OVARIAN CANCER SCREENING AND MANAGEMENT OF ADNEXAL MASSES

Alison Jacoby, MD
UCSF
Learning Objectives

• Review ovarian cancer risk factors
• Discuss ovarian cancer screening alternatives
• Analyze management strategies for premenopausal and postmenopausal adnexal masses
• Review ACOG guidelines for referring a patient with an adnexal mass to a gyn oncologist
• Compare CA 125 and OVA1 tests
Ovarian Cancer Screening
WL is a 54 yr old P0 who presents for an annual exam. She mentions seeing a segment on the evening news last week about improvements in ovarian cancer screening and she would like to be tested.

She is without abdominal complaints and has no family history of gynecologic or gastrointestinal cancers but she would feel better knowing the test was negative.

How would you counsel her?
Ovarian Cancer Screening options:

1. Perform a bimanual pelvic exam
2. Order a pelvic ultrasound
3. Send a serum CA 125
4. Discuss lack of efficacy of current screening tests
Case Two

SR is a 42 yr old woman who you are meeting for the first time. In the course of eliciting her medical and family history, you learn she has several relatives with breast and ovarian cancer. Her cousin and aunt had breast cancer in their 40’s and her grandmother died from ovarian cancer.

She’s been having routine screening mammograms but you wonder if you should be doing more surveillance.

What would you do?
What would you do next?

1. Send a serum CA 125
2. Order a pelvic US
3. Recommend both tests
4. Refer to a genetic counselor
# Cancer statistics, 2012

## Estimated New Cases*

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>241,740</td>
<td>29%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>119,470</td>
<td>14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>73,420</td>
<td>9%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>55,820</td>
<td>7%</td>
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<tr>
<td>Melanoma of the skin</td>
<td>44,250</td>
<td>5%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>40,250</td>
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</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>38,160</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>23,540</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>20,830</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>22,000</td>
<td>3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>843,170</strong></td>
<td><strong>100%</strong></td>
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<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
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<tbody>
<tr>
<td>Breast</td>
<td>226,870</td>
<td>29%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>109,690</td>
<td>14%</td>
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<tr>
<td>Colon &amp; rectum</td>
<td>70,040</td>
<td>9%</td>
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<tr>
<td>Uterine corpus</td>
<td>47,130</td>
<td>6%</td>
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<tr>
<td>Thyroid</td>
<td>43,210</td>
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<tr>
<td>Melanoma of the skin</td>
<td>32,000</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>31,970</td>
<td>4%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>24,520</td>
<td>3%</td>
</tr>
<tr>
<td>Ovary</td>
<td>22,260</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>21,830</td>
<td>3%</td>
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<tr>
<td><strong>All Sites</strong></td>
<td><strong>790,740</strong></td>
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## Estimated Deaths

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
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</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>87,750</td>
<td>29%</td>
</tr>
<tr>
<td>Prostate</td>
<td>28,170</td>
<td>9%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>25,470</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>18,850</td>
<td>6%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>13,900</td>
<td>5%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>13,500</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,040</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>10,510</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>10,320</td>
<td>3%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>8,850</td>
<td>3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>301,820</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>72,590</td>
<td>26%</td>
</tr>
<tr>
<td>Breast</td>
<td>39,510</td>
<td>14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>25,220</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>18,540</td>
<td>7%</td>
</tr>
<tr>
<td>Ovary</td>
<td>15,500</td>
<td>6%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>10,040</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>8,620</td>
<td>3%</td>
</tr>
<tr>
<td>Uterine Corpus</td>
<td>8,010</td>
<td>3%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>6,570</td>
<td>2%</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>5,980</td>
<td>2%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>275,370</strong></td>
<td><strong>100%</strong></td>
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</table>
Cancer of the ovaries is the leading cause of cancer death from gynecologic malignancies in the United States, with an annual incidence of over 25,000 and an annual mortality of approximately 14,000. Cancer incidence increases dramatically with age, being relatively rare prior to age 50.

Data from: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov).
## Ovarian Cancer Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR</th>
<th>Lifetime Probability (%)*</th>
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<tbody>
<tr>
<td>Familial Ovarian Ca Synd</td>
<td>Unknown</td>
<td>30-50</td>
</tr>
<tr>
<td>2-3 Relatives w/ Ovarian Ca</td>
<td>4.6</td>
<td>5.5</td>
</tr>
<tr>
<td>1 Relative w/ Ovarian Ca</td>
<td>3.1</td>
<td>3.7</td>
</tr>
<tr>
<td>No RF’s</td>
<td>1.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Past OC use</td>
<td>0.65</td>
<td>0.8</td>
</tr>
<tr>
<td>Past Pregnancy</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Infertility</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Past Breastfeeding</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Tubal Ligation</td>
<td>0.6</td>
<td></td>
</tr>
</tbody>
</table>

* Indicates probability of Ov Ca in a 50 yr old woman
Ovarian Cancer Risk Factors

Hormonal and Reproductive Factors
- Nulligravity
- Early menarche (age < 12)
- Late menopause (age > 50)
- Endometriosis
- PCOS

Genetic factors - 10-15% of cases
- BRCA mutations
- Lynch II Syndrome

Environmental
- Talc
- Smoking
- Diet ?
- Exercise ?
- Obesity (BMI > 30)
Ovarian Cancer Protective Factors

Combined E/P OC’s
- 45 studies from 21 countries
- Any use lowers risk compared to non-users
- Longer duration of use assoc’d w/ lower risk reduction
- Protective effect lasts 30 yrs
- No data for non-oral E/P contraceptives (patch, ring)

Hysterectomy and Tubal Ligation
- Both reduce RR by 34%

Multiparity
Ovarian Cancer Screening Rationale

5 year survival

75% present w/ Stage III disease

Detect Early Stage Ovarian Cancer

Decrease Mortality Rates

False Positive Results

Harm from Unnecessary Interventions
Screening test characteristics

What is an acceptable positive predictive value?

1. 90%
2. 60%
3. 30%
4. 10%
Screening test characteristics

• Given the low prevalence of ovarian cancer....
• Given a test with an 80% sensitivity.....
• To achieve a PPV of ____ would require a screening test to have a specificity of .....  
• 99.6%
Potential Screening Tests

- Pelvic examination
- Pap smears
- Tumor markers - CA 125, HE4
- Imaging tests - US, CT
- Combination of modalities
CA 125

- Glycoprotein antigen on tumor cells
- FDA approved for monitoring treatment response and recurrence in women w/ Ov Ca

**Sensitivity**
- Early stage disease: 50%
- Advanced stage disease: > 80%

**Specificity:** ~68%
- Increased in a variety of benign and malignant conditions
- Endometriosis, fibroids, PID, other cancers, etc.
CA 125

Prostate, Lung, Colorectal, Ovarian Cancer Screening (PLCO) Trial

- >78,000 healthy women, age 55-74
- Randomly assigned to screening or control groups
- Ov Ca Screening: annual serum CA 125, TVUS or both for 5 yrs
- Follow-up for 13 yrs
- At baseline, 436 women had elevated CA 125
- PPV 3.7%

Pelvic Ultrasonography

- 4526 women at high risk for Ov Ca screened annually

- After ~13,000 scans, all of the ovarian, fallopian tube and peritoneal cancers identified were Stage III

- NO cases of early disease detected

Pelvic Ultrasonography

- 37,293 Asx, low risk women age >50
- Study began in 1987, average f/u 5.8 yrs
- Specificity: 98.5%
- PPV: 8.9%
- NNT: 11 operations performed per case of Ov Ca
- Early detection: 70% of 47 screen-detected Ov Ca cases Stage I or II
- Lower mortality: 5 yr survival for screen-detected vs. unscreened Ov Ca cases: 84.6% vs. 53.7%

CT Colonography

- 2869 women screened
- 70 women incidental finding of adnexal abnormality
  - Number found to have Ovarian Ca? NONE
- 4 women with normal adnexae dx’d with Ov Ca within 4 yrs

CA 125 and TVUS

Prostate, Lung, Colorectal, Ovarian Cancer Screening (PLCO) Trial

• >78,000 healthy women, age 55-74
• Ov Ca Screening: annual serum CA 125, TVUS  or both for 5 yrs
• Follow-up for 13 yrs

• Early detection: NO
• Lower mortality: NO
• High false positive rate: 541 women underwent surgery without a cancer diagnosis
• Harm: 15% had at least 1 serious surgical complication
Case One

WL is a 54 yr old P0 who presents for an annual exam. She mentions seeing a segment on the evening news last week about improvements in ovarian cancer screening and she would like to be tested.

She is without abdominal complaints and has no family history of gynecologic or gastrointestinal cancers but she would feel better knowing the test was negative.

How would you counsel her?
Case One

Ovarian Cancer Screening options:
1. Perform a bimanual pelvic exam
2. Order a pelvic ultrasound
3. Send a serum CA 125
4. Discuss lack of efficacy of current screening tests
Case Two

SR is a 42 yr old woman who you are meeting for the first time. In the course of eliciting her medical and family history, you learn she has several relatives with breast and ovarian cancer. Her cousin and aunt had breast cancer in their 40’s and her grandmother died from ovarian cancer.

She’s been having routine screening mammograms but you wonder if you should be doing more surveillance.

What would you do?
Case Two

What would you do next?

1. Send a serum CA 125
2. Order a pelvic US
3. Recommend both tests
4. Refer to a genetic counselor
Management of Adnexal Masses

“Off hand, I'd say you're suffering from an arrow through your head, but just to play it safe, I'm ordering a bunch of tests.”
A healthy 32 y.o. P2 is referred to you for management of an asymptomatic pelvic mass discovered during a routine pelvic examination 10 wks ago. A pelvic US at that time revealed a 7 cm, anechoic right ovarian cyst without septations or mural nodularity. There is no free fluid in the pelvis. She continues to have regular cycles and takes no medications.

What are the key components of this scenario?
Right Ovarian Cyst
All of the following are in your DDx except:

1. Physiologic or functional cyst
2. Serous cystadenoma
3. Serous cystadenocarcinoma
4. Paratubal cyst
Additional information:

10 wks later, a physical examination confirms a mobile mass and a pelvic US reveals a slight increase in size of the cyst to 8.5 cm.
What is the most likely diagnosis now?

1. Physiologic or functional cyst
2. Serous cystadenoma
3. Serous cystadenocarcinoma
4. Paratubal cyst
What are her options?

- Observation
- Cyst content aspiration
- Laparoscopic ovarian cystectomy
- Laparoscopic oophorectomy
- Check tumor markers and refer to a gyn oncologist
<table>
<thead>
<tr>
<th>Observation vs. Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Asymptomatic</td>
</tr>
<tr>
<td>• Low likelihood of malignancy</td>
</tr>
<tr>
<td>• Risks of surgery</td>
</tr>
</tbody>
</table>

| Natural history suggests growth will continue |
| • Tissue sample to confirm benign |
| • Risk for ovarian torsion necessitating urgent surgery |
Cyst content aspiration

Easy to accomplish but.....
Cyst content aspiration

Easy to accomplish but…..

- Potential spillage of malignant cells
- Low diagnostic yield
- Reaccumulation of fluid/cyst
Laparoscopic cystectomy
What is the most likely diagnosis now?

1. Physiologic or functional cyst
2. Serous cystadenoma
3. Serous cystadenocarcinoma
4. Paratubal cyst
Case 4

- A 54 y.o. G0 post-menopausal woman is referred to you by an NP for evaluation of a left ovarian cystic mass. The patient was experiencing some non-specific abdominal bloating several weeks ago which prompted the pelvic ultrasound. A 5 cm, unilocular, anechoic cyst with an echogenic mural nodule is described. Color Doppler imaging shows normal vascular flow. There is no free fluid in the pelvis. Her grandmother died from ovarian cancer.

What would you do next?
Mural Nodule
What would you do next?

1. Repeat an ultrasound in 6-12 weeks
2. Refer to a gyn oncologist
3. Order a serum CA 125
4. Order a serum OVA1®
5. Perform a L/S oophorectomy
ACOG/SGO Referral Guidelines-
Preoperative consultation with a gynecologic oncologist for one or more of following criteria:

**Premenopausal women**
1. CA 125 greater than 200 units/mL
2. Ascites
3. Evidence of abdominal or distant metastasis
4. Family history of breast or ovarian cancer (in a first-degree relative)

The revisions to the College guidelines proposed by Dearking include:
1) eliminating the family history of one or more first-degree relatives with ovarian or breast cancer
2) lowering the CA 125 threshold in premenopausal women to 67 units/mL.
ACOG/SGO Referral Guidelines -
Preoperative consultation with a gynecologic oncologist for one or more of following criteria:

Postmenopausal women (older than 50 yrs)
1. Elevated CA 125 (> 35 units/mL)
2. Nodular or fixed pelvic mass
3. Ascites
4. Evidence of abdominal or distant metastasis
5. Family history of ovarian or breast cancer (in a first-degree relative)

The revisions to the College guidelines proposed by Dearking include: 1) eliminating the family history of one or more first-degree relatives with ovarian or breast cancer
OVA1®

Multivariate Index Assay
• Consists of 5 biomarkers
  CA125
  Prealbumin
  Apolipoprotein A1
  Beta 2 microglobulin
  Transferrin

• Cost- $600 vs. $100 for CA 125

Ovarian malignancy risk index score
OVA1®

Ovarian Malignancy Risk Index Score (0-10)

Premenopausal:  Low prob, < 5.0
               High prob, ≥ 5.0

Postmenopausal: Low prob, < 4.4
                High prob, ≥ 4.4
OVA1® vs. CA 125

<table>
<thead>
<tr>
<th></th>
<th>OVA1</th>
<th>CA 125</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>94</td>
<td>77</td>
</tr>
<tr>
<td>Specificity</td>
<td>35</td>
<td>68</td>
</tr>
<tr>
<td>PPV</td>
<td>40</td>
<td>52</td>
</tr>
<tr>
<td>NPV</td>
<td>93</td>
<td>87</td>
</tr>
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</table>

OVA1: When test is positive, 40% have cancer
When test is negative, 93% have a non-malignant mass

<table>
<thead>
<tr>
<th>Guideline Applied, by Menopausal Status</th>
<th>Probability of Malignancy Before Testing (Prevalence)</th>
<th>Proportion With Positive Test Results</th>
<th>Revised Probability of Malignancy When Test Result is Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal Modified College College-MIA</td>
<td>19</td>
<td>39 63</td>
<td>8 5</td>
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<tr>
<td>Postmenopausal Modified College College-MIA</td>
<td>41</td>
<td>51 83</td>
<td>16 12</td>
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</table>

Case 4

A 54 y.o. G0 post-menopausal woman is referred to you by an NP for evaluation of a left ovarian cystic mass. The patient was experiencing some non-specific abdominal bloating several weeks ago which prompted the pelvic ultrasound. A 5 cm, unilocular, anechoic cyst with an echogenic mural nodule is described. Color Doppler imaging shows normal vascular flow. There is no free fluid in the pelvis. Her grandmother died from ovarian cancer.

What would you do next?
What would you do next?

1. Repeat an ultrasound in 6-12 weeks
2. Refer to a gyn oncologist
3. Order a serum CA 125
4. Order a serum OVA1®
5. Perform a L/S oophorectomy
Recommendation

Women of average risk for ovarian cancer:

Do not offer screening

- ACOG, USPSTF, SGO, Canadian Task Force
Recommendation

Women with family history of Ov Ca but low suspicion for hereditary ovarian cancer syndrome (BRCA, Lynch II):

Limited evidence for effectiveness of screening and potential for adverse effects of screening
Recommendation

Women with high risk family history concerning for hereditary ovarian cancer syndrome:

Refer to Genetic counselor for discussion of BRCA mutation testing

SGO, National Comprehensive Cancer Network
In Conclusion…

The objectives of this presentation were to provide a….

- Reminder of Ovarian Cancer risk factors
- Evidence based review of Ovarian Cancer screening outcomes
- Clinically relevant examples of adnexal mass management
- Guidelines for referring patients to a gyn oncologist
- Balanced discussion of the new (heavily marketed) OVA1 test