The Early Detection of Ovarian Cancer: Are Biomarkers the Answer?

Joshua Cohen MD
Gynecologic Oncology Fellow
UCLA/Cedars-Sinai Medical Center
No conflicts of interest to disclose
Educational Objectives

• Recognize challenges in current paradigms associated with biomarker development in ovarian cancer screening

• Compare the benefits and disadvantages of existing screening strategies in the identification of early stage ovarian cancer.

• Apply current practice guidelines for ovarian cancer screening based on risk of disease
Contents

- Significance
- Challenges
- Biomarkers and Existing Algorithms
- Areas of Growth in Translational Approaches
- Imaging
- Symptom Based Screening
- Multimodality Screening
- High Risk Patients
- Future Considerations
Most Lethal Gynecologic Cancer

2009 Cancer Survival Rates*

<table>
<thead>
<tr>
<th></th>
<th>Deaths 269,800</th>
<th>Cases 713,220</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Brain/ONS</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>All other sites</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>All Other Sites</td>
<td>22%</td>
<td></td>
</tr>
</tbody>
</table>

Advanced Stage Disease

Stage III (III) Cancer

- Tumors throughout the pelvis
- Ovary
- Bladder
- Uterus
- Sigmoid colon
- Cancer has spread to the lymph nodes

Multiple lymph node metastasis
Survival Outcomes

<table>
<thead>
<tr>
<th>Stage</th>
<th>Relative 5-Year Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>94%</td>
</tr>
<tr>
<td>1B</td>
<td>91%</td>
</tr>
<tr>
<td>1C</td>
<td>80%</td>
</tr>
<tr>
<td>IIA</td>
<td>76%</td>
</tr>
<tr>
<td>IIB</td>
<td>67%</td>
</tr>
<tr>
<td>IIC</td>
<td>57%</td>
</tr>
<tr>
<td>IIIA</td>
<td>45%</td>
</tr>
<tr>
<td>IIIB</td>
<td>39%</td>
</tr>
<tr>
<td>IIIIC</td>
<td>35%</td>
</tr>
<tr>
<td>IV</td>
<td>18%</td>
</tr>
</tbody>
</table>

Survival Outcomes


<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5-yr Rel Survival</td>
<td>33.6%</td>
<td>38.1%</td>
<td>38.7%</td>
<td>37.2%</td>
<td>38.3%</td>
<td>44.1%</td>
<td>45.6%</td>
<td>43.9%</td>
</tr>
</tbody>
</table>
### Screening

**1 in 70 women**  
**1 in 2500 postmenopausal women**

**WE NEED:**  
- PPV 10%  
- Sensitivity >75%  
- Specificity 99.6%

**Will find one case of ovarian cancer for every 10 operations**

<table>
<thead>
<tr>
<th>Common Types of Cancer</th>
<th>Estimated New Cases 2013</th>
<th>Estimated Deaths 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Prostate Cancer</td>
<td>238,590</td>
<td>29,720</td>
</tr>
<tr>
<td>2. Breast Cancer</td>
<td>232,340</td>
<td>39,620</td>
</tr>
<tr>
<td>3. Lung and Bronchus Cancer</td>
<td>228,190</td>
<td>159,480</td>
</tr>
<tr>
<td>4. Colon and Rectum Cancer</td>
<td>142,820</td>
<td>50,830</td>
</tr>
<tr>
<td>5. Melanoma of the Skin</td>
<td>76,690</td>
<td>9,480</td>
</tr>
<tr>
<td>6. Bladder Cancer</td>
<td>72,570</td>
<td>15,210</td>
</tr>
<tr>
<td>7. Non-Hodgkin Lymphoma</td>
<td>69,740</td>
<td>19,020</td>
</tr>
<tr>
<td>8. Kidney and Renal Pelvis Cancer</td>
<td>65,150</td>
<td>13,680</td>
</tr>
<tr>
<td>9. Thyroid Cancer</td>
<td>60,220</td>
<td>1,850</td>
</tr>
<tr>
<td>10. Endometrial Cancer</td>
<td>49,560</td>
<td>8,190</td>
</tr>
<tr>
<td>16. Ovary Cancer</td>
<td>22,240</td>
<td>14,030</td>
</tr>
</tbody>
</table>

Ovary cancer represents 1.3% of all new cancer cases in the U.S.
The Age of the –omes”

The Cancer Genome Atlas

Metabolome

Metabolomics Australia

Proteome

Cancer Genomics Hub

Transcriptome

BROAD INSTITUTE

Genome

Wellcome Trust Sanger Institute
## Ovarian Cancer – A Misnomer

<table>
<thead>
<tr>
<th>Type</th>
<th>Putative Precursor</th>
<th>Most Frequent Mutation (s)</th>
<th>Level of chromosomal structural alteration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1 tumors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-grade serous carcinoma</td>
<td>Serous Borderline Tumor</td>
<td>KRAS, BRAF</td>
<td>Low</td>
</tr>
<tr>
<td>Low-grade endometrioid carcinoma</td>
<td>Endometrioma</td>
<td>CTNNB1, PIK3CA, PTEN, ARID1A</td>
<td>Low</td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>Endometrioma</td>
<td>PIK3CA, ARID1A, FBXW74</td>
<td>Low</td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
<td>Mucinous borderline tumor</td>
<td>KRAS</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Type II tumors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-grade serous carcinoma</td>
<td>Fallopian tube epithelium</td>
<td>TP53, BRCA 1 or 2</td>
<td>High</td>
</tr>
<tr>
<td>High-grade endometrioid carcinoma</td>
<td>Not recognized</td>
<td>TP53</td>
<td>High</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>Not recognized</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>Not recognized</td>
<td>TP53</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Fallopian tube either directly from an occult carcinoma or from tubal epithelium implanted in the ovary forming a cortical inclusion cyst.

Type 1 versus Type 2

Type I

- ARID1A
- CTNNB1
- PTEN
- PIK3CA
- PPP2RI

Mutation

Endometrioid
Clear cell
Low-grade serous

Type II

- TP53 mutation
- Chromosomal instability
- Mucinous

Inactivation of BRCA 1/2
(Mutation or hypermethylation)

Biomarkers and Existing Algorithms

- CA125 is elevated in approximately 50-60% of stage I epithelial ovarian cancers and 75-90% of patients with advanced stage disease.

- When values below 35 U/L are designated as normal, CA125 is elevated in 80% of epithelial ovarian cancers.

- The ideal biomarker or panel of biomarkers is obtained through noninvasive means:
  - blood,
  - saliva
  - urine
  - cervical mucous

How do we improve current strategies?

Five Phases of Biomarker Development

1) Preclinical exploratory phase
2) Clinical assay and validation stage
3) Retrospective longitudinal study
4) Prospective screening evaluation
5) Randomized controlled trials

Pepe, M S, et al. (2001)
Risk of Ovarian Cancer Algorithm

- A randomized control trial to evaluate ROCA consisted of 13,582 postmenopausal women over the age of 50 and demonstrated a specificity of 99.8% (CI 99.7 to 99.9%) and positive predictive value of 19% (CI 4.1 to 45.6%)

<table>
<thead>
<tr>
<th>ROCA (asymptomatic general population)</th>
<th>Compares a woman’s longitudinal CA-125 pattern to the change-point CA-125 profile seen in women with ovarian cancer and the flat CA-125 profiles seen in women without ovarian cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on the ROCA result, women get triaged into one of three groups:</td>
<td></td>
</tr>
<tr>
<td>- Low Risk- continue annual CA-125 testing</td>
<td></td>
</tr>
<tr>
<td>- Intermediate Risk- repeat CA-125 test 3 months later</td>
<td></td>
</tr>
<tr>
<td>- High Risk- receive TVS and referral to a gynecologic oncologist</td>
<td></td>
</tr>
<tr>
<td>After each additional CA-125 value, ROCA is recalculated and a new recommendation is made.</td>
<td></td>
</tr>
</tbody>
</table>

Is one biomarker enough?

Even with new technology, it is unlikely that an individual biomarker will reach a specificity of 99.6%, positive predictive value of 10%, and sensitivity greater than 75% when screening an asymptomatic general population.
HE4 and CA125

- HE4 is overexpressed in 50% of clear cell, 93% of serous, and 100% of endometrioid cancers but is not overexpressed in mucinous tumors.

- Identified initially as an mRNA transcript specific to the distal epididymal tissue, genomic advances with microarray gene expression profiling demonstrated HE4 is highly-expressed in ovarian cancer.

- HE4 has greater specificity in the premenopausal age group than CA125 given it does not appear to be expressed at high levels in the setting of benign conditions such as endometriomas.

- In a systemic review of women with suspected gynecologic disease HE4 demonstrated a higher specificity (93% versus 78%) and similar sensitivity (79%) to CA125 when distinguishing benign disease from ovarian cancer.

Drapkin, R, et al. (2005)
Ferraro, S, et al. (2013)
Have we made progress elsewhere?

- In efforts to further triage women in the detection of ovarian cancer, progress has been made in the development of algorithms to delineate malignancy in the setting of an adnexal mass.

- Woman appropriately referred to a gynecologic oncologist have better outcomes including survival, demonstrating the potential importance of these triage tests.

**Risk of Malignancy Index**

<table>
<thead>
<tr>
<th>RMI</th>
<th>Uses menopausal status, ultrasound findings, and serum CA-125 levels to determine malignancy risk.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(known pelvic mass)</td>
<td></td>
</tr>
</tbody>
</table>
## Risk of Ovarian Cancer Malignancy Algorithm

| ROMA (known pelvic mass) | - Uses both HE-4 and CA-125 test levels to evaluate patients as low or high risk for ovarian cancer.  
- A predictive index (PI) is calculated using different equations for pre-menopausal and post-menopausal women.  
- The PI is then inserted into the ROMA algorithm to predict the probability of ovarian cancer. |

Multivariate Index Assay

- A multivariate index assay that incorporates CA-125, transferrin, transthyretin (prealbumin), apolipoprotein A1, and beta-2-microglobulin.
- Used to generate an ovarian malignancy risk score between 0 and 10.
- OVA1 scores greater than or equal to 5.0 (premenopausal) or 4.4 (postmenopausal) result in high risk stratification and referral to a gynecologic oncologist.

Bristow, et al. (2013)
Trials Testing Clinical Screening Strategies in the Setting of a Pelvic Mass

<table>
<thead>
<tr>
<th>Algorithm or Assay</th>
<th>Study</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROMA</td>
<td>Karlsen et al.</td>
<td>94.4</td>
<td>76.5</td>
</tr>
<tr>
<td></td>
<td>Moore et al.</td>
<td>94.3</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Sandri et al.</td>
<td>91.2</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>89.3</td>
<td>81.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>84.4</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Chan et al.</td>
<td>89.2</td>
<td>87.3</td>
</tr>
<tr>
<td></td>
<td>Kaijser et al.</td>
<td>84.0</td>
<td>80.0</td>
</tr>
<tr>
<td>RMI</td>
<td>Karlsen et al.</td>
<td>94.4</td>
<td>81.5</td>
</tr>
<tr>
<td></td>
<td>Håkansson et al.</td>
<td>92</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>Moore et al.</td>
<td>84.6</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Van den Akker</td>
<td>81</td>
<td>85</td>
</tr>
<tr>
<td>OVA1</td>
<td>Bristow et al.</td>
<td>92.4</td>
<td>53.5</td>
</tr>
<tr>
<td></td>
<td>Longoria et al.</td>
<td>92.2</td>
<td>49.4</td>
</tr>
<tr>
<td>OVA1 + Clinical Assessment</td>
<td>Bristow et al.</td>
<td>95.7</td>
<td>50.7</td>
</tr>
<tr>
<td></td>
<td>Longoria et al.</td>
<td>95.3</td>
<td>44.2</td>
</tr>
<tr>
<td>Serum Marker(s)</td>
<td>Study</td>
<td>Sensitivity (%)</td>
<td>Specificity (%)</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>CA-125</td>
<td>*Karlsen et al.</td>
<td>91.7</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>*Chan et al.</td>
<td>90.8</td>
<td>67.2</td>
</tr>
<tr>
<td></td>
<td>*Leung et al.</td>
<td>89</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>*Sandri et al.</td>
<td>84.4</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>*Montagnana et al.</td>
<td>83</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>*Sandri et al.</td>
<td>73.1</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Yang et al.</td>
<td>62.5</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Havrilesky et al.</td>
<td>45.9-58.5</td>
<td>98.2</td>
</tr>
<tr>
<td></td>
<td>*Moore et al.</td>
<td>43.3</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Jacob et al.</td>
<td>12.5</td>
<td>90.1-93.9</td>
</tr>
<tr>
<td>HE-4</td>
<td>*Montagnana et al.</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Yang et al.</td>
<td>96.2</td>
<td>83.8</td>
</tr>
<tr>
<td></td>
<td>*Karlsen et al.</td>
<td>91.3</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>*Sandri et al.</td>
<td>83.1</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Havrilesky et al.</td>
<td>82.7-92.5</td>
<td>86.3</td>
</tr>
<tr>
<td>CA-125, HE-4</td>
<td>*Moore et al.</td>
<td>72.9</td>
<td>95</td>
</tr>
<tr>
<td>CA-125, leptin, PRL, OPN, IGFII, MIF</td>
<td>Visintin et al.</td>
<td>95.3</td>
<td>99.4</td>
</tr>
<tr>
<td>CA 125, CRP, SAA, IL-6, IL-8</td>
<td>Edgell et al.</td>
<td>94.1</td>
<td>91.3</td>
</tr>
<tr>
<td>CA-125, apoA-I, TTR, TF</td>
<td>Su et al.</td>
<td>89-97</td>
<td>91-99</td>
</tr>
<tr>
<td>CA 125, HE4, CEA, VCAM-1</td>
<td>Yurkovetsky et al.</td>
<td>86–93</td>
<td>98</td>
</tr>
<tr>
<td>CA 125, ApoA1, TTR</td>
<td>Kim et al.</td>
<td>93.9</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Zhang et al.</td>
<td>74</td>
<td>97</td>
</tr>
<tr>
<td>CA 125, CA 19-9, EGFR, CRP, myoglobin, ApoA1, ApoCIII, MIP-1α, IL-6, IL-18, tenascin C</td>
<td>*Amonkar et al.</td>
<td>91.3</td>
<td>88.5</td>
</tr>
</tbody>
</table>

*Study involved patients presenting with a pelvic mass
Considerations

- With all of these tests is the ultimate need to demonstrate benefit for patients through reduction in morbidity and mortality while minimizing harm.

- The advancements of technology combined with our exponentially growing knowledge of the human “–omes” have outpaced our ability to reliably test these discoveries through clinical settings in a timely fashion.
Areas of Growth in Biomarker Discovery

Genome → DNA

Transcriptome ← RNA

Proteome ← Proteins

Metabolome ← Sugars → Nucleotides → Amino acids → Lipids (Lipidome) → Metabolites

Phenotype/Function
Proteomics has not become the panacea we thought it would be

- sample choice
- reproducibility
Mass Spectrometry

- Glycomics
- Proteomics
- Metabolomics
- Autoantibody signatures
- MALDI-MS imaging
MicroRNA in Biomarker Discovery

Cheng, L et al. (2013)
Point-of-care diagnostics for noncommunicable diseases using synthetic urinary biomarkers and paper microfluidics

Andrew D. Warren\textsuperscript{a,b,1}, Gabriel A. Kwong\textsuperscript{a,b,1}, David K. Wood\textsuperscript{c,1}, Kevin Y. Lin\textsuperscript{b,d}, and Sangeeta N. Bhatia\textsuperscript{a,b,e,f,g,h,2}

\textsuperscript{a}Harvard-Massachusetts Institute of Technology Division of Health Sciences and Technology, Institute for Medical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139; \textsuperscript{b}David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA 02139; \textsuperscript{c}Department of Biomedical Engineering, University of Minnesota, Minneapolis, MN 55455; \textsuperscript{d}Chemical Engineering Technology, Cambridge, MA 02139; \textsuperscript{e}Electrical Engineering and Computer Science, Massachusetts Institute of Technology; \textsuperscript{f}Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA 02115; \textsuperscript{g}Broad Inst of Technology and Harvard, Cambridge, MA 02139; and \textsuperscript{h}Howard Hughes Medical Institute, Cambridge, MA 02139

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With noncommunicable diseases (NCs) now constituting the majority of global mortality, there is a growing need for low-cost, noninvasive methods to diagnose and treat this class of diseases, which significantly limits the types of NC POC (5–7).
Imaging

- A systematic approach to the diagnosis of ovarian tumors with imaging is necessary given the majority of women have benign lesions, and unnecessary interventions should be avoided.

- Available imaging modalities include ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET).

UKOCS Trial

- Single arm prospective screening cohort, asymptomatic women 25 years or older with a documented family history of ovarian cancer and asymptomatic women 50 years or older were screened with annual transvaginal ultrasound.

- Many ovarian abnormalities resolved in follow up: 63.2% of women with an initially abnormal ultrasound were found to have resolution on subsequent imaging.

- Of 37,293 women who underwent annual screening the five-year disease-free survival rate for women who developed ovarian cancer, including those who developed ovarian cancer within one year of a normal ultrasound (false negative) was 74.8% ± 6.6%, compared with 53.7% ± 2.3% for a group of unscreened women, p-value<0.01.

  Pavlik, E J, et al. (2013)
  van Nagell, J R, et al. (2011)
Trials Testing Clinical Screening Strategies in the Setting of a Pelvic Mass

<table>
<thead>
<tr>
<th>Algorithm or Assay</th>
<th>How It Works</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Screening Population)</td>
<td></td>
</tr>
</tbody>
</table>
| **LR-1** (known pelvic mass) | • An ultrasound-based prediction model  
• 12 variables are used to calculate a probability of malignancy:  
  ✓ 1. personal history of ovarian cancer  
  ✓ 2. current hormonal therapy  
  ✓ 3. age of the patient  
  ✓ 4. maximum diameter of the lesion  
  ✓ 5. pain during examination  
  ✓ 6. ascites  
  ✓ 7. blood flow within a solid papillary projection  
  ✓ 8. a purely solid tumor  
  ✓ 9. maximum diameter of the solid component  
  ✓ 10. irregular internal cyst walls  
  ✓ 11. acoustic shadows  
  ✓ 12. color score |
| **LR-2** (known pelvic mass) | • An ultrasound-based prediction model  
• Uses six variables to calculate a probability of malignancy:  
  ✓ 1. patient’s age  
  ✓ 2. presence of ascites  
  ✓ 3. presence of blood flow within a papillary projection  
  ✓ 4. maximal diameter of solid components  
  ✓ 5. irregular internal cyst walls  
  ✓ 6. presence of acoustic shadows |
Is Imaging the Answer?

- Currently no prospective randomized studies support the use of imaging as a single strategy in screening for ovarian cancer.

- In asymptomatic postmenopausal women, the ultrasound screening arm results of the UKCTOCS expected in 2015 will help elucidate the role of ultrasound in population-based screening strategies.

- At this time is it unlikely ultrasound will significantly reduce mortality in primary screening, but it may be extremely important in reducing false positive rates in multimodality screening.

Campbell, S, et al. (2012)
Symptom Based Screening

SYMPTOMS OF OVARIAN CANCER

If any of these symptoms last for more than two weeks or are unusual for you, please see your doctor:

- Bloating
- Feeling full quickly while eating
- Pelvic or abdominal pain
- Urinary urgency or frequency or changes in bowel habits
- Abnormal vaginal bleeding or discharge
- Back pain
Is Symptom Based Screening the Answer?

- In a case-control study comparing woman with ovarian cancer to age and race matched controls, more than 90% of cases reported at least one symptom and symptoms were cited as the most common reason for the doctor visit leading to diagnosis (74%).

- A symptom index was created with a sensitivity of 56.7% for early stage disease and 79.5% for advanced stage disease, and a specificity of 90% for women greater than 50 years of age and 86.7% for women less than 50 years of age.

- At this time, given no effective screening tool has been proven in a prospective model, physicians should continue to discuss potential symptoms with their patients in an effort to increase self-awareness regarding warning signs for ovarian cancer.

Goff, B A, et al. (2007)
Multimodality Screening
The PLCO Screening Trial

- 78,216 asymptomatic women aged 55 to 74 years underwent multimodality screening (transvaginal US/CA125) or usual care between November 1993 and July 2001 with management of positive screens left to the discretion of the patient’s physician.

- After four rounds the PPV per 10,000 women in the multimodality screening arm remained similar across screening rounds at 1.0 to 1.3% with the overall ratio of surgeries to screen detected cancers 19.5 to 1.

- After a median follow up of 12.4 years, no mortality benefit was found with combination transvaginal ultrasound and CA125 using an absolute cutoff: 118 deaths due to ovarian cancer (3.1 per 10,000 person-years) in the intervention group and 100 deaths (2.6 per 10,000 person-years) in the usual care group (mortality rate ratio, 1.18; 95% CI, 0.82-1.71).

Partridge, E, et al. (2009)
Buys, S, et al. (2011)
Shizuoka Cohort Study

- 82,487 low risk postmenopausal women between 1985 and 1999 with the intervention arm consisting of annual ultrasound and CA125 with a cutoff value.

- The strategy achieved a sensitivity of 77.1% and specificity of 99.9% with a nonsignificant difference in the proportion of stage I ovarian cancers identified, 63% in the screened group versus 38% in the control group, p-value=0.2285

- Mortality results from this trial have not yet been published and, as such, conclusions cannot be drawn from this trial regarding the benefit of screening in an asymptomatic population.

Partridge, E, et al. (2009)
Buys, S, et al. (2011)
United Kingdom Collaborative Trial of Ovarian Cancer Screening

Postmenopausal women 50-74 years (n=200 000)

Multimodal group
Annual CA125-ROCA (n=50 000)

Ultrasound group
Annual TVS (n=50 000)

Control group (n=100 000)

Screening until 31 December 2011; 7-11 annual screens

Primary end point: ovarian cancer mortality by 31 December 2014

All women followed up through Office for National Statistics (England and Wales)/Cancer Registry and Central Services Agency (Northern Ireland) as well as postal questionnaires

Menon, U, et al. (2008)
2-Stage Ovarian Cancer Screening Strategy Using ROCA

- Single-arm prospective cohort study of 4,051 average-risk postmenopausal women in the United States was performed over 11 years.

- Use of a two-stage ovarian cancer screening strategy (CA125 interpreted through ROCA with subsequent repeat CA125 or transvaginal ultrasound as indicated).

- PPV of 40% for invasive ovarian cancer.

- Specificity of 99.9% (95% CI, 99.7 to 100%).

Lu, K H, et al. (2013)
In its prevalence screen, the UKCTOCS multimodality arm (89.4% versus 51.7%) and the ultrasound arm (75.0% versus 67.4%) had higher sensitivities compared to the PLCO Screening Trial.

When CA125 values were retrospectively evaluated with ROCA within the PLCO data set no mortality benefit was seen.

Concerns for PLCO study:
- use of an absolute cutoff value for CA125
- management of positive screens left to the treating physician
- 40.6% of ovarian cancer diagnosis took place after the screening ended

Menon, U, et al. (2012)
Pinsky, P F, et al. (2013)
Menon, U, et al. (2011)
Familial genetic predisposition makes up approximately 10% of ovarian cancers with germline mutations in *BRCA1*/*BRCA2* and mismatch repair (MMR) genes in Lynch syndrome being the most common.

Staples, J, et al. (2013)
A systematic review and meta-analysis of available screening trials involving asymptomatic women found no reduction in ovarian cancer-specific or all-cause mortality (relative risk = 1.08, 95% CI, 0.84 to 1.38 and 1.0, 95% CI, 0.84 – 1.38 respectively).

In the PLCO trial 1,080 women underwent surgery in the setting of false positive results and 163 (15%) experienced a complication.

The goal of ovarian cancer screening is to demonstrate a mortality benefit in the studied population. This mortality benefit must be considered in the context of the number needed to treat to reach such a benefit.

Reade, C J, et al. (2013)
Buys, S, et al. (2011)
For women with Hereditary Breast/Ovarian Cancer Syndrome who have not undergone risk reducing BSO the NCCN recommends:

- screening with transvaginal ultrasound and CA125 every 6 months starting at age 30 or 5 to 10 years prior to the earliest age at diagnosis of ovarian cancer in relatives

The FOCSS phase II results and GOG 199 will provide evidence regarding potential screening benefits and assist with strategy optimization.

Currently, no prospective studies exist which demonstrate a mortality benefit by screening high risk asymptomatic patients.

NCCN Guidelines Version 4.2013
- PRoBE mandates samples are collected prospectively, stored in a similar fashion, and once outcome status is defined, used to validate biomarkers in a blinded fashion with randomly selected cases and controls.

- Given the low prevalence of ovarian cancer in the general population, pooling of resources is necessary to make advances in biomarker discovery.
Large scale collection of samples prospectively in asymptomatic women
Current Consensus

Ovarian cancer screening in the asymptomatic general population results in potential harms without proven benefit at this time.

Guidelines from the American College of Obstetrics and Gynecology, the Society of Gynecologic Oncologists, the United States Preventive Services Task Force, and the American Cancer Society do not recommend screening for ovarian cancer in asymptomatic low-risk women in the general population.
Don’t screen low risk women with CA-125 or ultrasound for ovarian cancer.

CA-125 and ultrasound in low risk, asymptomatic women have not led to diagnosis of ovarian cancer in earlier stages of disease or reduced ovarian cancer mortality. False positive results of either test can lead to unnecessary procedures which have risks of complication.
Future Considerations

- Focus on the identification of the origins of groups of tumors that have been called “epithelial ovarian cancer”
  - (ie STICs as a precursor lesion for serous tumors)

- Biomarker panels and multimodality screening may achieve better sensitivity and specificity with screening strategies based on differences in both cell origin and genetics among these varied tumors

- Better understanding of time course (different for type 1 vs type 2)
Attainable Goal

Success.
Thank you

UCLA Gynecologic Oncology

- Robin Farias-Eisner MD
- Matt White BS
- Ana Cruz MS

Cedars-Sinai
Women’s Cancer Program

- Beth Karlan MD
- Christine Walsh MD
- Ilana Cass MD
- Andy Li MD
- BJ Rimel MD
- Ron Leuchter MD

- Dept of OB/GYN
- Dr. Kilpatrick
Ovarian Cancer Awareness

It Whispers... So Listen!