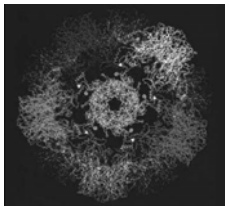
What Initiates Transformation?



Pathophysiology



HPV vaccine

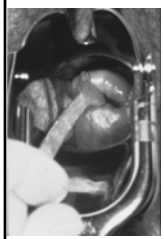
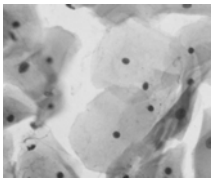
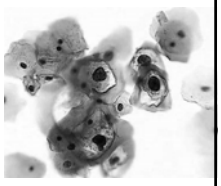


Virus-like particles (VLP) made from the L1 protein of HPV 16

- approved for use in 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?

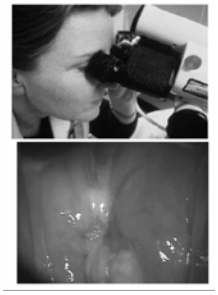
How Do We Detect Early Cervical Cancer?

Pap Smear

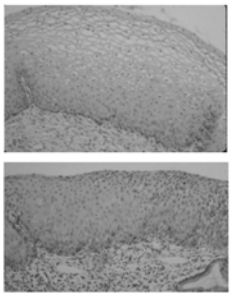
- 50,000-300,000 cells/per slide
- Cytotechnologists review slides (<100/day)
- Se = 62% → 3%
- Sp = 78% → $6B

Colposcopy and Biopsy



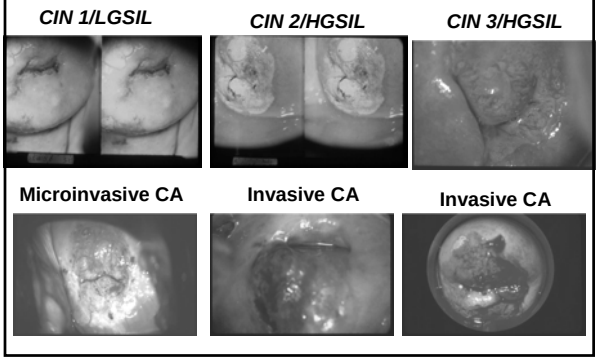
Colposcope

Se = 95%
Sp = 44%



Biopsy sections

Colposcopy and Treatment



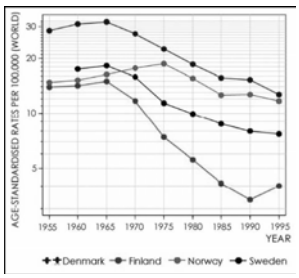
Detection and Treatment

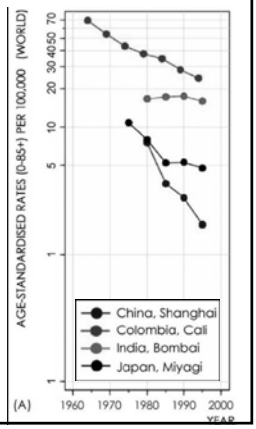
- Screening:
  - Pap smear
- Diagnosis:
  - Colposcopy + biopsy
- Treatment:
  - Surgery, radiotherapy, chemotherapy
- 5 year survival
  - Localized disease: 92% (56% diagnosed at this stage)

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:

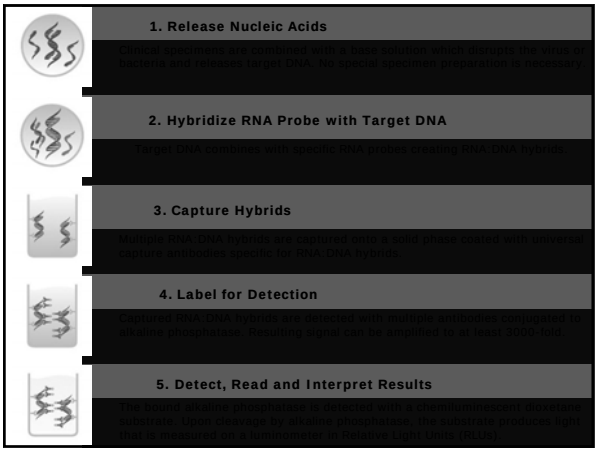
- Reduce the false positive and false negative rates
- Give instantaneous results
- Reduce the costs

HPV DNA Test

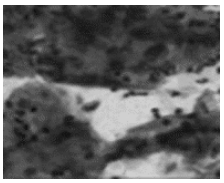
- The DNA with Pap Test is FDA-approved for routine adjunctive screening with a Pap test for women age 30 and older.

Se= 80-90%

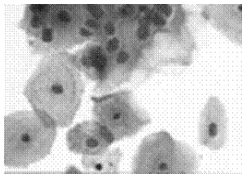
Sp= 57-89%



Liquid Based Pap Smear



Conventional Pap



Liquid Based Pap

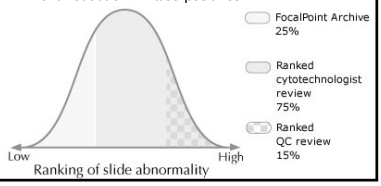
Automated Pap Smear Screening

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

Next Time

- Exam 2: March 13th
- HW5 due today