Controversies in the Prevention of Ovarian Cancer

Ira R. Horowitz, MD, SM, FACOG, FACS
Interim Director, Emory Clinic
Interim Physician Group President, Emory Healthcare
Executive Associate Dean, Faculty Affairs and Professional Development
John D. Thompson Professor, Department of Gynecology and Obstetrics
<table>
<thead>
<tr>
<th>External Industry Relationships</th>
<th>Company Name(s)</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equity, stock, or options in biomedical industry companies or publishers</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Board of Directors or officer</td>
<td>Emory Healthcare Board of Directors Clifton Casualty Insurance Company Emory Medical Care Foundation The Emory Clinic</td>
<td>Department Chair Physician Director, Vice Chair Member Chair</td>
</tr>
<tr>
<td>Royalties from Emory or from external entity</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Industry funds to Emory for my research</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>
Ovarian Cancer

- New Cases: 22,440
  - 3% of Female Cancers
  – 2nd Gynecologic Cancer

- Deaths: 14,080
  - 5% of Female Cancer Deaths
  – 1st Gynecologic Cancer Deaths
Ovarian Cancer Population

- Fatality: Case Ratio 70.3%
- Incidence 1/70
- Mortality 1/100
Ovarian Cancer

- Epithelial 85-90%
- Sex Cord Stromal
- Germ Cell
- Mesenchymal
- Metastatic
- Unclassified
Ovarian Epithelial Cancer

- Serous: 53%
- Endometrioid: 20%
- Clear Cell: 10%
- Mucinous: 7%
- Transitional: 1%
- Mixed: 2%
- Undifferentiated: 5%
- Unclassified: 1%
Symptoms

- Abdominal pain
- Urinary frequency and urgency
- Constipation or diarrhea
- Abnormal vaginal bleeding
- Abdominal distention (from ascites)
- Dyspnea
Signs

- Abdominal mass
- Pelvic mass
- Pleural effusion
- Ascites
- Ventral hernia
- Inguinal nodes
Omental Cake
Diaphragmatic Implants
Ovarian Carcinoma FIGO Stages

5-year Survival Incidence

FIGO=International Federation of Gynecology and Obstetrics
5 Year Survival

1970  36%
1996  50%
Advanced Ovarian Cancer

Median Survival: 1975 - 2006

- 1975: 12 months
- 1983: 14 months
- 1986: 24 months
- 1996: 37 months (optimal)
- 1998: 52 months
- 2003: 57.4 months
- 2006: 66.9 months (optimal)

Chemotherapies:
- Alkeran
- Cisplatin
- Paclitaxel
- IP Tx
### Ovarian Cancer Survival by Stage at Diagnosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>5 year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>89</td>
</tr>
<tr>
<td>II</td>
<td>65</td>
</tr>
<tr>
<td>III</td>
<td>33.5</td>
</tr>
<tr>
<td>IV</td>
<td>18</td>
</tr>
</tbody>
</table>
Familial Ovarian Cancer Syndromes

- Sporadic - 90%
- Linked to inherited mutation – 10%
• Ovarian Cancer Syndrome – 10 – 15%

• Hereditary Breast/Ovarian Cancer Syndrome (HBOC) – 65 – 75%

• Hereditary Nonpolyposis Colorectal Cancer Syndrome (HNPCC) – 10 – 15%

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>44%</td>
</tr>
<tr>
<td>BRCA2</td>
<td>27%</td>
</tr>
<tr>
<td>HNPCC</td>
<td>12%</td>
</tr>
<tr>
<td>Population (USA)</td>
<td>1.5%</td>
</tr>
<tr>
<td>African American</td>
<td>1.08%</td>
</tr>
</tbody>
</table>
Screening For Ovarian Cancer
The Statistics

- Median Age 63
- 1.4% Lifetime Risk (1 in 71)
  (Breast 12% - 1 in 8)
- 1.0 % Lifetime Risk of dying – 1 in 95
- Incidence 13/100,000
  (Colon  55.1 / 100,000)
  (Breast 123 / 100,000)
OVARIAN CANCER
LIFETIME RISK

Negative Family Hx 1.4%
1-Second Degree Relative 3.0%
1-First Degree Relative 5.0%
>2-First Degree Relatives 40.0%
Screening For Ovarian Cancer Test Criteria

- Patient Acceptability
- Simple to Perform
- Cost Effectiveness
- Reproducible Results
- Accuracy
- Precursor Lesion???
Screening With CA125

Positive Predictive Value 20%
Median Survival 72.9 mos vs 41.8 mos
Overall Mortality Not significant

1st trial: Jacobs, et al
Screening For Ovarian Cancer Tests - PPV

Pelvic Examination 0.2%
Ultrasonography 1 - 27%
CA 125 3.7 - 19%
CA 125/Ultrasonography 35.1%
Risk of Ovarian Cancer Algorithm on basis of Ca-125 levels
Screening For Ovarian Cancer

ROMA
- Ca125/HE4
- Menopausal Status

OVA1
- Transthyretin
- Apolipoprotein
- A-1
- B-2 Microglobulin
- Transferrin
- Ca125
Long-Term Survival of Women With Ovarian Cancer Detected By Ultrasound Screening

University of Kentucky – 1987-2011

• 37,293 women
• >50 years of age
• >25 years with family history
• Annual Ultrasounds
### Morphology Index

<table>
<thead>
<tr>
<th>TUMOR VOLUME</th>
<th>TUMOR STRUCTURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;10 cm³</td>
</tr>
<tr>
<td>1</td>
<td>10-50 cm³</td>
</tr>
<tr>
<td>2</td>
<td>&gt;50-100 cm³</td>
</tr>
<tr>
<td>3</td>
<td>&gt;100-200 cm³</td>
</tr>
<tr>
<td>4</td>
<td>&gt;200-500 cm³</td>
</tr>
<tr>
<td>5</td>
<td>&gt;500 cm³</td>
</tr>
<tr>
<td>Term</td>
<td>Screen Finding</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>True-positive</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>Histology confirms ovarian cancer</td>
</tr>
<tr>
<td>False-positive</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>Benign ovarian histology</td>
</tr>
<tr>
<td>True-negative</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>No evidence of disease 12 months after negative screen</td>
</tr>
<tr>
<td>False-negative</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Ovarian cancer diagnosed within 12 months of negative screen</td>
</tr>
</tbody>
</table>

Sensitivity: 86.4% (95% confidence interval [CI] 84.6–88.2); specificity: 98.8% (95% CI 98.7–98.9); positive predictive value positive: 14.53% (95% CI 12.99–16.07); positive predictive value negative 99.97% (95% CI 99.95–99.99).
Long-Term Survival of Women with Epithelial Ovarian Cancer Detected by Ultrasonographic Screening

37,293 Women
523 Operations (1.4%)
47 Invasive Ovarian Ca
15 LMP
9 Metastatic
5 Non-epithelial OvCa
Survival Screened – Non Screened

74.8% +/- 6.6% vs 53.7%+/-2.3%
Prostate Lung Colorectal Ovarian (PLCO) Trial

• 64,261 Women
• Age 55 – 74
• Screening 1. Annual CA125
  2. Annual TVS

Buys S, et al. JAMA 2011:8;305(22):2295-03
PLCO – Ovarian Cancer

- 3,388 (11.1%) – abnormal test
- 1,170 (34.5%) – surgery
- 1/20 had ovarian cancer
- 72% Stage III/IV
- 17 Stage I/II
  - 10 abnormal TUS/Normal CA125
PLCO – Ovarian Cancer Mortality

- Screened 3.1/100,000 person years
- Unscreened 2.6/100,000 person years
  - No significance identified
• 202,638 Women
• Ages 50 – 74
  – Ultrasound
  – CA125 with ultrasound if abnormal
  – Observation

Shizuokan Ovarian Cancer Screening 1985 - 1999

- 41,688 Women – Intervention
- 40,799 Women – Control
- Sequential Ultrasound & CA125
- Abnormal Ultrasound or Elevated CA125 referred to Gyn Oncologist for surgery

Shizuokan Ovarian Cancer Screening

- December 2002 – Code Broken

  Screened – 27 cancers
  Controls – 32 cancers

  p. 0.2285
## Shizuokan Ovarian Cancer Screening

<table>
<thead>
<tr>
<th>STAGE</th>
<th>SCREENED (%)</th>
<th>CONTROL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>17 (63)</td>
<td>12 (38)</td>
</tr>
<tr>
<td>II</td>
<td>1 (4)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>III</td>
<td>7 (26)</td>
<td>16 (50)</td>
</tr>
<tr>
<td>IV</td>
<td>2 (7)</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

p 0.2285
PREVENTION
AND
RISK REDUCING SURGERY
Cancer & Steroid Hormone (CASH)

- Risk Reduction 40% - 3-6 mos OCP
  50% - >4 yrs OCP

- Risk Reduction 50% - BRCA ½

- Mechanism – Unknown?

CASH, NEJM 1987, Mar 12:316(11) 650-55
Nurses Health Study

• Tubal Ligation 70% Risk Reduction
  – Decreased environmental exposure
  – Decreased ovarian blood flow
  – Ovarian suppression

• Full Term Pregnancy 20-40% Risk Reduction
• Subsequent Pregnancy additional 14%

Vachun, CM et.al. Epidemiol. 2002:Jan 13(1);66-71
Risk Reducing Surgery

• Bilateral Salpingo-oophorectomy

• Risk Reduction 9-% both in general population and BRCA

• 50% reduction in breast cancer
OVARIAN CANCER
VS
FALLOPIAN TUBE CANCER
Ovary vs Fallopian Tube
High Grade Serous Carcinomas

- 80% Stage III/IV
- Ovary – Fallopian Tube – Peritoneum
  Histologically identical
- Intraepithelial tubal lesions
  - p53
  - Ki67
Tubal Carcinoma

- 1997 identified BRCA2 mutations
- 2000 identified BRCA1 mutations
- Occult cancers in 4.4 – 17% of BRCA patients undergoing risk reducing salpingectomy
- Data does not support risk reducing salpingectomy in BRCA patient

The rate of accumulation of mutations may be influenced by retrograde menstruation, with passage of menstrual blood containing inflammatory cytokines along the tubal epithelium, by damage and repair caused by ovulation, by the presence of infectious agents or irritants, or by loss or absence of DNA damage repair genes such as BRCA-1 or 2.

Reade C, et al. JOGC 2014;36(2)133-140
RISK REDUCING SALPINGECTOMY

Denmark 1982-2011

Case controlled study
13,241 – Ovarian Cancer
3,605 Borderline Risk Reduction
Bilateral Salpingectomy – 42%

## Risk of Epithelial Ovarian Cancer By Unilateral and Bilateral Salpingectomy

<table>
<thead>
<tr>
<th>Salpingectomy history</th>
<th>Cases (n)</th>
<th>Controls (n)</th>
<th>Age-matched OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No salpingectomy</td>
<td>13,135</td>
<td>192,896</td>
<td>ref</td>
<td>ref</td>
<td></td>
<td>ref</td>
</tr>
<tr>
<td>Unilateral</td>
<td>89</td>
<td>1,382</td>
<td>0.94</td>
<td>0.76-1.18</td>
<td>0.90</td>
<td>0.72-1.12</td>
</tr>
<tr>
<td>Bilateral</td>
<td>17</td>
<td>411</td>
<td>0.61</td>
<td>0.37-0.99</td>
<td>0.58</td>
<td>0.36-0.95</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio.

*a*Adjusted for age, parity (0, 1, 2, >3), and tubal ligation.
One hundred ninety two responders
25% Response Rate
37% unaware of data
3,870 unsure RRS would help patients
## Demographic characteristics of survey respondents

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of time in practice, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resident or fellow</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>≤ 5</td>
<td>41</td>
<td>21</td>
</tr>
<tr>
<td>6 to 10</td>
<td>31</td>
<td>16</td>
</tr>
<tr>
<td>11 to 20</td>
<td>46</td>
<td>24</td>
</tr>
<tr>
<td>≥ 21</td>
<td>61</td>
<td>32</td>
</tr>
<tr>
<td>Type of practice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General obstetrician-gynaecologist</td>
<td>102</td>
<td>53</td>
</tr>
<tr>
<td>Subspecialist</td>
<td>90</td>
<td>47</td>
</tr>
<tr>
<td>Practice setting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic centre</td>
<td>93</td>
<td>48</td>
</tr>
<tr>
<td>University-affiliated community centre</td>
<td>70</td>
<td>36</td>
</tr>
<tr>
<td>Non-university affiliated community centre</td>
<td>27</td>
<td>14</td>
</tr>
<tr>
<td>Community of practice, population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 49 999</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>50 000 to 99 999</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>100 000 to 299 999</td>
<td>37</td>
<td>19</td>
</tr>
<tr>
<td>300 000 to 499 999</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>≥ 500 000</td>
<td>104</td>
<td>54</td>
</tr>
</tbody>
</table>
Figure 1. Average number of hysterectomies performed annually

- None: 9%
- 1-10: 9%
- 11-25: 17%
- 26-50: 28%
- 51-75: 13%
- 76 and more: 24%
Figure 2. Average number of tubal ligations performed annually

<table>
<thead>
<tr>
<th>Range</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>32%</td>
</tr>
<tr>
<td>1–10</td>
<td>19%</td>
</tr>
<tr>
<td>11–20</td>
<td>18%</td>
</tr>
<tr>
<td>21–30</td>
<td>12%</td>
</tr>
<tr>
<td>31–40</td>
<td>8%</td>
</tr>
<tr>
<td>41–50</td>
<td>7%</td>
</tr>
<tr>
<td>51 and more</td>
<td>4%</td>
</tr>
</tbody>
</table>
Canadian Physician Risk Reducing Salpingectomy Barriers

Figure 3. Reasons for leaving fallopian tubes in situ at the time of hysterectomy

- No good reason to take them out: 51%
- Increase surgical morbidity: 36%
- Increase operative time: 19%
- Increase surgical complexity: 8%
- Other: 34%
Figure 4. Barriers to implementation of salpingectomy

- Increase operating time: 68% (Hysterectomy), 43% (Tubal ligation)
- Increase in complications: 63% (Hysterectomy), 52% (Tubal ligation)
- Extra time needed to counsel my patients: 33% (Hysterectomy), 28% (Tubal ligation)
- Colleagues/RN or staff distrust in this change in practice: 11% (Hysterectomy), 7% (Tubal ligation)
- Irreversible: 55% (Tubal ligation)
- Concern about premature ovarian failure: 27% (Tubal ligation), 0% (Hysterectomy)
- Other: 31% (Tubal ligation), 17% (Hysterectomy)
WHAT’S PROTEOMICS
### Classification of serum samples from masked validation set by proteomic pattern

<table>
<thead>
<tr>
<th>Category</th>
<th>Classification by proteomic pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaffected women</td>
<td></td>
</tr>
<tr>
<td>No evidence of ovarian cysts</td>
<td>2/24</td>
</tr>
<tr>
<td>Benign ovarian cysts &lt;2-5 cm</td>
<td>18/19</td>
</tr>
<tr>
<td>Benign ovarian cysts &gt;2-5 cm</td>
<td>6/6</td>
</tr>
<tr>
<td>Benign gynecological disease</td>
<td>1/10</td>
</tr>
<tr>
<td>Non-gynecological inflammatory disorder</td>
<td>0/7</td>
</tr>
<tr>
<td>Women with ovarian cancer</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>18/18</td>
</tr>
<tr>
<td>Stage II, III, IV</td>
<td>32/32</td>
</tr>
</tbody>
</table>

Screening For Ovarian Cancer Carcinogenesis

Low Grade (Type I)
• Slowly Developing
• Endometrioid, Mucinous, LG Serous Ca

High Grade Serous Carcinoma (Type II)
• Precursor Lesion Unidentified
• Rapidly Progressive
Low Grade Tumors

- LOW GRADE SEROUS – KRAS
- ENDOMETRIOID - ARID1A
High Grade

- HIGH GRADE SEROUS
  - BRCA1/2
  - P53

- CLEAR CELL
  - PIK3CA
SCREENING AND PREVENTION
SGO and ACOG Referral Guidelines for a Newly Diagnosed Pelvic Mass

- Premenopausal (< 50 years old)
  - CA 125 >200 U/ml
  - Ascites
  - Evidence of abdominal or distant metastasis (by exam or imaging study)
  - Family history of breast or ovarian cancer (in a first degree relative)
- Postmenopausal (≥ 50 years old)
  - CA 125 >35 U/ml
  - Ascites
  - Nodular or fixed pelvic masses
  - Evidence of abdominal or distant metastasis
  - Family history of breast or ovarian cancer (in a first degree relative)
Screening for Ovarian Cancer High Risk - Screening

USPSTF/ACOG/CTFPHC

• Recommend Genetic Counseling
• Not Ovarian Cancer Screening
SGO Recommends Risk Reducing Surgery as No Evidence Suggests that Screening Reduces Mortality.

Age 35 (NCCN)
If Patient Refuses RRS
Ultrasound + Ca125 q6 months
Bilateral Salpingectomy Has No Role Today
NO Professional Organization or Government Agency or Task Force Recommends Routine Screening in The General Population.
The Role of Salpingectomy at the Time of an Operative Procedure continues to Gain Acceptance.
HUMAN GENOME
THE ELUSIVE CHIP
OVARIAN CANCER
THE JOURNEY
ANTIANGIOGENESIS
Figure 1: Multiple Pathways Are Under Investigation for the Treatment of Gynecologic Malignancies—Shown here are therapeutic targets in the VEGF- and non-VEGF-dependent angiogenesis cascade. Ang = angiopoietin; EGF = epidermal growth factor; EGFR = EGF receptor; ERK = extracellular signal-regulated kinase; FGF = fibroblast growth factor; FGFR = FGF receptor; HGF = hepatocyte growth factor; HIF1α = hypoxia inducible factor 1a; MAPK = mitogen-activated protein kinase; MEK = MAPK/ERK kinase; mTORC = mammalian target of rapamycin complex; PDGF = platelet-derived growth factor; PDGFR = PDGF receptor; PI3K = phosphatidylinositol 3-kinase; OS = overall survival; VEGF = vascular endothelial cell growth factor; VEGFR = VEGF receptor. Adapted from Eskander RN, Tewari, KS. Gynecol Oncol. 2014[69]; expanded by Liu FW based on a concept by Tewari KS.
New Concepts

- Anti-Angiogenesis
- PARP Inhibitors
- P13K
- AKT
- mTOR
P13K/AKT/mTOR Pathway Inhibitors

- mTOR Inhibitors
- PI3K Inhibitors
- Dual mTOR/P13K Inhibitors
- AKT Inhibitors
Fig. 2. Schematic representation of the PI3K/AKT/mTOR signaling pathway.

Conclusion

• Old Ways Remain
  – Surgery/Chemotherapy

• Moving Forward
  – Targeted Therapy