Ovarian Cancer Screening: The Time is Now

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Objectives
- Review epidemiology of ovarian cancer
- Discuss new concepts of classification and origin of ovarian cancer
- Review recent screening studies
- Present model for current and future screening of ovarian cancer

Current Status

US Preventive Services Task Force, Sept 2012 – Annals of Internal Medicine

Breast Cancer

Year 2014
- 235,030 new cases
- 40,430 deaths (17%)

Cancer Statistics- 2014

Ovarian Cancer

Year 2014
- 21,980 new cases
- 14,270 deaths (65%)*

*: (64 % in Europe)
Ovarian Cancer

**Risk Factors**

- Advancing age
- Family history of cancer
- Nulliparity / late childbearing

**Advancing Age**

- Rate is ~ 8 / 100,000 if younger than 65 years
- Rate is ~ 47 / 100,000 if 65 years or older

Ovarian Cancer

**Syndromes**

- Site-Specific Ovarian Cancer (SSOC)
- Breast & Ovarian Cancer (BOC)
- Hereditary Non-Polyposis Colorectal Cancer (HNPCC)

( < 10% of Ovarian CA cases)

Ovarian Cancer Genetics

Walsh et al. PNAS. 2011;108:18032-18037.

Ovarian Cancer

Not a silent disease, symptoms common in early stages

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Olson et al. 2007 All Stages (95% CI)</th>
<th>Olson et al. 2007 Early Stages (95% CI)</th>
<th>Goff et al. 2008 All Stages (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty eating/tack of appetite</td>
<td>8.8 (4.3-18.2)</td>
<td>6.0 (3.7-9.7)</td>
<td>3.4 (2.6-4.4)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3.5 (2.0-6.3)</td>
<td>1.6 (1.0-2.4)</td>
<td>3.5 (2.0-6.3)</td>
</tr>
<tr>
<td>Urinary symptoms</td>
<td>6.2 (4.0-9.6)</td>
<td>3.5 (2.0-6.3)</td>
<td>3.5 (2.0-6.3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1.4 (0.7-2.7)</td>
<td>3.5 (2.0-6.3)</td>
<td>3.5 (2.0-6.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.4 (0.7-2.7)</td>
<td>3.5 (2.0-6.3)</td>
<td>3.5 (2.0-6.3)</td>
</tr>
</tbody>
</table>

Ovarian Cancer

**Pathologic Types**

- High-Grade Serous (HGSC) – 70%
- Endometrioid (EC) – 10%
- Clear Cell (CCC) – 10%
- Mucinous (MC) – 3%
- Low-Grade Serous (LGSC) - <5%

Post - Annals of Oncology 23 (Supplement 10): x111-x117, 2012

Ovarian Cancer

Pathologic Types

**Origin of Ovarian Cancer**

From: Chan et al. Obstet Gynecol 2012;120:935-40

Prevention of Ovarian Cancer

- Hysterectomy: 600,000 / year in US
- Tubal ligations: 700,000 / year in US
- Recommending salpingectomy, may significantly reduce HGSC


Prevention of Ovarian Cancer

Canadian Society of Gynecologic Oncology (2011):
Recommended that bilateral salpingectomy at the time of hysterectomy should be discussed and considered for the prevention of ovarian Cancer.

http://www.g-o-c.org/uploads/11sept15_goc_evidentiary_statement_final_en.pdf...

High Risk Women

BRCA Positive

- Standard recommendation is BSO at age 40
- BSO reduces risk of ovarian ca by 80-90%
- Only 60 % of HR women chose BSO


Biomarkers of Ovarian Cancer

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Expression changes</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>The early association</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA125</td>
<td>Increase</td>
<td>62-90%</td>
<td>66-90%</td>
<td>3 years before diagnosis</td>
</tr>
<tr>
<td>HE4</td>
<td>Increase</td>
<td>72-74%–94%</td>
<td>82-95%</td>
<td>3 years before diagnosis</td>
</tr>
<tr>
<td>Microdialin</td>
<td>Increase</td>
<td>68-72%</td>
<td>85%</td>
<td>3 years before diagnosis</td>
</tr>
<tr>
<td>Osteopontin</td>
<td>Increase</td>
<td>81-93%</td>
<td>34%</td>
<td>–</td>
</tr>
<tr>
<td>Rf-144</td>
<td>Increase</td>
<td>–</td>
<td>97%</td>
<td>Late</td>
</tr>
<tr>
<td>Proteasmin</td>
<td>Increase</td>
<td>92%</td>
<td>94%</td>
<td>Late</td>
</tr>
<tr>
<td>Macrophage colony-stimulating factor</td>
<td>Increase</td>
<td>90%</td>
<td>98%</td>
<td>–</td>
</tr>
<tr>
<td>VEGF</td>
<td>Increase</td>
<td>77%</td>
<td>87%</td>
<td>–</td>
</tr>
</tbody>
</table>

* When combined use with other biomarkers

Modified from Zhang et al, Appl Biochem Biotechnol, 2012

CA-125 & Ovarian Cancer

- Use of CA-125 in premenopausal women is controversial
- ACOG does not currently recommend routine use of CA-125 in premenopausal women with pelvic mass
- ACOG include CA-125 levels of > 200 U/mL in premenopausal women
- Cut-off for postmenopausal women is 35 U/ml


CA-125 & Ovarian Cancer

The UK Collaborative Trial of Ovarian Cancer Screening showed improved detection when using ultrasound after assessing CA125 levels relative to a woman’s baseline value rather than a “standard” clinical value:

Early-stage detection was doubled (48%), and the number of operations per cancer case detected was remarkably low (4 vs 36 for ultrasound alone).

Screening for Ovarian Cancer

Ovarian Cancer

“Screening” - General Population

Screen 3030 women to detect 1 cancer

(Need for efficient method)

Ovarian Cancer

“Screening” - Postmenopausal women

- Sensitivity: > 75% to shift to Stage 1
- Specificity: > 99.6% to give a PPV of 10%

Maximum of 10 operations / cancer detected

Can we achieve screening with 10 operations/ cancer detected?

Ovarian Cancer Screening

Screening Studies

- The University of Kentucky Study
- The Japanese Shizuoka Cohort Study
- The Prostate Lung Colorectal and Ovarian
- The UK Collaborative Trial

Ovarian Cancer Screening

U/S - Kentucky Experience

Long-Term Survival of Women With Epithelial Ovarian Cancer Detected by Ultrasonographic Screening

John Remenar von Neumeyer Jr, MD, Rachel Ware Miller, MD, Christopher P. Del Simone, MD, Frederick R. Ueland, MD, Laura Polidroni, MD, Scott T. Goodnick, MD, Jeff W. Elder, MD, Bin Huang, MD, Richard J. Krysan, MD, and Edward John Paddock, MD

Obstet Gynecol 2011;118:1212–21

Ovarian Cancer

“Screening” - General Population

Screen 3030 women to detect 1 cancer

(Need for efficient method)
Ovarian Cancer Screening

U/S - Kentucky Experience

CONCLUSION: Annual ultrasonographic screening of asymptomatic women achieved increased detection of early-stage ovarian cancer cases and an increase in 5-year disease-specific survival rate for women with ovarian cancer.

(level of evidence: II)

Ovarian Cancer Screening

U/S - Kentucky Experience

- Women > 50 yrs, or > 24 yrs with family hx
- TVS (37, 293 women)
- Ovarian volume > 20 ml in premenopausal
- Ovarian volume > 10 ml in postmenopausal
- Any internal septations / projections

Ovarian Cancer Screening

Kentucky Experience

(1) Repeat U/S
(2) CA 125
(3) Tumor morphology indexing
(4) Color Doppler U/S

Ovarian Cancer Screening

Kentucky Experience

Stage | # Patients
--- | ---
1 | 22
2 | 11
3 | 14
4 | 0

Ovarian Cancer Screening

PLCO Study

Effect of Screening on Ovarian Cancer Mortality
The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial

5 year survival: 75% vs 54%
Randomized controlled of 78,216 aged 55-74
Annual screening: serum CA 125 (35 U/ml) x 6 years & US x 4 years
Routine care
Follow up for a median of 12 years

Follow up for a median of 12 years
Routine care
Annual screening: serum CA 125 (35 U/ml)

Conclusions Among women in the general US population, simultaneous screening with CA-125 and transvaginal ultrasound compared with usual care did not reduce ovarian cancer mortality. Diagnostic evaluation following a false-positive screening test result was associated with complications.

**Ovarian Cancer**

**PLCO Study**

PLCO: 19.5 surgeries / ovarian cancer detected
UK: 6.9 surgeries / ovarian cancer detected

**Ovarian Cancer Screening**

**Hirosaki Experience**

- Following pap smear, TVS (183,034 women)
- 1 minute allowed for screening (4 U/S planes)
- Secondary screening for mass > 30 mm

Cancer 2000;89:582

**Stage**

<table>
<thead>
<tr>
<th># Patients</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>11 (30%)</td>
<td>5 (13.5%)</td>
<td>16 (43%)</td>
<td>5 (13.5%)</td>
</tr>
<tr>
<td>After</td>
<td>50 (60%)</td>
<td>8 (9.4%)</td>
<td>19 (22%)</td>
<td>8 (9.4%)</td>
</tr>
</tbody>
</table>

Cancer 2000;89:582

**Ovarian Cancer Screening**

**UKCTOCS Study**

**Ovarian Cancer**

**UKCTOCS Study**

**Interpretation** The sensitivity of the MMS and USS screening strategies is encouraging. Specificity was higher in the MMS than in the USS group, resulting in lower rates of repeat testing and surgery. This in part reflects the high prevalence of benign abdominal abnormalities and the more frequent detection of borderline tumours in the USS group. The prevalence screen has established that these screening strategies are feasible. The results of ongoing screening are awaited so that the effect of screening on mortality can be determined.


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**Ovarian Cancer**

**CA-125 & Ovarian Cancer**

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**Ovarian Cancer**

**Ultrasound Characteristics**

Benign vs. Malignant

Pathologic results from the United Kingdom collaborative trial of ovarian cancer screening prevalence screen

<table>
<thead>
<tr>
<th>Participants Undergoing Surgery</th>
<th>MMS</th>
<th>USS</th>
<th>Overall</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>153</td>
<td>153</td>
<td>153</td>
<td>1.00</td>
</tr>
<tr>
<td>Number of patients</td>
<td>4168</td>
<td>4168</td>
<td>4168</td>
<td>1.00</td>
</tr>
<tr>
<td>Number of cancers</td>
<td>97</td>
<td>97</td>
<td>97</td>
<td>1.00</td>
</tr>
<tr>
<td>Primary ovarian malignant</td>
<td>5</td>
<td>9</td>
<td>7</td>
<td>0.06</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
</tr>
<tr>
<td>Metastatic</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>0.35</td>
</tr>
<tr>
<td>Early stage disease</td>
<td>42</td>
<td>79</td>
<td>61.5%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Ovarian Cancer

**Endovaginal U/S**

- Size
- Irregular wall
- Septations
- Hyperechogenic sites
- Papillary projections

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Morphologic Criteria

- Histopathologic review of 1000 specimens:
  
  *Papillary projections best correlated with malignancy*

  Gynecol Oncol 1989;35:139

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Ovarian Masses

**Decision Process**

- Surgery
- Follow-up (when)
- No follow-up

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Sonographic Characteristics

- Simple cyst
- Polycystic ovaries
- Hemorrhagic cyst
- Endometrioma
- Dermoid
- Myoma

90 %

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Simple Cyst
Hemorrhagic Cyst

Endometrioma

**TABLE 12.2 Characteristics of an Ovarian Hemorrhagic Cyst**

- Excellent sound transmission
- Thin reticular lacy pattern
- Temporal changes
- Solid – fluid level
- Siggles when probed
- Absence of vascular signals on low-velocity color Doppler
- Single mass of clotted blood when retracted
- Follow-up shows resolution

Endometrioid CA

Endometrioma
**TABLE 12.3 Sonographic Characteristics of Endometriomas**

- Excellent sound transmission
- Homogeneous, ground glass appearance
- Typically unilocular
- No or minimal temporal changes
- Hyperechoic foci
- Absence of vascular signals on low-velocity, low-filter color Doppler settings

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**Dermoid Cyst**

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**Peritoneal Inclusion Cysts**

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**TABLE 12.4 Sonographic Characteristics of Dermoid Cysts**

- Poor sound transmission (tip of iceberg effect)
- Complex, solid tumors, heterogeneous content
- White echogenic ball (Rokitansky nodule)
- Thin linear strands
- Superior location in pelvis
- Absence of vascular signals on low-velocity, low-filter, color Doppler settings

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**TABLE 12.8 Sonographic Characteristics of Peritoneal Inclusion Cysts**

- Multiple primarily thin septations
- Septations attach to pelvic organs
- Fluid within the cysts is primarily clear
- Normal looking ovaries can be occasionally seen
**Myoma**

TABLE 12.5  Sonographic Characteristics of Pedunculated Leiomyomas

- Poor sound transmission
- Solid tumors, regular striped echogenicity
- Vascular pedicle to the uterus
- “Venetian blinds shadowing”
- Separate freely movable ovary

**Myoma**

**Myoma**

**TABLE 12.6  Sonographic Characteristics of Hydosalpinges**

- Fluid filled, sausage shaped structure
- Structure tapers near the uterine origin
- Thin walls
- Multiple and incomplete septations
- Absence of peristalsis
- Cogwheel appearance on cross section
TABLE 12.7  Sonographic Characteristics of Tubo-Ovarian Abscesses

- Multilocular mass with thick walls
- Thick incomplete septae
- Fluid content is echogenic, with ground-glass appearance
- Involvement of the ovary
**Cancer**

**E-Book: Ultrasound in Obstetrics & Gynecology: A Practical Guide**

**Doppler & Ovarian Cancer**

**Practical Aspects**

- Value in post-menopausal ovary, where benign angiogenesis is non existent

**Frequency of Screening for Ovarian Cancer ??**

**TABLE 12.9** Sonographic Characteristics of Borderline and Malignant Adnexal Masses

- Irregularities in capsule and content
- Thick septations
- Solid content
- Papillary projections
- Vascularity on color Doppler

**46 year old – 11/25/03**


**Ovarian Cancer**

**Ready for Screening If:**

- High risk population - Q 6 months
- Should consider patient’s baseline for biologic markers (Ca 125)
- Should rely on expert sonography for defining benign and malignant masses
- Should have a well defined protocol for evaluating and managing screen positive abnormalities
- Have a quality assurance program for follow-up of cases and program

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**Ovarian Cancer**

**What About the Low-Risk Population?**

- Once data is out supporting this approach, screening for low-risk women will be feasible within a structured approach:
  - Protocol driven
  - Expert sonography
  - Close follow-up