Options for Managing Ovarian (and Tubal) Cancer Risk: Current Strategies 2017

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Disclosures

• Nothing to disclose

Ovarian cancer: Scope of the Problem

• 22,440 new cases are predicted in 2017: ovary, tube, peritoneum
• The majority present at a late stage
• Overall survival has not changed significantly
• Only 10-15% of all ovarian cancers are due to inheritable genetic mutations

Site of origin BRCA-associated gynecologic cancers is unclear

Breast Cancer Genes BRCA1, BRCA2

Strategies to Prevent Cancer in BRCA Mutation Carriers
Screening for ovarian cancer

Can screening improve the outcome?

• CA125
  – Elevated in ovarian cancers
  – Poor specificity and sensitivity
• Pelvic US
  – Best imaging evaluation of ovaries
  – Limited predictive value of determining malignancy

PLCO trial: No benefit to screening in general population

Extended mortality results for ovarian cancer screening in the PLCO trial with median 15 years follow-up

• 78,000 women randomized to CA125/US screening or routine care
• Higher rate of surgical intervention and complications in screening arm
• No mortality benefit from screening
**Ovarian cancer screening UKCTOCS:**

*General postmenopausal women*

202,638 women recruited 2001-2005 followed until 2015

- 101,359 no screening
- 50,639 annual TVS
- 50,640 Multimodal screening

**ROCA CA 125 (MMS)**

<table>
<thead>
<tr>
<th>Arm</th>
<th>Sens.</th>
<th>Sp 1</th>
<th>Deaths from cancer</th>
<th>Complication rate among benign surgeries</th>
<th>Mortality reduction over 14 yrs study (excluding prevalent cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No screen</td>
<td>-</td>
<td>-</td>
<td>347 (0.34%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual TVS</td>
<td>1634</td>
<td>73%</td>
<td>10</td>
<td>154 (0.3%)</td>
<td>11% p=0.21</td>
</tr>
<tr>
<td>MMS</td>
<td>488</td>
<td>84%</td>
<td>2</td>
<td>148 (0.29%)</td>
<td>15% (p=0.1 20%</td>
</tr>
</tbody>
</table>

Why does screening fail?

- Serous
- Endometrioid
- Mucinous
- Clear cell

Ovarian cancer is not a uniform disease

- **Type 1:**
  - Endometrioid, mucinous, clear cell histologies
  - Less common, present at lower stage, arise from precursor lesion
- **Type 2:**
  - High grade serous histology
  - Advanced stage, responsible for more deaths
  - Majority may arise from the fallopian tube

Jacobs L. Lancet 2015
## Obstacles to Early Ovarian Cancer Detection

- "Natural history" poorly defined
- ? Premalignant lesion
- ? Screening window
- Anatomic barriers/intraperitoneal location
- Non-specific early symptoms
- Poor sensitivity and sensitivity of available tests: CA 125, transvaginal ultrasound

## What strategies can reduce risk?

- **Oral contraceptives**
  - Considered acceptable intervention
  - Small risks
  - Appropriate in general population and high risk women

- **Surgery**
  - Removal of ovaries and tubes
  - Minimally invasive, low risk procedure
  - Loss of ovarian function a clinical issue
  - Strongly recommended in high risk women

## Benefits of oral contraceptives

**Oral Contraceptive Use for the Primary Prevention of Ovarian Cancer**

- Multiple case control studies confirm decreased risk of ovarian cancer with OCP use in the general population (40-50% risk reduction)
- Greater benefit with duration of use
- Both current low-dose and prior high-dose formulations provide benefit
Risks of OCP use

• 44 breast cancer studies show slight increase with OCP use (HR 1.08, CI 1.00-1.17)
• 12 cervical cancer studies show increase risk with duration of use; heterogeneity prevented meta-analysis

Population-based studies confirm OCP use decreases risk

• 46,000 women recruited to the UK Royal College of General Practitioners’ Oral Contraception Study in 1968-1969
• Ever-users of OCPs had a 33% decrease in the incidence of ovarian cancer
• Increased risks of breast and cervical cancer lost after 5 years of stopping OCP use

OCP use in a high-risk population

• Meta-analysis of 18 studies showed risk reduction of ovarian cancer by 50%
• No increase risk of breast cancer
• Duration of use confirms additional benefit
Surgical options for prevention

- Tubal ligation
- Risk-reducing salpingo-oophorectomy (RRSO)
- Salpingectomy

Bilateral tubal ligation

- Commonly performed procedure following childbearing for contraceptive purposes

Tubal Ligation and Ovarian Cancers

These histologies may arise from retrograde menstruation of endometrial cells
Tubal ligation decreases ovarian cancer risk

- Two prospective studies of 230,000 women
- BTL was associated with 24% decreased risk of ovarian cancer
- Effect was greater (30%) in non-serous ovarian cancers: endometrioid and clear cell

BTL reduces ovarian cancer risk

- 13 selected studies showed reduced risk by 34%
- Risk reduction greatest for endometrioid histology (40%)
- No risk reduction for mucinous histology

BTL in the BRCA population

- BTL reduced risk in BRCA1 carriers > 50%
- No definite conclusions for BRCA2 carriers
- Other studies (Narod 2001) confirm these findings
- Risk reduction is similar to that with OCP use
Risk-reducing salpingo-oophorectomy

- RRSO – most proven method for prevention

Risk-benefits Removing Tubes/Ovaries in Young BRCA Mutation Carriers

<table>
<thead>
<tr>
<th>Increased risk of:</th>
<th>Decreased risk of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality</td>
<td>Ovarian cancer</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td></td>
</tr>
<tr>
<td>Parkinsonism</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis and fractures</td>
<td></td>
</tr>
<tr>
<td>Psychiatric symptoms</td>
<td></td>
</tr>
<tr>
<td>Impaired sexual function</td>
<td></td>
</tr>
</tbody>
</table>

Unilateral salpingo-oophorectomy not associated with risks

Shuster LT Menopause Int. 14(3);2008

RRSO in BRCA+ women

- 70-85% reduction in ovarian/tubal cancers
- 37-54% reduction in breast cancer

- Guidelines recommend RRSO between ages of 35-40 years
  - May delay ages 45-50 for BRCA2 women
  - Same for other hereditary syndromes

- 8-11% of BRCA patients will have incidental malignancy at time of RRSO
RRSO reduces risk of “ovarian” cancer in BRCA mutation carriers

<table>
<thead>
<tr>
<th>Study</th>
<th>N=RRSO</th>
<th>RR ovarian Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kauff NEJM 2002 Pro</td>
<td>98</td>
<td>0.15 85%</td>
</tr>
<tr>
<td>Rebbeck NEJM 2002 Retro</td>
<td>259</td>
<td>0.04 96%</td>
</tr>
<tr>
<td>Rutter JNCI 2003 Retro</td>
<td>251</td>
<td>0.29 71%</td>
</tr>
<tr>
<td>Finch JAMA 2006 Pro</td>
<td>1034</td>
<td>0.2 80%</td>
</tr>
<tr>
<td>Domcheck Lancet 2006 Pro</td>
<td>155</td>
<td>0.05 95%</td>
</tr>
<tr>
<td>Kauff JCO 2008 Pro</td>
<td>509</td>
<td>0.12 88%</td>
</tr>
<tr>
<td>Rebbeck JNCI 2009</td>
<td>10 studies</td>
<td>0.21 80%</td>
</tr>
<tr>
<td>Domcheck JAM 2010 Pro</td>
<td>2482</td>
<td>0.28 78%</td>
</tr>
</tbody>
</table>

80% reduction "ovarian", 50% reduction breast cancer risks

Cumulative Risks of Ovarian Cancer among Jewish BRCA mutation Carriers

<table>
<thead>
<tr>
<th>Risk by Age</th>
<th>Ovarian Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BRCA1</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>40</td>
<td>3%</td>
</tr>
<tr>
<td>50</td>
<td>21%</td>
</tr>
<tr>
<td>60</td>
<td>40%</td>
</tr>
<tr>
<td>70</td>
<td>46%</td>
</tr>
<tr>
<td>80</td>
<td>54%</td>
</tr>
</tbody>
</table>

Average age menopause

Cumulative Risks of Ovarian Cancer among BRCA mutation Carriers

- Detailed family history 1,948 families collected through genetic counseling clinics
  - 676 Ashkenazi Jews, 1,272 other ethnicities

<table>
<thead>
<tr>
<th>Ovarian Cancer risk by Mutation</th>
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<tbody>
<tr>
<td>Age yrs</td>
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<tr>
<td>---------</td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>60</td>
</tr>
<tr>
<td>70</td>
</tr>
</tbody>
</table>

Average age menopause

Chen S et al. JCO 2006;24:863-871.
Optimal risk-reducing bilateral salpingo-oophorectomy procedure

- Remove entire ovary and as much fallopian tube as possible
- Cytology sample “peritoneal washings”
  - Limited efficacy additional biopsies or staging
- Comprehensive evaluation of entire ovary/tube
  - Communicate with pathologist to follow protocol

Powell 2005

Comprehensive pathology assessment

Increased detection rate of occult ovarian/tubal malignancy in BRCA mutation carriers from 2.5% to 17%; range in most studies 3-11%

Powell B et al JCO 2005;23:127

RRSO in the general population

Salpingo-oophorectomy at the Time of Benign Hysterectomy
A Systematic Review

Elizabeth Carter Evans, SM, Kristen A. Matusick, MS, Emily J. Gonzalez, MD, Stacy M. Frazee, MD, SC, Jennifer L. Graham, MD, Krista Green, MD, Terry A. Johns, MD, Renee Harbers, MD, Thomas L. Harris, MD, and Mike Murphy, MD, for the Society of Gynecologic Oncologists Systematic Review Group

VOL. 35, NO. 1, SEPTEMBER 2015

- All-cause mortality higher in those undergoing BSO, especially due to cardiovascular death
- Estrogen replacement therapy did not abrogate risks of death
- RRSO recommended only for high risk women
- Preserve ovaries in those with average risk
Prophylactic BSO increases all cause risk death

Risk of death almost twice as high for women had BSO < 45 yrs

Should prophylactic RRSO include hysterectomy?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Remove entire tube</td>
<td>• Adds cost, recovery, complications</td>
</tr>
<tr>
<td>• Simplifies hormonal management</td>
<td>• NO reports cornual cancers after RRSO</td>
</tr>
<tr>
<td>• BRCA may cause endometrial ca ?</td>
<td>• Uterine cancer does not appear to be part BRCA phenotype</td>
</tr>
<tr>
<td>– 2-3 fold increased risk of uterine cancer with Tamoxifen</td>
<td>– Uterine cancer usually presents with early symptoms</td>
</tr>
<tr>
<td>• Other gynecologic symptoms or pathology</td>
<td></td>
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</table>

Hysterectomy at time of RRSO

- 1083 participants: 8 uterine cancers observed (4.3 expected)
- Conclude BRCA1 women at risk for serous uterine cancers
Salpingectomy: how does tube relate to ovarian cancer?

- Tubal neoplasia may be the primary lesion in serous ovarian/peritoneal cancers:
  - Occult tubal cancers are found at prophylactic surgeries on \textit{BRCA}\textsuperscript{mut} carriers
  - Fallopian tubes in ovarian cancer patients demonstrate serous tubal intraepithelial carcinoma (STIC) lesions
  - Bilateral tubal ligations decrease the risk of ovarian cancer
  - Animal models support a tubal origin of peritoneal cancers

<table>
<thead>
<tr>
<th>Author</th>
<th>Number</th>
<th>Tumor (%)</th>
<th>Tubal Involvement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colgan (2001)</td>
<td>39</td>
<td>5 (13)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Leeper (2002)</td>
<td>30</td>
<td>5 (17)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Powell (2005)</td>
<td>67</td>
<td>7 (10)</td>
<td>4 (57)</td>
</tr>
<tr>
<td>Carcangiu (2006)</td>
<td>50</td>
<td>6 (12)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>Finch (2008)</td>
<td>159</td>
<td>7 (4)</td>
<td>6 (86)</td>
</tr>
<tr>
<td>Callahan (2007)</td>
<td>100</td>
<td>7 (7)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Hirst (2009)</td>
<td>45</td>
<td>4 (9)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>490</td>
<td>41 (8%)</td>
<td>32 (78%)</td>
</tr>
</tbody>
</table>

Most Occult Cancers at RRSO in \textit{BRCA}\textsuperscript{mut} Carriers are in the Tubes, Not the Ovaries

- Serous Tubal Intraepithelial Carcinoma (STIC) may represent a precursor lesion
**Animal Models Further Support a Tubal Origin of Ovarian Cancer**

Animals with conditional Dicer-Pten deletions develop ascites and fallopian tube tumors that spread to ovaries, and have peritoneal metastases resembling human disease.

Tumor histology is highly characteristic of serous ovarian cancers.

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**Salpingectomy in Animal Models Prevents Tumor Development**

- **Unilateral oophorectomy**
- **Unilateral salpingectomy**
- **Bilateral oophorectomy**
- **Bilateral salpingectomy**

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**Salpingectomy in BRCA+ women**

- Option for those wishing to preserve ovarian function
- Salpingectomy may be considered as a “bridge” to oophorectomy
- No evidence to date
  - Reduction in ovarian/tubal/peritoneal incidence
  - Effect on cancer mortality
Opportunistic salpingectomies in the general population

Committee Opinion

Does bilateral salpingectomy actually reduce ovarian cancer mortality?
Is the procedure safe?
Does it alter ovarian function?
Is it cost effective?
Will patients and doctors accept it?

Maybe...but some unanswered questions

Does salpingectomy reduce ovarian cancer?

Ovarian Cancer Risk After Salpingectomy: A Nationwide Population-Based Study

>250,000 women who had surgery for benign indications and 5.5 million controls

- Salpingectomy significantly reduced ovarian cancer risk: HR = 0.65 (95% CI=0.52-0.81)
- "Dose Response": Bil-Salpingectomy twice as effective as Unilateral: HR 0.35 vs 0.71

Conclusion: Removal of fallopian tubes by itself is an effective measure to reduce ovarian cancer risk in the general population.
<table>
<thead>
<tr>
<th>Does Salpingectomy Reduce Ovarian Cancer?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Case-control study using Rochester Epidemiology Project</td>
</tr>
<tr>
<td>• Cancer cases (1966-2009) age-matched to 2 controls</td>
</tr>
<tr>
<td>• Model adjusted for known OC risk factors (prior hyst, BSO, OCP use, endometriosis, infertility, gravity/parity)</td>
</tr>
<tr>
<td><strong>Risk of Ovarian Cancer decreased by 64%</strong> after excisional tubal sterilization ([OR 0.36 [95%CI 0.13-1.02]]) compared to no sterilization or non-excisional BTL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Is Salpingectomy Safe and Does It Affect Ovarian Function?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-term effects of salpingectomy during laparoscopic hystectomy on ovarian reserve: a pilot randomized controlled trial</strong></td>
</tr>
<tr>
<td>• 30 premenopausal women randomized to +/- bilateral salpingectomy</td>
</tr>
<tr>
<td>• AMH assayed pre-op and at 4 and 12 weeks post-op</td>
</tr>
<tr>
<td>• No statistically significant differences in AMH levels, OR time, or EBL observed between groups</td>
</tr>
<tr>
<td><strong>CONCLUSION:</strong> bilateral salpingectomy at TLH is safe and does not have any short-term deleterious effects on ovarian reserve</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Is Salpingectomy Safe and Does It Affect Ovarian Function?</th>
</tr>
</thead>
<tbody>
<tr>
<td>158 women undergoing TLH +/- bilateral salpingectomy:</td>
</tr>
<tr>
<td>• No difference in ovarian function at 3 months— assessed by AMH, FSH, antral follicle count, ovarian size and blood flow by TVS and Doppler</td>
</tr>
<tr>
<td>• No difference in OR time, post-op Hgb, hospital stay, or recovery</td>
</tr>
<tr>
<td><strong>CONCLUSION:</strong> BSO appears safe and should be widely considered to prevent ovarian cancer</td>
</tr>
</tbody>
</table>
**Does Salpingectomy Affect Ovarian Function in Women Desiring Fertility?**

A retrospective analysis of the effect of salpingectomy on serum antiMüllerian hormone level and ovarian reserve

- Retrospective review of 198 women under 40 years presenting for IVF: 83 with unilateral salpingectomy, 41 with bilateral, and 74 with no tubal surgery
- Mean AMH levels higher and mean FSH levels lower in women without tubal surgery
- AMH did not correlate with number of oocytes retrieved

In women undergoing IVF, salpingectomy may affect ovarian reserve

**Is Salpingectomy Cost-Effective?**

Salpingectomy as standard at hysterectomy? A Danish cohort study, 1977–2010

- Population-based study including 170,000 women over 3 decades
  - At least doubled risk of subsequent pelvic surgery in women undergoing hysterectomy or sterilization
  - Routine removal of tubes at hysterectomy should be recommended to prevent subsequent surgical interventions
  - Salpingectomy for sterilization should be discussed

Salpingectomy improves women’s health and reduces healthcare costs

**Does Insurance Cover Opportunistic Salpingectomy?**

- Many will cover salpingectomy in women with high risk of ovarian/tubal cancer
- No published data to date regarding insurance denials for opportunistic salpingectomy
Female Tubal Sterilization
The Time Has Come to Routinely Consider Removal
Mitchell D. Cusimano, MD, and Nidhi Ziu, MD, MSc

“We should ask why this revelation has not occurred sooner…”

- Risk of serous ovarian cancer reduced by more than 60% after salpingectomy
- Plus no BTL “failures” (pregnancy) and avoidance of future pelvic surgeries for ectopic pregnancy or hydrosalpinx

Routine Salpingectomy May Be Considered A New Standard of Care

- It’s safe and may prevent ovarian cancers of serous, endometrioid, and clear cell histology
- It is unlikely to affect hormonal function
- It can be performed:
  - As a standard part of hysterectomy procedures
  - For sterilization in place of tubal ligation/occlusion
  - At C-sections, if childbearing complete

Recommendations for Prevention
Society of Gynecologic Oncology Recommendations for the Prevention of Ovarian Cancer

- OCP use
- Tubal sterilization
- RRBSO in women at high hereditary risk
- Genetic counseling and testing
- Salpingectomy