Gynecologic Cancer Screening Update

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Disclosure

- I served once as a proctor for Intuitive Surgical.
Objectives

- Have an understanding of updates on the Pap test for screening and HPV natural history
- Be able to convey the updates on screening in low risk women, pregnant women, and adolescents
- Be able to convey the updates on HPV testing and HPV genotyping
- Be aware of changes in cervical cancer screening in other areas of the globe

Prevalence: 2,274,000 women have cervical cancer

Incidence: 510,000 new cases each year

2000 estimated incidence of invasive cervical cancer by selected region

Mortality: Second leading cause of female cancer-related deaths (288,000 annually)

Epidemiology

- Incidence: 1975 14.8 per 100,000
  2006 6.5 per 100,000
- Mortality: 2009 11,270 new cases in the US
  4070 deaths in 2009
- Mortality: 500,000 new cases and 240,000 deaths per year in the world
- Cervical cytology screening programs reduce incidence of cervical cancer
- What is the best available evidence on screening for cervical cancer
Background

- 50% of the women with cervical cancer never had cervical cytology testing.
- Another 10% had not been screened within the 5 years before diagnosis.
- Although rate of cervical cancer are on the decline in US born women, immigrants of US from countries without routine cervical cytology screening remain a high-risk group.
Natural History of Cervical Intraepithelial Neoplasia (CIN)

- Most HPV-infected women will never develop cervical abnormalities.
- Most young women have effective immune response that clears the infections or reduce the viral load in an average of 8-24 months.
- Cigarette smoking and a compromised immune system are factors that may disrupt this immunity.
Human Papillomavirus

- Circular, double-stranded DNA virus
- Highly species specific and epithelial tropic
- Many cancer-causing or ‘high risk’ HPV types
  - Most common types in US are HPV 16 and 18
Human Papillomavirus is Necessary for Cervical Cancer

- HPV DNA sequences detected in more than 99% of invasive cervical carcinomas¹
  - The association between HPV and cervical cancer is higher than that between smoking and lung cancer
- Most common sexually transmitted infection

HPV and Cervical Cancer

HPV and Cervical Cancer

HPV and Cervical Cancer

HPV and Cervical Cancer

HPV and Cervical Cancer

US HPV Statistics

- Lifetime risk for sexually active men and women approaching 80%.
- Point prevalence rate of HPV infection around 27%.
- About 34% of 14-24 year olds infected with HPV.
- Condoms are, at best, only marginally effective for preventing HPV infection.
  - Social barriers also limit condom effectiveness.

Pathway to Cervical Cancer

Exposure → HPV infection → Persistent infection → High Grade CIN → CANCER

Adopted from Einstein and Burk, Papillomavirus Report, 2001
Cytologic Reporting

- Specimen adequacy: Satisfactory or unsatisfactory for interpretation
- Atypical Squamous Cells: The degree of nuclear atypia is insufficient to warrant a precancerous diagnosis
  - Atypical Squamous cells of undetermined significance (ASC-US)
  - Atypical squamous cells cannot exclude a high grade squamous intraepithelial lesion (ASC-H)
Cytologic Reporting

- Atypical Glandular Cells: Used to be called Atypical glandular cells of undetermined significance (AGUS), potentially more aggressive work-up.
- Low-grade squamous intraepithelial lesions
- High-grade squamous intraepithelial lesions
- Squamous cell carcinoma
Natural History of HPV Infection

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># Patients Followed</strong></td>
<td>241</td>
<td>608</td>
<td>1075</td>
<td>496</td>
</tr>
<tr>
<td><strong># Patients HPV (-)</strong></td>
<td>198</td>
<td>399</td>
<td>1075</td>
<td>105</td>
</tr>
<tr>
<td><strong>Average age of population</strong></td>
<td>26 ± 7</td>
<td>20 ± 3</td>
<td>18 ± 1</td>
<td>20 ± 2</td>
</tr>
<tr>
<td><strong>Median Duration of F/U</strong></td>
<td>25 months</td>
<td>36 months</td>
<td>36 months</td>
<td>26 months</td>
</tr>
<tr>
<td><strong>% of HPV(+) patients</strong></td>
<td>28% with CIN 2-3</td>
<td>26% with any CIN</td>
<td>44%</td>
<td>22%</td>
</tr>
<tr>
<td><strong>Likelihood of developing CIN if HPV(+)</strong> (Relative Risk)</td>
<td>11</td>
<td>3</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td><strong>Median duration of HPV infection</strong></td>
<td>N.D.*</td>
<td>8 months (7-10)</td>
<td>14 months (8-25)</td>
<td>N.D.</td>
</tr>
</tbody>
</table>

*ND, not described in publication

1Einstein MH and Burk RD. Papillomavirus Report, 2001
Age-Specific Rates of HPV Infection and Cervical Cancer

Model of Progressive Cervical Dysplasia

Regression 50-60%
Progress 11%

Regression 32-43%
Progress 14-22%

CIN1/HPV
Months-Years

CIN 2, 3
Months-Years

HPV Clearance

Cancer
Years-10s of Years

The Papanicolaou (PAP) Test

Dr. Papanicolaou
Decreasing Trends of Cervical Cancer Incidence in the U.S.

- With the advent of the Pap smear, the incidence of cervical cancer has dramatically declined.
- The curve has been stable for the past decade because we are not reaching the unscreened population.

Reprinted by permission of the American Cancer Society, Inc.
Pap Test Technology

Conventional Smear

Liquid Based Pap Test
Why Do Pap Tests Fail?

**Exfoliation**
- Lesion Unavailable For Sampling
- Barrier to Exfoliation
- Lesion not Exfoliating Normal Cells

**Collection**
- Cervix
- Areas Missed by Pap Smear
- Area Sampled with Pap Spatula

**Transfer**

**Evaluation**
Liquid Based versus Conventional Pap

- Performance of conventional cytology requires avoidance of contaminating blood, lubricants, discharge
  - Minimal difference in performance
- Liquid based cytology filters out artifact
- Nearly 90% of Pap performed in the US is liquid based
- Benefits of liquid based cytology include molecular testing of HPV and other STDs

ACOG Practice Bulletin Number 109, December 2009
Issues with screening algorithms and additional molecular testing

- Too complicated
- Future algorithms and additional molecular testing meant to maximize identification of clinically relevant disease while minimizing:
  - Equivocal Paps (ASCUS and LSIL)
  - Colposcopy
  - Overtreatment, particularly in young women
- Medical-legal fears of providers in missed disease or patient non-compliance
Recommended times for a follow-up Pap test for a 35 year-old female with normal Pap tests and HPV negative

Herzog TJ, Huh W, Einstein MH. Gynecol Oncol. 2010.
Recommended times for a follow-up HPV test for a 35 year-old female with normal Pap tests and HPV negative

Herzog TJ, Huh W, Einstein MH. Gynecol Oncol. 2010.
CIN3 is the Most Significant Clinical Target for Screening

- Although not all CIN3 lesions will progress to cancer, it is generally considered to be a cancer precursor\(^1\)
  - CIN3 prevalence peaks between ages 25 years and 30 years\(^2\)
  - Progression to cancer usually takes at least a decade or longer

- The significance of CIN2 is less clear\(^2\)
  - The risk of progression to CIN3 or cancer appears greater for women with CIN2 than for women with CIN1
  - However, many women with CIN2 will have regression of their lesions without therapy\(^3\)
  - Opportunities for biomarker development

\(^1\)McCredie et al, *Lancet Oncology*, 2008
Biomarkers under development for prediction of progressive CIN

- P16\textsuperscript{INK4A} +/- Ki-67
- 3q26 gain
- mRNA
- Epigenetic profiling
Risk of cervical precancer and results of screening and clinical management for cervical cancer prevention

Castle et al. J Low Genit Tact Dis 2008
Cytologic Abnormalities in Adolescents

- Adolescent = 20 years of age and younger (ASCCP)
- High prevalence of HPV and minor cytologic abnormalities
- Very low risk of invasive cervical cancer
- Majority of HPV infections spontaneously clear in 2 years
# Cytologic Abnormalities in Pregnant Patients

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Management</th>
</tr>
</thead>
</table>
| ASC-US      | - Identical to non-pregnant  
|             | - Can defer colposcopy until 6 weeks postpartum  
|             | - ECC unacceptable  |
| LSIL        | - Colposcopy preferred  
|             | - Can delay colposcopy until 6 weeks postpartum  
|             | - No CIN 2 or 3, follow-up postpartum  |
| HSIL        | - Colposcopy  
|             | - Biopsy lesions consistent with CIN 2 or 3  
|             | - Repeat evaluation 6 weeks postpartum  |
## Cervical Cancer Screening Recommendations for Low Risk Women

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation</td>
<td>3 yrs after intercourse. Not later than age 21</td>
<td>Age 21</td>
</tr>
<tr>
<td>Age &lt; 30</td>
<td>Every other year</td>
<td>Every other year</td>
</tr>
<tr>
<td>Age ≥ 30</td>
<td>Cytology annually</td>
<td>Every 3 years with liquid-based or conventional cytology*</td>
</tr>
<tr>
<td></td>
<td>Liquid-based every other year*</td>
<td></td>
</tr>
<tr>
<td>When to stop if low risk</td>
<td>Age 70</td>
<td>Age 65 or 70</td>
</tr>
<tr>
<td></td>
<td>3 consecutive negative cytology</td>
<td>3 consecutive negative cytology</td>
</tr>
</tbody>
</table>

*Establish ‘low risk’ classification and less frequent screening if HPV co-test negative

Cervista®

- FDA approved March 2009
  - Cervista™ HPV HR¹
  - Cervista™ HPV 16/18

- Enzymatic DNA amplification with fluorescent read out
  - Approved for use with ThinPrep

Einstein et al. Gynecol Oncol. 2010
Cervista® HPV HR

- Detection of 14 high risk HPV types
  - 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 and 66
  - Similar to 13 of Hybrid Capture 2 plus HPV 66

- FDA-approved indications:
  - Used adjunctively with cervical cytology to screen women 30 years and older to assess the presence or absence of high-risk HPV types
  - To screen patients with ASC-US cervical cytology results to determine the need for referral to colposcopy

ASCCP HPV Genotyping Clinical Update.
Cervista® HPV 16/18

- Specific detection of HPV 16 and 18
- FDA-approved indications:
  - In women 30 years and older the test may be used adjunctively with the Cervista™ HPV HR test in combination with cervical cytology to assess the presence or absence of specific high-risk HPV types
  - Used adjunctively with the Cervista™ HPV HR test in patients with ASC-US cervical cytology results to assess the presence or absence of specific high-risk HPV types. The results of this test are not intended to prevent women from proceeding to colposcopy.

ASCCP HPV Genotyping Clinical Update.
## Cervista® HPV HR Compared to hc2®

<table>
<thead>
<tr>
<th></th>
<th>hc2</th>
<th>Cervista HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year of FDA Approval</strong></td>
<td>1999</td>
<td>2009</td>
</tr>
<tr>
<td><strong>Internal Control</strong></td>
<td>No</td>
<td>Yes¹</td>
</tr>
<tr>
<td><strong>HPV Types Detected</strong></td>
<td>13 High-Risk Types</td>
<td>14 High-Risk Types</td>
</tr>
<tr>
<td></td>
<td>(genotypes covered by hc2 plus HPV 66)</td>
<td></td>
</tr>
<tr>
<td><strong>Sample Size Requirement</strong></td>
<td>4 mL</td>
<td>2 mL¹</td>
</tr>
<tr>
<td><strong>Cross-Reactivity With Common Low-Risk Types</strong></td>
<td>Yes⁴,⁵</td>
<td>None¹</td>
</tr>
<tr>
<td><strong>Genotyping</strong></td>
<td>No</td>
<td>Yes; same 2mL sample¹</td>
</tr>
<tr>
<td><strong>CIN3 Sensitivity</strong></td>
<td>96.3% (CI: 91.6%-98.8%)³</td>
<td>100% (CI: 85.1%-100%)¹,²</td>
</tr>
</tbody>
</table>

²Einstein MH et al, Gynecol Oncol. 2010.
ATHENA HPV study populations
Clinical validation of cobas 4800 HPV test

Overall population
≥25 yrs
n=∼40,000
(“Primary screening”)

Normal Paps
≥30 yrs
n=32,260
(Adjunct screening)

ASC-US
≥21 yrs
n=1918
# ATHENA HPV Study results: cobas 4800 HPV Test and hc2 in ASC-US: Detection of CIN2+ in side by side comparison

<table>
<thead>
<tr>
<th></th>
<th>cobas 4800 HPV Test</th>
<th>hc2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Point Estimate</td>
<td>95% CI</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>90.0 (72/80)</td>
<td>(81.5, 94.8)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>70.5 (1,056/1,498)</td>
<td>(68.1, 72.7)</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>14.0 (72/514)</td>
<td>(12.8, 15.3)</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>99.2 (1,056/1,064)</td>
<td>(98.6, 99.6)</td>
</tr>
</tbody>
</table>

\(^1\)Two subjects with CIN2+ had indeterminate results; \(^2\)Thirteen subjects with <CIN2 had indeterminate results

*FDA approval of cobas 4800 for cervical cancer screening April, 2011

Risk of Cervical Precancer and Cancer in Women with HPV 16 or 18

*Positive for the non-HPV 16/18 types in Hybrid Capture 2.

Use of HPV Genotyping to Manage HPV HR* Positive / Cytology Negative Women 30 Years and Older

HPV HR Positive / Cytology Negative

HPV 16/18 (+)
- Repeat BOTH cytology and HR HPV test @ 12 months
  - Both negative
    - Routine screening @ 3 years
    - Colposcopy
  - Cytology negative HPV (+)
  - Cytology abnormal any HPV result
    - Manage per ASCCP Guideline

HPV 16/18 (-)
- Colposcopy
HPV 16/18 for ASC-US

- ALTS two-year cumulative risk of CIN 2+: 25%
  - HPV 16/18 positive ASC-US risk of CIN 2+: 40%
  - Other (non 16/18) HPV positive ASC-US risk of CIN 2+: 20%
  - Similar patterns for women 21-29 and those 30 and older

- HPV genotyping *does* stratify risk of CIN 2+

- The risk of CIN 2+ remains high enough in non HPV 16/18 + ASC-US that colposcopy is *still* warranted

- ASCCP do **NOT** recommend HPV genotyping in women with HPV-positive ASC-US

ASCCP HPV Genotyping Clinical Update.
HPV Testing in Primary Screening

- HPV testing used in combination with cytology as primary screening in women 30 years of age and older
- Pooled screening study data on HPV testing
  - Sensitivity for CIN 2+: 95%
    - Higher when using combination
  - Specificity for CIN 2+: 93%
- Women negative by cytology and HPV testing have less than 1 in 1000 chance of having CIN 2+

HPV Testing in Primary Screening

- Cytology and HPV negative
  - Should not be re-screened before 3 years

- Cytology negative, HPV positive
  - Review of over 213,000 women over 30 yo found 6.5% HPV positive (58% negative cytology)
  - Risk of CIN 2+ 2.4-5.1%
  - Most become HPV negative
  - Repeat cytology and HPV testing at 12 months
  - Persistently HPV positive women should undergo colposcopy

HPV Test in Women Aged 25-64

- Positive
  - Cytology
    - Normal, Equivocal or Mild
      - HPV 16 typing or mRNA or p16
        - Negative
          - Repeat in 3-5 years
        - Positive
          - Repeat in 5 years
    - Moderate or worse
      - Colposcopy

- Negative
  - Repeat in 5 years

Adopted from Cuzick J. et al. Eurogin 2009. Nice, France
HPV Testing in Primary Screening

- Used in Rural India in over 130,000 women between 30 and 59 randomized to one of 4 groups: HPV testing, cytologic testing, VIA, or standard care (control group).
- Cervical cancer diagnosed more frequently in the HPV testing group (127) compared with 118 in the control group (of which 82 had advanced disease). No significant reductions in death in the VIA or standard cytology group.
- In a low-resource setting, a single round of HPV testing was associated with a significant reduction in the numbers of advanced cervical cancers and deaths from cervical cancer.

Sankaranarayanan R et al NEJM, 2009
HPV/VIA Screening/Treatment Algorithm

HPV Test in Women Aged >25 (Point of Care)

- Negative: Repeat in 5 years
- Positive: VIA
  - Normal, Equivocal or Mild: Cryotherapy
  - Possible disease: LEEP/Cone
    - Or Cryo, if not available
      - Try to biopsy any potential cancer
Conclusions

- All guidelines are shifting to doing more with less testing
- Future guidelines will be targeting even less frequent intervals
  - Also the potential for alternate algorithms in ‘vaccinated patients’
- Do little in adolescents and pregnant patients, particularly with equivocal cytology
- HPV 16/18 genotyping has triage role
- HPV testing as a primary screen appears to be an effective strategy, but not being considered in US screening for now
‘Early diagnosis of ovarian cancer is a matter of luck rather than a triumph of scientific approach’

Hugh Barber
What Are My Chances?

- Lifetime probability of developing OC is 1.8%
- With one first degree relative - 5%
- With two or more first degree relatives - 7%
- Ashkenazi Jewish - 16.5% lifetime risk

Risk Assessment

- Genetic risk factors
  - Family History
  - Site-specific ovarian syndromes
- Environmental risk factors
- Hormonal risk factors
Clinical Classification of Familial Ovarian Cancer: 1970s

- Site-specific ovarian cancer syndrome
- Breast /ovarian cancer syndrome
- Lynch type II syndrome (HNPCC)
Genetic Classification of Familial Ovarian Cancer: 1990s

- Site-specific ovarian cancer syndrome
  - BRCA1 and BRCA2
- Breast /ovarian cancer syndrome
  - BRCA1 and BRCA2
- Lynch type II syndrome (HNPCC)
  - MSH2 and MLH1
All Cancers are Genetic

“Hereditary” Cancer:

Birth

Mut 1 Inherited

Mut 2 Somatic

Mut 3 Somatic

Mut 4 Somatic

Mut 5 Somatic

Mut 6 Somatic

Cancer

“Sporadic” Cancer:

Birth

Mut 1 Somatic

Mut 2 Somatic

Mut 3 Somatic

Mut 4 Somatic

Mut 5 Somatic

Mut 6 Somatic

Cancer
### Genetic Predisposition to Ovarian Cancer

<table>
<thead>
<tr>
<th>Alteration</th>
<th>Prevalence</th>
<th>RR</th>
<th>Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>&lt;0.5%</td>
<td>10-20 fold</td>
<td>6%</td>
</tr>
<tr>
<td>BRCA2</td>
<td>&lt;0.5%</td>
<td>5-10 fold</td>
<td>3%</td>
</tr>
<tr>
<td>DNA repair</td>
<td>&lt;0.5%</td>
<td>3-5 fold</td>
<td>1%</td>
</tr>
<tr>
<td>Polymorphisms</td>
<td>?5-45%</td>
<td>2-3 fold</td>
<td>?15%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td><strong>25%</strong></td>
</tr>
</tbody>
</table>
Genetic Diversity - Polymorphisms

- Polymorphism - a genomic locus that varies between individuals
- Causes - extrinsic (UV, chemicals), intrinsic (hydrolysis, replication errors)
- Change must escape DNA repair to be fixed in the genome
- Drives evolution and accounts for variation between individuals within a species
Evolution
Genetic Diversity

Chimpanzee: 30 million bases
Human: 1%
Human Genetic Diversity

Honest Abe 3 million bases  Slick Willie

0.1%
Single Nucleotide Polymorphisms (SNPs)

- SNPs account for 80% of genetic variations between individuals
- Several hundred thousand in the human genome
- Most are relatively ancient and 80% have rare allele frequencies >10%
- Most SNPs are either outside genes or silent
Pathogenesis of Ovarian Cancer

- Ovulation
- Pregnancy
- Breastfeeding
- OCP

Genetic damage

Nulliparity

Ovarian cancer

Apoptosis

+ (+)

- (-)
Strategies for Primary and Secondary Prevention of Ovarian Cancer

Low risk
- No genetic susceptibility

Moderate risk
- Polymorphism

High risk
- BRCA

Chemoprevention

Oophorectomy

Screening
Criteria for an Effective Screening Test

- Large burden of disease
- Recognizable preclinical stages
- Curative potential much greater in early stages
- Acceptable to the screener and the person being screened
- Reasonable sensitivity, specificity, predictive values
- Improvement in cause specific mortality
CA-125

- Antigenic determinant on a high molecular weight glycoprotein
- Recognized by the muring monoclonal antibody OC-125
- Derived from coelemic epithelium
  - In tubal, endometrial, and endocervical epithelium
- 85% of pts with levels >35 U/ml have OC
- PPV-4%
Benign Conditions Which Elevate CA-125

- Pregnancy
- Menstruation
- PID
- Endometriosis
- Fibrocystic disease of the breast
- Liver disease
- Renal failure
Risk of Ovarian Cancer Algorithm

- Not only elevated levels, but the rate of elevation
- Based on logarithmic rises in CA-125
- Higher slopes

Other Tumor Markers

- **CA 19-9**
  - Antigen that is part of the Lewis blood group
  - Elevated in ovarian, pancreatic, GI, lung, and EMCA

- **CA 15-3**
  - Tumor associated antigen in milk fat
  - Elevated in breast cancer

- **TAG 72-3**
  - Glycoprotein surface antigen
  - Found in colon, gastric, and ovarian cancers
Tumor Markers

- **Tetranectin**
  - Binds to kringle 4 of plasminogen
  - Enhances t-PA
  - Influences cells to proliferate
- **CASA**
  - Assay which uses antibody which binds to MUC1 receptor on mucin cells
- **OVX1**
  - Monoclonal antibody generated by immunizing mice with multiple ovarian cancer cell lines
  - Does not bind to normal epithelium
Tumor Markers

- LASA
  - Lipid-associated sialic acid
  - Assay which determines glycoprotein-bound sialic acid
  - Positive in leukemia, sarcoma, melanoma, oropharyngeal tumors and ovarian cancer

- VEGF
  - Vascular endothelial growth factor
  - Promoter of angiogenesis
Ultrasound

- Multiple scoring systems
  - Solid vs. cystic
  - Septations
  - Color Doppler Imaging (CDI)

- All agree that papillary vegetations are a poor prognostic sign

- Due to time and expense, USS cannot be used as more than a second-level modality for screening
### General Population Volunteers

<table>
<thead>
<tr>
<th>Report</th>
<th>Country</th>
<th>Participants</th>
<th>Stage I</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Einhorn et al. (1992)</td>
<td>Sweden</td>
<td>5,550</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Campbell et al. (1990)</td>
<td>UK</td>
<td>5,479</td>
<td>5</td>
<td>9</td>
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<tr>
<td>Jacobs et al. (1993)</td>
<td>UK</td>
<td>21,959</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>DePriest et al. (1993)</td>
<td>USA</td>
<td>3,220</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>TOTAL</td>
<td>All</td>
<td>36,208</td>
<td>12</td>
<td>29</td>
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</table>
### Uncontrolled Trials of Ovarian Cancer Screening

<table>
<thead>
<tr>
<th>Report</th>
<th>Location</th>
<th>Participants</th>
<th>Stage I</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bourne et al. (1993)</td>
<td>UK</td>
<td>1,601</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Karlan et al. (1993)</td>
<td>Los Angeles</td>
<td>597</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Schwartz et al. (1991)</td>
<td>Connecticut</td>
<td>&gt;200</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Muto et al. (1993)</td>
<td>Boston</td>
<td>386</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Crade (1993)</td>
<td>Long Beach</td>
<td>389</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
22,000 women randomized

Screened women were offered three annual screens that included CA-125 and USS

- If 30 U/ml or more, or ovarian volume more than 8.8 ml, referral to gynecologist
Results of Study

- 16 total cancers identified in screened group
- 20 cancers identified in control group
- Slight survival benefit in screened group and no difference in mortality
Further Trials

- Expanding the Royal College Study
- NIH PLCO (Prostate, Lung, Colon, Ovary)
  - Larger study
  - Older women
- Multiple small studies
Management of Hereditary Cancer

- Obtain personal and family history of cancer
- Confirm cancer diagnosis in affected individuals
- Estimate risk of hereditary cancer syndrome
- Education and informed consent
- Genetic testing
- Post test counseling and follow-up
Screening Guidelines for Genetic Testing

- Breast and OC in same family
  - Particularly if in same woman
- Cases of male breast cancer
- Multiple cases of early onset disease
- Bilateral breast cancers

Based on statistical models, a patient should have at least a 10% probability of carrying a mutation before genetic testing is recommended.

Statement from ASCO-JCO 14:1730-6, 1996.
Risk Factors for BRCA Mutations

- Two or more affected first degree relatives
- Early onset of breast cancer (<50 years old)
- Male breast cancer (BRCA2 only)
- Ovarian cancer at any age
- Ashkenazi Jewish heritage
Testing

Test a living affected member

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Gene</th>
<th>Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>185delAG</td>
<td>BRCA1</td>
<td>17q21</td>
</tr>
<tr>
<td>5382 insC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6174delT</td>
<td>BRCA2</td>
<td>13q</td>
</tr>
</tbody>
</table>

If no mutations identified, full sequencing can be offered
Inherited Mutations in BRCA1 and BRCA2 Increase the Risk of Breast and Ovarian Cancer

Breast Cancer Risk by Age 70

Ovarian Cancer Risk by Age 70

Lancet 343:692, 1994
Am J Hum Genet 56:265, 1995

### Stage and Diagnosis and Prevalence of Screen Detected Ovarian Cancer in High Risk Women

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Screen Detected OC [LMP]</th>
<th>Prevalence Screen Detected OC per 100,000</th>
<th>Proportion Diagnosed at Stage 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muto (1993)</td>
<td>384</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Schwartz (1995)</td>
<td>247</td>
<td>0</td>
<td>0</td>
<td>0/1</td>
</tr>
<tr>
<td>Belinson (1995)</td>
<td>137</td>
<td>1</td>
<td>730</td>
<td>0/1</td>
</tr>
<tr>
<td><strong>All Studies</strong></td>
<td>3810</td>
<td>24 [8]</td>
<td>630</td>
<td>11/24 (46%)</td>
</tr>
<tr>
<td><strong>Excluding [LMP]</strong></td>
<td>16</td>
<td>420</td>
<td></td>
<td>3/16 (19%)</td>
</tr>
</tbody>
</table>

Ovarian Cancer Screening in Women Who Carry BRCA1 and 2 Mutations

- CA 125 and ultrasound screening are not approved for population screening.
- The relative risk of ovarian cancer is increased at least 10-fold in BRCA1 and BRCA2 carriers.
- Ovarian cancer screening in mutation carriers with ovaries seems reasonable.
Mutations were found in 34% of 824 women with ovarian cancer (199 BRCA1, 82 BRCA2)

- 60% frameshift, 25% nonsense, 12% intronic, 3% missense

- Median age at diagnosis was 49 for BRCA1 and 55 for BRCA2

Social, Ethical and Legal Implications of BRCA1/2 Testing

- Anxiety, depression and guilt
- Insurance concerns
- Medical record documentation
- Obligation to inform other family members
- Reproductive strategies
Tubal Ligation

- Decreases ovarian cancer risk
- Relationship between tubal ligation and decreased risk is strong, but based on subjective data.
  - - Nurses health study
Chemoprevention

- **OC’s**
  - Use of OC’s 6 or more years decreased risk of hereditary ovarian cancer by 60%.
  - The longer the use, the greater the risk reduction
  - Risk protective for 15 years\(^1\)
  - Low-dose OC’s have weaker protection

- **ASA**
  - Small, subjective studies
  - Possibly COX-II specific

- **Retinoids**
  - Cell line data
  - Phase II trials beginning 2001

\(^1\) Narod, *NEJM* 339:424-8, 1998
Oral Contraceptives May Prevent Ovarian Cancer in BRCA1 and 2 Carriers

- 207 BRCA1/2 carriers with ovarian cancer
- 163 sisters without ovarian cancer
  - 53 mutation carriers
  - 42 non-carriers
  - 66 not tested
- Risk of ovarian cancer
  - < 3 years OCP 0.7
  - 3-6 years OCP 0.4
  - > 6 years OCP 0.3

Prophylactic Oophorectomy

- 1000 ovarian cancer cases would be prevented if PO were done at the time of hysterectomy in all women over 40 in the U.S.\(^1\)
- Should be encouraged in all women with hereditary forms of ovarian cancer after childbearing.
  - Decreases risk by at least 50\(^2\)
  - Still at risk for primary peritoneal cancer
- Should be performed on women at increased risk who are having other abdominal surgery

\(^1\) Lepine, Mor, Mortal Wkly Rep CDC Surveillance Summary 46:1-15, 1997
Should Prophylactic Oophorectomy Be Performed at Laparotomy / Laparoscopy For Non-Gynecologic Indications?

- Women ≥40 years
- Family history of breast, ovarian, endometrial or colon cancer
- At time of colorectal surgery
- Cholecystectomy
- GYN / GYN Onc consult pre- or intraop
Laparoscopic Prophylactic Oophorectomy

Surgical Issues

- Discuss risks: anesthesia, infection, bleeding and damage to adjacent organs
- Discuss potential conversion to laparotomy
- Discuss concomitant hysterectomy
- Remove both ovaries and tubes completely
- Perform pelvic peritoneal cytology
- Multiple blocks from each tube and ovary
Prophylactic Oophorectomy in BRCA Carriers

**Pros**

- Decreases ovarian cancer incidence and mortality
- Can be delayed to allow completion of childbearing
- Ease of laparoscopic approach
- Acceptable effect on body image and self esteem
- Estrogen replacement can prevent surgical menopause
- Lowers breast cancer risk
Prophylactic Oophorectomy in BRCA Carriers

Cons

- Surgery may not be covered by insurance
- Potential for surgical morbidity and mortality
- Potential for primary peritoneal carcinoma
- Premature surgical menopause
Breast Cancer Risk After Prophylactic BSO in BRCA1 Mutation Carriers

- Surgery Subjects (n=43)  
  mut\textit{BRCA1} and Prophylactic BSO
- Control Subjects (n=79)  
  mut\textit{BRCA1} but no BSO
- Result: Reduction in breast cancer risk with surgery  
  HR = 0.53 (95% CI: 0.33 - 0.84)
- HRT did not negate the risk reduction

Prophylactic Oophorectomy and HRT

- Compliance: Varies 31-89% up to 5 years, 13-71% >5 years
- Risks: Osteoporosis /cardiac disease vs. breast cancer
- Speroff: ↓ life expectancy with non-compliance
- ERT vs. combined HRT
Cost-Effectiveness

- Cost per screen highest in the first year
- At the lowest (in 1997) screening costs per patient is $39 US
- Costs per life saved may be more than $10 million
Conclusions

- Few women are at increased risk of ovarian cancer
- Screening should be reserved for those at risk
- Surgical or chemopreventive options are available