

BIOE 301

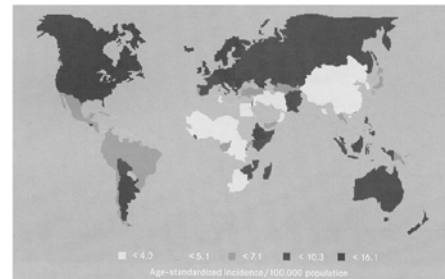
Lecture Fifteen

Bioengineering and Ovarian Cancer

Statistics on Ovarian Cancer

- United States:
 - Incidence: 22,430
 - Mortality: 15,280
- Worldwide:
 - Incidence: 190,000
 - Mortality: 114,000

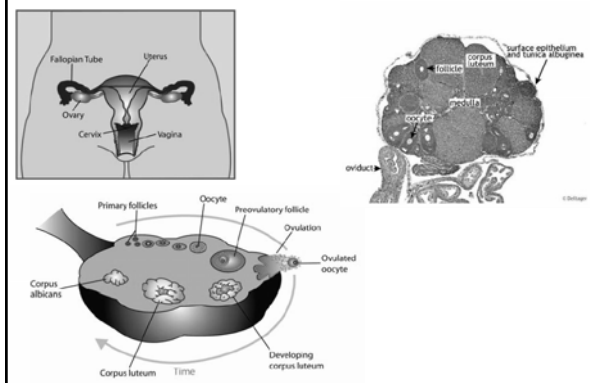
Global Burden of Ovarian Cancer



Risk factors

- Age
 - Most ovarian cancers develop after menopause
- Personal or family history of breast, ovarian, endometrial, prostate or colon cancer.
- Reproductive history
 - Increases with the more lifetime cycles of ovulation that a woman has undergone. Thus, women who have undergone hormonal treatment for infertility, never used birth control pills, and who never became pregnant are at higher risk for ovarian cancer

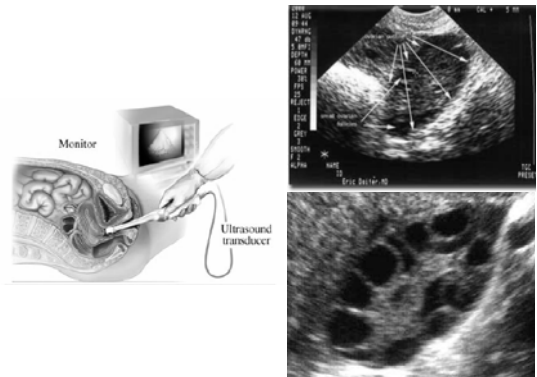
Pathophysiology



Screening of Ovarian Cancer

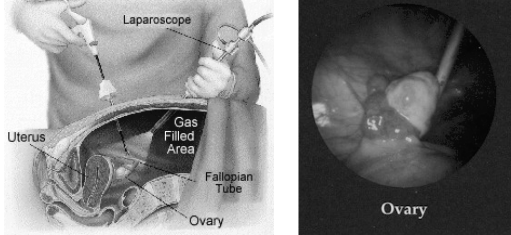
- Pelvic and rectal exam
- CA125 test
- Transvaginal sonography

Transvaginal Sonography



Diagnostic Laparoscopy

Laparoscopic Procedure



Complication Rate = 0.5 – 1%

Detection and Treatment

- Screening
 - Pelvic exam
 - CA125 test
 - Transvaginal ultrasound
- Diagnosis
 - Diagnostic laparoscopy
- Treatment:
 - Surgery, radiation therapy, chemotherapy
- 5 year survival
 - Localized disease: 93% (20% diagnosed at this stage)

Screening Scenarios

- Scenario #1:
 - Screen 1,000,000 women with CA125
 - $p = .0001$ (100 cancers)
 - Se=35%, Sp=98.5%
 - Cost = \$30
 - Follow with laparoscopy
 - Complication rate = 1%
 - Cost=\$2,000
 - TP=35 FP=14,999 Complications=150
 - PPV =0.23% NPV = 99.99%
 - Cost per cancer found = \$1,716,200

Screening Scenarios

- Scenario #2:
 - Screen 1,000,000 women with transvaginal US
 - P = .0001 (100 cancers)
 - Se=100%, Sp=96%
 - Cost = \$150
 - Follow with laparoscopy
 - Complication rate = 1%
 - Cost=\$2,000
 - TP=100 FP=39,996 Complications=401
 - PPV =0.25% NPV = 100%
 - Cost per cancer found = \$300,672

Screening Scenarios

- Scenario #3:
 - Screen 1,000,000 women >age 50 with TVUS
 - P = .0005 (500 cancers)
 - Se=100%, Sp=96%
 - Cost = \$150
 - Follow with laparoscopy
 - Complication rate = 1%
 - Cost=\$2,000
 - TP=500 FP=39,980 Complications=405
 - PPV =1.24% NPV =100%
 - Cost per cancer found = \$60,670

Screening Scenarios

- Scenario #3 cont.:
 - Screen 1,000,000 women > age 50 with TVUS
 - P = .0005 (500 cancers)
 - Se=100%, Sp=??%
 - Cost = \$150
 - How high does Sp need to be for PPV to reach 25%?
 - Sp = 99.985%

Does Ultrasound Screening Work?

- Two studies of over 10,000 low-risk women:
 - The positive predictive value was only 2.6%
 - Ultrasound screening of 100,000 women over age 45 would:
 - Detect 40 cases of ovarian cancer,
 - Result in 5,398 false positives
 - Result in over 160 complications from diagnostic laparoscopy
 - Jacobs I. Screening for early ovarian cancer. Lancet; 2:171-172, 1988.

Ongoing Clinical Trials

- United Kingdom
 - 200,000 postmenopausal women
 - CA 125 level plus transvaginal ultrasound examination
 - Transvaginal ultrasound alone
 - No screening
- United States:
 - 37,000 women (aged 55–74)
 - Annual CA 125 level and transvaginal ultrasound examination
 - No screening
- Europe:
 - 120,000 postmenopausal women
 - No screening,
 - Transvaginal ultrasound at intervals of 18 months
 - Transvaginal ultrasound at intervals of 3 years

http://www.mja.com.au/public/issues/178_12_160603/and10666_fm.pdf

Challenge

Better screening methods to detect early stages of ovarian cancer

Cancer Screening Exams

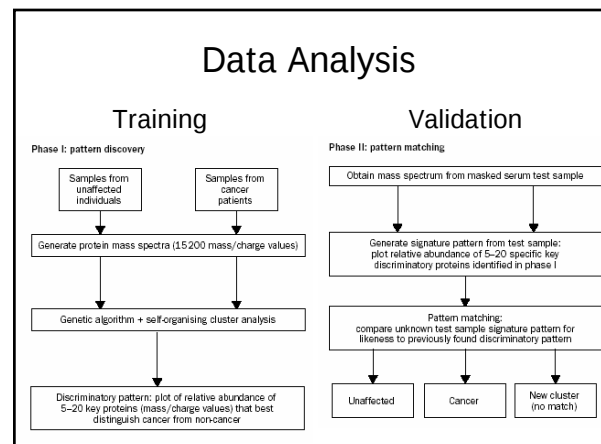
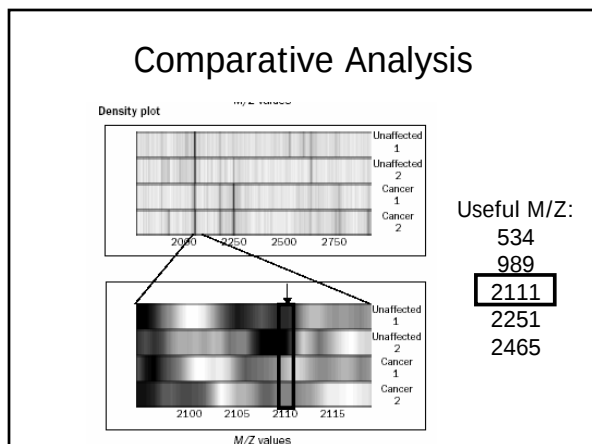
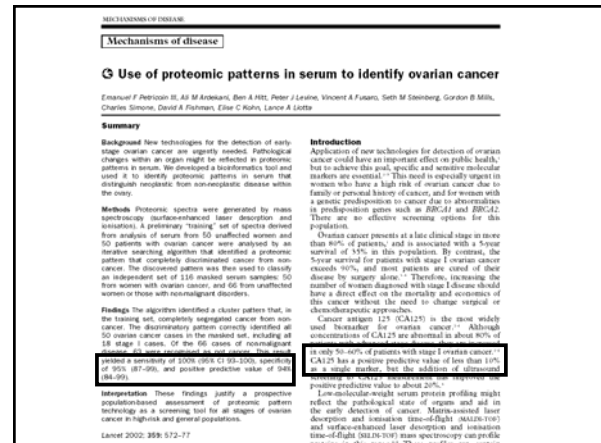
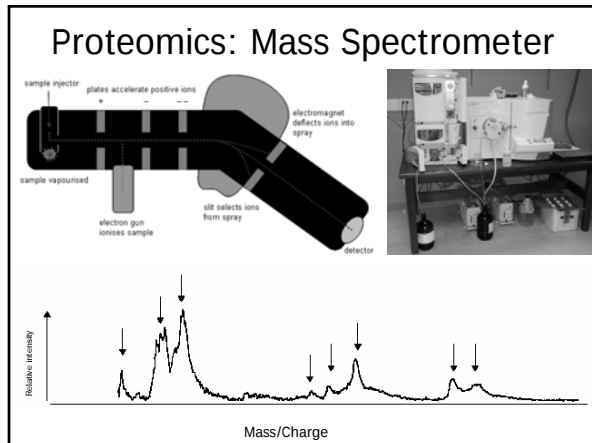
- Cellular Changes
 - Pap smear
- Serum Proteins
 - PSA
 - CA125
 - OvaCheck
- Genetic Changes
 - HPV DNA

New Screening Tool

- Current screening tests look for 1 protein:
 - CA125
 - PSA
- Many serum proteins
- Can complex fingerprint predictive of cancer can be identified?
- PROTEOMICS:
 - Don't try to understand disease mechanisms
 - Use proteomics to analyze patterns made by all proteins in the blood, without even knowing what they are

How do we measure serum proteins?

- Mass Spectrometry:
 - Serum proteins are vaporized, given an electric charge and propelled down a tube
 - How fast they make the trip depends on their mass
 - Produces graph that shows distribution of masses in the sample
 - Use computer program to analyze patterns and distinguish blood from patients with cancer and from those without



OvaCheck

- Quest Diagnostics and LabCorp:
 - Will analyze blood samples sent by doctors, rather than sell test kits to doctors and hospitals
 - Tests performed at a central location do not require F.D.A. approval
 - Will be available in a few months
 - Cost: \$100-\$200

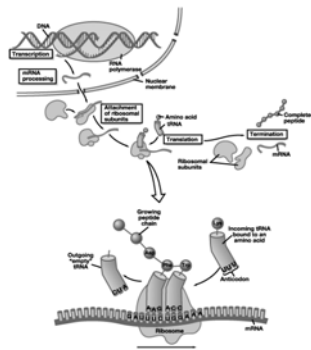
Response

- Dr. Eleftherios P. Diamandis, head of clinical biochem at Mount Sinai Hospital in Toronto.
 - "If you don't know what you're measuring, it's a dangerous black-box technology... They are rushing into something and it could be a disaster."
- Dr. Nicole Urban, head of gynecologic cancer research at the Fred Hutchinson Cancer Research Center in Seattle.
 - "Certainly there's no published work that would make me tell a woman she should get this test."
- Dr. Beth Karlan, director of gynecologic oncology at Cedars-Sinai Medical Center
 - "Before you mass-market to the uninformed, fearful population, it should be peer-reviewed."
 - When asked whether she would recommend her patients not get tested, she said: "It doesn't matter what I recommend. They are going to do it anyway."

<http://www.ovarian.org/press.asp?releaseID=263>

Gene Expression Analysis

- Human Genome
 - 30,000 unique genes
 - Which genes are active?
- DNA Microarrays
 - Tool to study gene expression
 - Which genes are turned on or off as cells grow, divide, respond to hormones, etc



What is a DNA Microarray?

- Glass slide
 - Large number of DNA fragments
 - Each contains nucleotide sequence to probe for a specific gene
 - Short oligos synthesized on surface of glass wafer
 - Large DNA fragments generated by PCR and spotted onto slide by robot
 - Each gene has unique physical address on slide

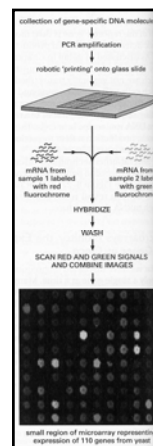


How Do We Use a DNA Microarray?

- Extract mRNA from cells under study
- Convert mRNA to cDNA
- Label cDNA with fluorescent probe
- Incubate labeled cDNA with microarray
- Wash slide to remove unbound cDNA
- Scan slide with laser scanning fluorescence microscope
- Determine which genes are expressed in test sample



DNA Microarrays



From: Molecular Biology of the Cell

New screening technologies

- New screening technologies
 - Proteomics
 - DNA microarrays