Screening for Ovarian Cancer: Are We Doing This Now?

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Disclosure

• I have no relevant financial relationships with commercial interests that create any conflicts of interest
Objectives

1. Discuss characteristics of good screening tests
2. Review the current evidence with regard to ovarian cancer screening
3. Discuss the findings and implications of UKCTOCS and its relevance to current practice
**Important Note**

- This presentation addresses the AVERAGE RISK woman

- Women at elevated risk for ovarian cancer (BRCA 1/2, other proven genes) are outside the scope of presented trials and USPSTF and society statements
  - Consider q6 month TVUS + CA-125
  - Risk-reducing BSO
  - Awaiting mature results from UKFOCCS trial

www.nccn.org
Population-Based Screening

• Goals of population based screening:
  • Reduce number of deaths
  • Increase life expectancy
    • Ovarian cancer mortality rate
  • Stage I 90% 5 year survival
  • Stage III or IV 30% 5 year survival

• Before a screening program is implemented, its impact on ovarian cancer mortality must be confirmed
Attributes of Good Screening Test

1. Disease has a presymptomatic stage in which treatment is more effective (vs symptomatic stage)
   - Early stage OC may be present for >4yrs before advanced stage dx
2. Screening procedures available and acceptable to patients
3. Reasonable cost
4. High sensitivity: Detects a significant fraction of all existing cases in the population
   - But OC low prevalence in the target population
5. High specificity: Avoids generating an excessive number of false-positive screens
   - In OC, evaluation of an abnormal screen includes an invasive surgical procedure

Ovarian Cancer Assessment Tools

- Pelvic exam
- CA-125
- Risk of Ovarian Cancer Algorithm (ROCA)
- Transvaginal Ultrasound
Pelvic Examination

- Bimanual examinations do not lead to early detection of ovarian cancer
  - Insensitive and does not result in significant shift to earlier-stage OC detection

CA-125 alone

- Early prospective trial: high enough specificity to study further (98.5% for postmenopausal women)
- Lacks sensitivity for early stage OC
  - Elevated in only ~50% of women with early stage OC
- Elevated in other cancers and various nonmalignant conditions (i.e. liver disease and heart failure)

References:
Risk of Ovarian Cancer Algorithm (ROCA)

- Differential longitudinal behavior in CA-125 instead of single values
  - Women without OC have less longitudinal variation
  - Built on statistical models of OC cases vs all other women

- Risk calculation (final odds) = initial odds x odds ratio
  - Initial odds: risk based on the woman’s age as derived from population tumor registries multiplied by two years, the estimated average duration of pre-clinical ovarian cancer

Transvaginal Ultrasound

• Generally associated with high rate of false-positive screens
  • Large number of surgical procedures that do not identify OC
• Used in prior studies as initial and secondary screening exam
• Various US-based prediction models
  • Morphology index, index including CA-125, risk of malignancy index (RMI; menopausal status + US), and more advanced math models using logistic regression, neural networks, etc.

## Morphology Index

<table>
<thead>
<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>Benign simple cyst</td>
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<td>1</td>
<td>Benign hemorrhagic cyst</td>
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<tr>
<td>2</td>
<td>Benign cyst with septation(s)</td>
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<td>3</td>
<td>Malignancy with papillary projections</td>
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<tr>
<td>4</td>
<td>Malignancy with solid components</td>
</tr>
<tr>
<td>5</td>
<td>Solid malignancy with ascites</td>
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</table>

Multimodality Screening

Published RCTs in Average Risk Women:

1. Shizuoka Cohort Study of Ovarian Cancer Screening
2. PLCO (Prostate Lung Colorectal Ovarian) Cancer Screening Trial
3. UKCTOCS (United Kingdom Collaborative Trial of Ovarian Cancer Screening)
Shizuoka Cohort Study of Ovarian Cancer Screening Trial

• Prospective randomized trial (1985-1999)
• 41,688 asymptomatic post menopausal women
• Screening arm (annual pelvic exam, TVUS and CA-125) vs control
  • TVUS screen positive: malignant impression, > 4 cm
  • Management at discretion of oncologist
• Detection rates of OC 0.31 per 1000 at prevalent screen and 0.38–0.74 per 1000 at subsequent screens
  • Increased with successive screening rounds
• Screening associated with increase in stage 1 (63% vs 38%)- not statistically significant
• Mortality results pending

PLCO (Prostate Lung Colorectal Ovarian)

- RCT: To determine whether annual screening with CA-125 and TVUS can reduce mortality from OC

Screening Results—PLCO

• **TVUS**
  - 71% of OC detected by TVUS alone were stage I-II. May preferentially detect low grade/stage tumors
  - Abn screen resulted in surgery in 40%
  - Ratio of surgeries to neoplasms detected 24:1

• **CA-125**
  - Abn screen resulted in surgery in 15.4%
  - Ratio of surgeries to neoplasms detected 4:1

• **Multimodality screening**
  - If only choose to evaluate subjects in which both are abnormal, wound miss 70% neoplasms and 60% cancers
  - Ratio of surgeries to neoplasms detected 3:1

Screening Results—PLCO

- Follow-up diagnostic procedures
  - 570 underwent surgical procedure
    - 325 laparotomy/245 laparoscopy
    - 541 (32.3%) had surgery and did not have LMP or cancer

Mortality—PLCO

- 118 deaths caused by OC in the intervention group and 100 deaths in the usual care group
  - (mortality RR, 1.18; 95% CI, 0.82-1.71)

Conclusion: No benefit of screening for ovarian cancer in PLCO

• Screening
  • 1 neoplasm diagnosed for every 994 screens
  • 1 cancer diagnosed for every 1517 screens
  • Ratio of surgeries to screen detected OC 20:1

• Final conclusions
  • No evidence of a shift to earlier stage disease with screening
  • MMS did not reduce OC mortality compared with usual care

Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial

Multicenter Randomized Controlled Trial

Inclusion Criteria:

• Postmenopausal women
• Age 50-74
• 13 centers in National Health Service Trusts
  • England
  • Wales
  • Northern Ireland

Exclusion Criteria:

• Previous bilateral oophorectomy
• Previous ovarian malignancy
• Increase risk of familial ovarian cancer
• Active non-ovarian malignancy

Methods—UKCTOCS

- Multimodality screening (MMS) group
  - Annual CA-125- pattern over time interpreted by ROCA
    - ROCA triaging
      - Normal- annual screening
      - Intermediate- Repeat CA-125 in 3 months
      - Elevated- Repeat CA-125 and TVUS in 6 weeks

- Ultrasound screening (USS) group
  - Annual TVUS
    - Normal- annual screening
    - Unsatisfactory- repeat in 3 months
    - Abnormal- scan with senior US in 6 weeks

- Both groups:
  - Clinical assessment for abnormalities and additional investigations by trial physician

Outcomes—UKCTOCS

- Primary outcome*
  - Ovarian cancer death
    - OC defined as
      - Non-EOC
      - Borderline EOC
      - Invasive EOC
      - FT cancer
      - Undesignated malignancies of the ovaries, FT, peritoneum

- Secondary outcome
  - Death due to OC + PPC
  - Compliance with screening
  - Complications related to screening and false positive surgery

* does not include PPC

6/1/2001-10/21/2005

134,328 women assessed for eligibility
103,819 ineligible
78,225 self-reported as not meeting inclusion criteria
17,149 declined to participate
77,762 did not respond
10,192 not recruited because target reached

305,990 enrolled
2452 excluded
1,402 did not meet inclusion criteria
1,050 declined to participate

202,638 randomised

101,359 assigned no screening
50,639 assigned USS
50,640 assigned MMS

2389 were not screened
28 died
27 ovaries removed
2334 declined intervention

60 excluded*
42 oophorectomy before recruitment
18 exited registry before recruitment

16 excluded*
12 oophorectomy before recruitment
2 ovarian cancer diagnosed before randomisation
2 exited registry before recruitment

557 were not screened
2 died
5 ovaries removed
550 declined

16 excluded*
11 oophorectomy before recruitment
2 ovarian cancer diagnosed before randomisation
3 exited registry before recruitment

101,299 included in primary analysis
50,623 included in primary analysis
50,624 included in primary analysis

1,150 incomplete follow-up
3 declined flagging with national registries
1,147 exited registry before Dec 31, 2014

563 incomplete follow-up
2 declined flagging with national registries
561 exited registry before Dec 31, 2014

540 incomplete follow-up
1 declined flagging with national registries
539 exited registry before Dec 31, 2014

100,149 complete follow-up
50,060 complete follow-up
50,084 complete follow-up
<table>
<thead>
<tr>
<th></th>
<th>MMS (n=50624)</th>
<th>USS (n=50623)</th>
<th>No screening (n=101299)*</th>
<th>Overall (n=202546)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at randomisation (years)</td>
<td>60.61 (56.03-66.15)</td>
<td>60.61 (55.99-66.15)</td>
<td>60.58 (55.97-66.15)</td>
<td>60.59 (55.99-66.15)</td>
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<tr>
<td>Time since last period at randomisation (years)</td>
<td>11.36 (5.26-18.49)</td>
<td>11.34 (5.24-18.46)</td>
<td>11.26 (5.22-18.46)</td>
<td>11.3 (5.23-18.47)</td>
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<tr>
<td>Duration of HRT use in those who were on HRT at randomisation (years)</td>
<td>8.09 (4.56-11.99)</td>
<td>8.15 (4.55-12.11)</td>
<td>8.17 (4.5-12.09)</td>
<td>8.15 (4.53-12.07)</td>
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<tr>
<td>Duration of OCP use in those who had used it (years)</td>
<td>5 (2-10)</td>
<td>5 (2-10)</td>
<td>5 (2-10)</td>
<td>5 (2-10)</td>
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<tr>
<td>Pregnancies &lt;6 months</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
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<tr>
<td>Children (pregnancies &gt;6 months)</td>
<td>2 (2-3)</td>
<td>2 (2-3)</td>
<td>2 (2-3)</td>
<td>2 (2-3)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.6 (157.5-165.1)</td>
<td>162.6 (157.5-165.1)</td>
<td>162.6 (157.5-165.1)</td>
<td>162.6 (157.5-165.1)</td>
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<tr>
<td>Weight (kg)</td>
<td>67.6 (60.3-76.2)</td>
<td>67.6 (60.3-76.2)</td>
<td>67.6 (60.3-76.2)</td>
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<tr>
<td><strong>Ethnic origin</strong></td>
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<tr>
<td>White</td>
<td>48845 (96.5%)</td>
<td>48749 (96.3%)</td>
<td>97598 (96.3%)</td>
<td>195192 (96.4%)</td>
</tr>
<tr>
<td>Black</td>
<td>670 (1.3%)</td>
<td>717 (1.4%)</td>
<td>1377 (1.4%)</td>
<td>2764 (1.4%)</td>
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<tr>
<td>Asian</td>
<td>442 (0.9%)</td>
<td>477 (0.9%)</td>
<td>936 (0.9%)</td>
<td>1855 (0.9%)</td>
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<tr>
<td>Other</td>
<td>428 (0.8%)</td>
<td>424 (0.8%)</td>
<td>839 (0.8%)</td>
<td>1691 (0.8%)</td>
</tr>
<tr>
<td>Missing</td>
<td>239 (0.5%)</td>
<td>256 (0.5%)</td>
<td>549 (0.5%)</td>
<td>1044 (0.5%)</td>
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<tr>
<td>Hysterectomy</td>
<td>9680 (19.1%)</td>
<td>9496 (18.8%)</td>
<td>18990 (18.7%)</td>
<td>38166 (18.8%)</td>
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<tr>
<td>Ever use of OCP</td>
<td>30098 (59.5%)</td>
<td>30308 (59.9%)</td>
<td>60284 (59.5%)</td>
<td>120690 (59.6%)</td>
</tr>
<tr>
<td>Use of HRT at recruitment</td>
<td>9457 (18.7%)</td>
<td>9383 (18.5%)</td>
<td>19150 (18.9%)</td>
<td>37990 (18.8%)</td>
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<tr>
<td>Personal history of cancer</td>
<td>2973 (5.9%)</td>
<td>2974 (5.9%)</td>
<td>6105 (6.0%)</td>
<td>12052 (6.0%)</td>
</tr>
<tr>
<td>Personal history of breast cancer</td>
<td>1848 (3.7%)</td>
<td>1891 (3.7%)</td>
<td>3912 (3.9%)</td>
<td>7651 (3.8%)</td>
</tr>
<tr>
<td>Maternal history of ovarian cancer</td>
<td>802 (1.6%)</td>
<td>778 (1.5%)</td>
<td>1579 (1.6%)</td>
<td>3159 (1.6%)</td>
</tr>
<tr>
<td>Maternal history of breast cancer</td>
<td>3159 (6.2%)</td>
<td>3206 (6.3%)</td>
<td>6619 (6.5%)</td>
<td>12984 (6.4%)</td>
</tr>
</tbody>
</table>

Data are n (%) or median (IQR). MMS = multimodal screening. USS = ultrasound screening. HRT = hormone replacement therapy. OCP = oral contraceptive pill. *One woman asked for all her details to be removed. †Includes those with personal history of breast cancer.

Table 1: Baseline characteristics

Results—UKCTOCS

• 1282 confirmed OCs

• Overall sensitivity
  • MMS 84%
  • USS 73%

• Higher number of EOC and PPC with low-volume disease (stage I, II, IIIA) in MMS group vs no screening (119 [40%] of 299; p<0.0001)
  • Not in the USS group (62 [24%] of 259; p=0.57)

### Table 3: Summary of analyses of relative reduction of ovarian and primary peritoneal cancer deaths

<table>
<thead>
<tr>
<th></th>
<th>Number of women (n)</th>
<th>Deaths (n)</th>
<th>Mortality reduction 0-14 years (%)</th>
<th>p value</th>
<th>Mortality reduction 0-7 years (%)</th>
<th>Mortality reduction 7-14 years (%)</th>
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</thead>
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<tr>
<td><strong>Ovarian cancer (primary analysis)</strong></td>
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<td>Cox model</td>
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<tr>
<td>MMSc</td>
<td>50,624</td>
<td>148</td>
<td>15% (3-30)</td>
<td>0.10</td>
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<tr>
<td>USS</td>
<td>50,623</td>
<td>154</td>
<td>11% (7-27)</td>
<td>0.21</td>
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<td></td>
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<tr>
<td>No screening</td>
<td>101,299</td>
<td>347</td>
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<tr>
<td>Royston-Parmar model</td>
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</tr>
<tr>
<td>MMSc</td>
<td>50,624</td>
<td>148</td>
<td>16% (-1 to 33)</td>
<td>0.11</td>
<td>8% (-20 to 21)</td>
<td>23% (11 to 46)</td>
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<tr>
<td>USS</td>
<td>50,623</td>
<td>154</td>
<td>12% (-6 to 29)</td>
<td>0.18</td>
<td>2% (-27 to 26)</td>
<td>21% (-2 to 42)</td>
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<td>101,299</td>
<td>347</td>
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<tr>
<td>Royston-Parmar model (excluding prevalent cases)</td>
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<tr>
<td>MMSc</td>
<td>50,561</td>
<td>120</td>
<td>20% (-2 to 40)</td>
<td>0.021</td>
<td>8% (-77 to 42)</td>
<td>28% (-2 to 49)</td>
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<tr>
<td>USS</td>
<td>50,623</td>
<td>154</td>
<td>20% (0 to 35)</td>
<td>0.049</td>
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<td>101,299</td>
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<tr>
<td><strong>Weighted log-rank (post-hoc)</strong></td>
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<td>MMSc</td>
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<td>22% (2 to 38)</td>
<td>0.032</td>
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<td><strong>Ovarian and primary peritoneal cancer (secondary analysis)</strong></td>
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<td></td>
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<tr>
<td>USS</td>
<td>50,623</td>
<td>163</td>
<td>9% (-9 to 24)</td>
<td>0.21</td>
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<tr>
<td>No screening</td>
<td>101,299</td>
<td>358</td>
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<tr>
<td>Royston-Parmar model</td>
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<td>MMSc</td>
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<td>11% (-7 to 28)</td>
<td>0.15</td>
<td>4% (-25 to 27)</td>
<td>18% (-5 to 40)</td>
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<td>17% (-3 to 33)</td>
<td>0.097</td>
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<td>358</td>
<td></td>
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</tr>
</tbody>
</table>

Data in parentheses are 95% CIs. MMSc = multimodal screening, USS = ultrasound screening. *Mortality reduction from hazard ratio weighted by pooled cumulative ovarian cancer mortality.

Original Planned Analyses

No difference with original planned analysis


Excluding PPCs

Ovarian cancer deaths

Ovarian + PPC deaths
• No screening group HR continues to rise throughout the study period
• MMS and USS group HRs starts levelling off
  • However, substantially lower than the no screening group at around 7 years

Cumulative death rates after exclusion of prevalent cases

- OC mortality 20% lower in MMS group vs no screening

- Similarly, mortality reduction higher in years 7-14 (28%) than in years 0-7 (8%)

Results—UKCTOCS

• Compliance
  • 80.8% in MMS (345,570/427,448 attended)
  • 78.0% in USS (327,775/420,047 attended)

• Number needed to screen to prevent 1 death from OC was 641 (95% CI, 375–1934)

• Sensitivity analyses show no differences

• False-positive surgeries per 10,000 screens
  • 14 in MMS
  • 50 in USS

• Overall ratio of surgery showing benign or normal to malignant pathology
  • 1.2 in no screening
  • 2.7 in MMS
  • 6.4 in USS

Final Conclusions—UKCTOCS

• Multimodal approach to screening might detect ovarian cancer sufficiently early to reduce mortality

• Further follow-up needed to assess extent of mortality reduction before firm conclusions can be reached on long-term efficacy and cost-effectiveness of OC screening

The ROCA Test

- Released shortly after Lancet publication (2015)
- UKCTOCS investigators’ company
- Not FDA approved – FDA warning issued 9/7/16
  - “especially concerned about delaying effective preventative treatments for women who show no symptoms, but who are still at increased risk of ovarian cancer”
- FDA move praised by Ovarian Cancer Research Fund Alliance
- Advertising doesn’t reflect UKCTOCS findings

Is the ROCA Test Right for You?

You may be eligible for the ROCA Test if you are between 50 and 85 years old and have been through menopause, or are between 35 and 85 years old with a family history of ovarian and/or breast cancer, are of Ashkenazi Jewish descent with a known family history of ovarian or breast cancer, or have tested positive for BRCA1, BRCA2 or Lynch syndrome gene mutation.

FIND OUT IF YOU MAY BE ELIGIBLE
Final Research Plan

Final Research Plan for Ovarian Cancer: Screening

Recommendations made by the USPSTF are independent of the U.S. government. They should not be construed as an official position of the Agency for Healthcare Research and Quality of the U.S. Department of Health and Human Services.

The final Research Plan will be used to guide a systematic review of the evidence by researchers at an Evidence-based Practice Center. The resulting Evidence Review will form the basis of the USPSTF Recommendation Statement on this topic.

The draft Research Plan was available for comment from March 26 until April 22, 2015 at 5:00 p.m., ET.

Analytic Framework

Ovarian cancer screening

Key Questions to Be Systematically Reviewed

1. Does screening for ovarian cancer in asymptomatic women using a single test or combined algorithm (such as, but not limited to, testing for serum cancer antigen (CA)-125 and ultrasonography) reduce all-cause or disease-specific morbidity and mortality?
2. What are the harms of screening for ovarian cancer, including harms of the screening test and of diagnostic evaluation?

Contextual Questions

1. Is there trial evidence that the stage or type of ovarian cancer diagnosed through screening contributes to reduced all-cause or disease-specific morbidity and mortality?
2. Are there new screening approaches for detecting ovarian cancer that have better yield or accuracy than those evaluated in trials?
No current benefit in screening the asymptomatic, average risk woman

- US Preventative Services Task Force
- ACOG
- NCCN
- National Cancer Institute
- Canadian Task Force on the Periodic Health Exam
- National Breast and Ovarian Cancer Centre
- American Task Force
- Australian Society of Gynaecology Oncologists
- RANZCOG
- RCOG
Questions?