Opportunistic Salpingectomy for Ovarian Cancer Prevention

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Disclosures

• nothing to disclose/no conflicts of interest
Objectives

• Describe the current understanding of ovarian carcinogenesis
• Understand current literature about the protective effects and risks of salpingectomy for ovarian cancer prevention in women at average risk for ovarian cancer
• Counsel patients undergoing benign pelvic surgery about potential benefits of opportunistic salpingectomy
Opportunistic Salpingectomy

- Elective removal of fallopian tubes at the time of benign hysterectomy or instead of tubal ligation in a patient at average risk for ovarian cancer
Ovarian cancer- Epidemiology

• Ovarian cancer is the leading cause of gynecologic cancer mortality worldwide
  – 2015 → 21,980 cases; 14,270 deaths in US
• Median age at diagnosis 63
• Lifetime risk of developing ovarian cancer 1.4%

Seigel 2014
Ovarian cancer - Epidemiology

• Risk factors

<table>
<thead>
<tr>
<th>Increase</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Oral Contraceptive Use</td>
</tr>
<tr>
<td>Family history</td>
<td>Pregnancy and Breastfeeding</td>
</tr>
<tr>
<td>Infertility/low parity</td>
<td>Tubal ligation</td>
</tr>
<tr>
<td>Personal cancer history</td>
<td>Hysterectomy/Removal of Both Ovaries</td>
</tr>
</tbody>
</table>
Ovarian cancer- Epidemiology

<table>
<thead>
<tr>
<th>stage</th>
<th>Percent</th>
<th>5yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>24</td>
<td>90%</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>65%</td>
</tr>
<tr>
<td>III</td>
<td>55</td>
<td>15-30%</td>
</tr>
<tr>
<td>IV</td>
<td>15</td>
<td>0-20%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>50%</td>
</tr>
</tbody>
</table>

- Diagnosed at a late stage when wide spread metastasis has already occurred
- Can achieve complete clinical response with surgery plus chemotherapy
- Most patients recur

Ovarian cancer- the clinical problem

- Ovarian cancer is diagnosed at late stages- early stages are asymptomatic
  - 70% diagnosed at stage 3-4
  - Likely metastasizes early
  - No screening test to detect early disease
Results from the PLCO study

• 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.
• **NEED TO FOCUS ON PREVENTION**

Buys, SS et al. JAMA 2011
Ovarian cancer-prevention

• Oral contraceptive pills
  – Meta-analysis of fifty-five studies
  – significant reduction in ovarian cancer incidence in ever-users compared with never-users
  – significant duration-response relationship, with reduction in incidence of more than 50% among women using OCPs for 10 or more years
  – Benefit also seen in BRCA 1/2 carriers

Opportunistic Salpingectomy for Ovarian Cancer Prevention

Ovarian cancer-prevention

<table>
<thead>
<tr>
<th>Author</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ness, 2000</td>
<td>0.600</td>
<td>0.472</td>
<td>0.763</td>
</tr>
<tr>
<td>Parazzini, 2000</td>
<td>0.830</td>
<td>0.636</td>
<td>1.083</td>
</tr>
<tr>
<td>Sanderson, 2000</td>
<td>0.800</td>
<td>0.621</td>
<td>1.031</td>
</tr>
<tr>
<td>Beard, 2000</td>
<td>1.100</td>
<td>0.561</td>
<td>2.155</td>
</tr>
<tr>
<td>Greggi, 2000</td>
<td>0.400</td>
<td>0.280</td>
<td>0.571</td>
</tr>
<tr>
<td>Purdie, 2001</td>
<td>0.630</td>
<td>0.490</td>
<td>0.810</td>
</tr>
<tr>
<td>Chiaffarino, 2001</td>
<td>0.900</td>
<td>0.688</td>
<td>1.177</td>
</tr>
<tr>
<td>Riman, 2001</td>
<td>1.230</td>
<td>0.860</td>
<td>1.760</td>
</tr>
<tr>
<td>Royar, 2001</td>
<td>0.480</td>
<td>0.334</td>
<td>0.689</td>
</tr>
<tr>
<td>Riman, 2002</td>
<td>0.730</td>
<td>0.591</td>
<td>0.902</td>
</tr>
<tr>
<td>McGuire, 2004</td>
<td>0.550</td>
<td>0.420</td>
<td>0.720</td>
</tr>
<tr>
<td>Quirk, 2004</td>
<td>1.220</td>
<td>0.883</td>
<td>1.686</td>
</tr>
<tr>
<td>Huusom, 2006</td>
<td>0.810</td>
<td>0.563</td>
<td>1.166</td>
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<tr>
<td>Lurie, 2008</td>
<td>0.590</td>
<td>0.417</td>
<td>0.834</td>
</tr>
<tr>
<td>Soegaard, 2007</td>
<td>0.700</td>
<td>0.521</td>
<td>0.941</td>
</tr>
<tr>
<td>Moorman, 2008</td>
<td>0.703</td>
<td>0.543</td>
<td>0.910</td>
</tr>
<tr>
<td>Ness, 2011</td>
<td>0.670</td>
<td>0.552</td>
<td>0.813</td>
</tr>
<tr>
<td>Wilailak, 2012</td>
<td>0.710</td>
<td>0.512</td>
<td>0.984</td>
</tr>
<tr>
<td>Urban, 2012</td>
<td>0.880</td>
<td>0.518</td>
<td>1.495</td>
</tr>
<tr>
<td>Meta-analysis result</td>
<td>0.721</td>
<td>0.643</td>
<td>0.808</td>
</tr>
</tbody>
</table>

Ovarian cancer - Prevention

• Tubal ligation
  – Meta-analysis of 13 studies
  – reduced risk of epithelial ovarian cancer (endometrioid and serous) by 34%
  – Effect is long-lasting
  – Possible retrograde transport of endometrial cells
  – 72% risk reduction in BRCA 1 and 2 carriers if OCP use and TL

Cibula, D et al. *Hum Reprod update*, 2010
Ovarian cancer- Prevention

Relative risk for ovarian cancer after tubal ligation, analysis of two sets of studies (strict/extended selection) and result of overall meta-analysis.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Relative risk (95%CI)</th>
<th>% weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>STRICT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morl 1988</td>
<td>0.47 (0.21-1.01)</td>
<td>0.9</td>
</tr>
<tr>
<td>Booth 1989</td>
<td>0.20 (0.10-0.60)</td>
<td>0.7</td>
</tr>
<tr>
<td>Shu 1989</td>
<td>0.80 (0.40-1.60)</td>
<td>1.2</td>
</tr>
<tr>
<td>Inwit 1991</td>
<td>0.69 (0.30-0.90)</td>
<td>5.4</td>
</tr>
<tr>
<td>Chen 1992</td>
<td>1.00 (0.50-2.30)</td>
<td>1.0</td>
</tr>
<tr>
<td>Whittemore 1992a</td>
<td>0.59 (0.38-0.93)</td>
<td>2.8</td>
</tr>
<tr>
<td>Whittemore 1992b</td>
<td>0.57 (0.32-1.00)</td>
<td>5.1</td>
</tr>
<tr>
<td>Risch 1996</td>
<td>0.67 (0.47-0.94)</td>
<td>4.6</td>
</tr>
<tr>
<td>Rosenblatt 1996</td>
<td>0.71 (0.47-1.08)</td>
<td>3.2</td>
</tr>
<tr>
<td>Green 1997</td>
<td>0.61 (0.46-0.82)</td>
<td>5.8</td>
</tr>
<tr>
<td>McGuire 2004</td>
<td>0.68 (0.45-0.95)</td>
<td>4.0</td>
</tr>
<tr>
<td>Modugno 2004</td>
<td>0.63 (0.54-0.73)</td>
<td>24.3</td>
</tr>
<tr>
<td>Pike 2004</td>
<td>0.82 (0.63-1.28)</td>
<td>2.9</td>
</tr>
<tr>
<td>Subtotal (I-squared = 12.7%, p = 0.317)</td>
<td>0.66 (0.50-0.73)</td>
<td>61.6</td>
</tr>
</tbody>
</table>

| EXTENDED          |                       |          |
| Koch 1984         | 2.76 (0.96-7.56)       | 0.5      |
| Rosenberg 1994    | 0.60 (0.40-0.90)       | 3.4      |
| Comelison 1997    | 0.32 (0.31-0.85)       | 2.2      |
| Kreijer 1997      | 0.57 (0.41-0.80)       | 4.9      |
| Kjaer 2004        | 0.82 (0.60-1.00)       | 8.4      |
| Twongoer 2007     | 0.50 (0.30-0.87)       | 7.2      |
| Jordan 2008       | 0.87 (0.69-1.00)       | 10.5     |
| Dorobzech 2009    | 1.17 (0.62-2.30)       | 1.3      |
| Subtotal (I-squared = 57.1%, p = 0.023) | 0.74 (0.66-0.84) | 38.4 |

Heterogeneity between groups: p = 0.125
Overall (I-squared = 38.3%, p = 0.039) | 0.69 (0.64-0.75) | 100.0 |

Cibula, D et al. Hum Reprod update, 2010
Ovarian cancer- prevention

• Risk reducing salpingo-oophorectomy (RRSO)
  – Most proven method for prevention in BRCA patients
  – 70-85% reduction in ovarian cancer
  – 37-54% reduction in breast cancer
  – RRSO should be done between 35 and 40yo
### Ovarian cancer- prevention

#### Table 1.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year of Publication</th>
<th>Design</th>
<th>No. of Patients Who Underwent RRSO</th>
<th>Gynecologic Cancer HR</th>
<th>95% CI</th>
<th>Breast Cancer HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kauff et al</td>
<td>2002</td>
<td>Prospective</td>
<td>98</td>
<td>0.15</td>
<td>0.02 to 1.31</td>
<td>0.32</td>
<td>0.08 to 1.20</td>
</tr>
<tr>
<td>Rebbeck et al</td>
<td>2002</td>
<td>Retrospective</td>
<td>259</td>
<td>0.04</td>
<td>0.01 to 0.16</td>
<td>0.53</td>
<td>0.33 to 0.84</td>
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<tr>
<td>Rutter et al</td>
<td>2003</td>
<td>Retrospective</td>
<td>251</td>
<td>0.29</td>
<td>0.12 to 0.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eisen et al</td>
<td>2005</td>
<td>Retrospective</td>
<td>1,439</td>
<td>0.46</td>
<td>0.32 to 0.65</td>
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<td></td>
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<tr>
<td>Domchek et al</td>
<td>2006</td>
<td>Prospective</td>
<td>155</td>
<td>0.11</td>
<td>0.03 to 0.47</td>
<td>0.36</td>
<td>0.20 to 0.67</td>
</tr>
<tr>
<td>Finch et al</td>
<td>2006</td>
<td>Combined</td>
<td>1,045</td>
<td>0.20</td>
<td>0.07 to 0.58</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Abbreviations: RRSO, risk-reducing salpingo-oophorectomy; HR, hazard ratio.
- * Values are odds ratios with 95% CIs.

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Kauff, ND et al. JCO 2007
Ovarian cancer- prevention

• RRSO in the average risk population
  – increases death from all causes
    • patients <50yo who have never been on HRT
  – Increases CV mortality in patients <45yo without HRT
  – does not improve survival at any age
  – Ovarian conservation benefits long term survival until age 65yo

High risk patients

- BRCA 1 and 2
- Tumor suppressor gene
- Autosomal dominant
Identifying high risk patients

• To prevent we need to identify those at risk
• Risk of ovarian cancer in BRCA 1: 18-54%
• Risk of ovarian cancer in BRCA 2: 2.4-19%
• Refer to genetic counseling
  – Personal history of ovarian cancer
    • In 2012, 24% of ovarian cancer patients underwent genetic testing
  – Strong family history of breast/ovarian cancer or ovarian/endometrial/colon cancer
  – Male breast cancer
• Take a family history- **it will save lives!!**
NCCN guidelines

An individual with a cancer diagnosis meeting any of the following:
- A known mutation in a cancer susceptibility gene within the family
- Early-onset breast cancer
- Triple negative (ER- PR- HER2-) breast cancer ≤50 y
- Two breast cancer primaries in a single individual
- Breast cancer at any age, and
  - ≥1 close blood relative with breast cancer ≤50 y, or
  - ≥1 close blood relative with invasive ovarian cancer at any age, or
  - ≥2 close blood relatives with breast cancer and/or pancreatic cancer at any age, or
  - From a population at increased risk
- Personal and/or family history of three or more of the following (especially if early onset): pancreatic cancer, prostate cancer (Gleason score ≥7); sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polyps of gastrointestinal (GI) tract; diffuse gastric cancer (can include multiple primary cancers in same individual)
- Invasive ovarian cancer
- Male breast cancer

An individual with no personal history of cancer, but with a family history of any of the following:
- A known mutation in a cancer susceptibility gene within the family
- ≥2 breast cancer primaries in a single individual
- ≥2 individuals with breast cancer primaries on the same side of family
- ≥1 invasive ovarian cancer primary
- First- or second-degree relative with breast cancer ≤35 y
- Personal and/or family history of three or more of the following (especially if early onset): pancreatic cancer, prostate cancer (Gleason score ≥7); sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polyps of GI tract; diffuse gastric cancer (can include multiple primary cancers in same individual)
- Male breast cancer

Referral to cancer genetics professional recommended
See Assessment (BR/OV-2)

Ovarian cancer- Histology

- Ovarian surface epithelium derived from coelomic epithelium
- Gene expression studies show that genes expressed in each epithelial subset are expressed in the tissue they resemble

Ovaries
Fallopian Tubes
Uterus

Surface Epithelium
Serous
Mucinous
Endometrioid
Clear cell
Transitional cell

Sex cord-stroma
Granulosa cell
Thecoma
Fibroma
Sertoli cell
Sertoli-Leydig
Steroid

Germ cells
Dysgerminoma
Yolk sac
Embryonal carcinoma
Choriocarcinoma
Teratoma

75% of cases
90% of deaths
Ovarian carcinogenesis

• Used to think of ovarian cancer as different histological subtypes
  – Serous, mucinous, endometrioid, clear cell
• Based on new information ovarian cancer is now divided into 2 categories
  – Type 1 and Type 2 carcinomas
Ovarian carcinogenesis

- Type I → low grade serous and endometrioid tumors, clear cell and mucinous histology
  - Younger age
  - Less common
  - Less lethal
  - Diagnosed at early stage, well-differentiated
  - Indolent
  - Associated with benign precursor lesion - endometriosis
  - Each histological subtype has distinct molecular abnormalities
    - KRAS, BRAF, ERBB2, PIK3CA
    - BRCA, p53 wild type
    - Chemoresistant/platinum resistant

Vercellini, P. *Hum Reprod* 2011
Kurman, RJ. *Hum Pathol* 2011
Ovarian carcinogenesis

- Type 2→ high-grade serous and endometrioid carcinomas, undifferentiated carcinomas, carcinosarcomas
  - Presents at late stages
  - Aggressive/early metastasis
  - High grade
  - High mortality
  - p53 and BRCA mutations
  - Chemosensitive/platinum sensitive
  - Fallopian tube precursor lesion

Vercellini, P. Hum Reprod 2011
Kurman, RJ. Hum Pathol 2011
Opportunistic Salpingectomy for Ovarian Cancer Prevention

Type I serous ovarian cancers
- Progress from LMP
- Usually low grade
- Ras pathway frequently mutated
- BRCA wild type
- Generally TP53 wild type
- Chromosomally stable
- Frequently platinum insensitive

High-grade serous ovarian cancers (Type II)
- De novo invasive tumours
- High grade
- Ras wild type
- BRCA dysfunction
- TP53 mutant
- Widespread DNA copy number change
- Usually platinum sensitive

Nature Reviews Cancer

Bowtell, D. Nature Reviews Cancer 2010
Ovarian carcinogenesis: Is this really ovarian cancer?

- Recent shift in understanding of the origins of ovarian cancer
- Historically, accepted that ovary is origin
  - wide spread disease at diagnosis
  - no precursor lesion
  - Undifferentiated mouse ovarian surface epithelium can differentiate into all histotypes
    - HOX genes

Naora et al, 2008
Kim et al, PNAS 2012
Ovarian carcinogenesis

- Fallopian tube as origin of high grade serous cancers
  - Pathology from BRCA patients- prophylactic BSO
    - $\approx 10\%$ of cases $\rightarrow$ small cancers and pre-invasive lesions (STICs)
    - Most of these cases involved fallopian tubes
    - Rare to see only ovaries involved and no precursor lesions seen in the ovaries
  - Molecular studies of high grade serous cancers
    - STICs seen in 50-60% of sporadic serous ovarian cancers
    - Serous tumors express biomarkers that resemble fallopian tube; lack markers that resemble ovary

Callahan, MJ JCO 2007
Leeper, K Gynecol Oncol. 2002
http://www.ovariancancerprevention.org/?page_id=191
Ovarian carcinogenesis

• Mouse model study
  – Mouse model created that develops high grade serous fallopian tube cancer, spreads to cover the ovaries, ascites, widespread abdominal disease
  – Histologically and molecularly resemble human ovarian cancer
  – Ovaries removed, still developed ovarian cancer
  – Fallopian tubes removed, no cancer

Kim, J. Proc Natl Acad Sci 2012
Opportunistic salpingectomy

• Most high-grade serous ovarian cancers show a precursor lesion in the fallopian tube
  – Even in patients without a genetic predisposition
• Risk-reducing bilateral salpingo-oophorectomy (RRSO) is used in BRCA patients
• Can opportunistic salpingectomy reduce the incidence and death rate from ovarian cancer in the general population?
Opportunistic salpingectomy

• No data that shows a reduction in ovarian cancer risk
• It will take decades to show a change in mortality from opportunistic salpingectomy
• Known benefits to retaining ovaries at time of hysterectomy, but not fallopian tubes
  – 12% risk of future surgery to remove retained adnexa

Opportunistic salpingectomy - risks

• ovarian function
  – Most studies show no detrimental effect on ovarian function
  – Some studies suggest reduction in follicle number, increases in FSH, and reduced blood flow to the ovaries

• Intraoperative complications
  – No difference in blood transfusion rates, intraoperative complications, or readmission rates
  – Additional 16 minutes of OR time at time of hysterectomy, 10 minutes at time of sterilization

• effectiveness of salpingectomy for sterilization unknown
• Not reversible

Dar, P. Hum Reprod 2000
Opportunistic salpingectomy-benefits

• Theoretical
  – based on what we know about carcinogenesis
• Extrapolate from tubal ligation literature
• It will be a long time until we can prove a survival benefit
Opportunistic salpingectomy—benefits

• Salpingectomy saves patients from the risks of salpingo-oophorectomy
• Salpingo-oophorectomy (BSO) reduces risk of ovarian cancer but has risks that outweigh benefits until age 65
  – Increased CV disease, osteoporosis, cognitive impairment
  – Nurses Health Study
    • Increased all-cause and cancer mortality in those who underwent BSO
Opportunistic salpingectomy-benefits

• Cost-effectiveness analysis of opportunistic salpingectomy as an ovarian cancer prevention strategy in the general population

• Simulation model estimated costs and benefits of opportunistic salpingectomy at the time of benign hysterectomy or surgical sterilization

• Effectiveness= life expectancy gained
Opportunistic salpingectomy—benefits

• Results
  – Salpingectomy with hysterectomy was less costly than hysterectomy alone or with BSO and more effective with average gains of 1 week to 2 months
  – Salpingectomy was more costly than tubal ligation, but more effective with average gain of 1 week
  – Salpingectomy would reduce ovarian cancer risk by 38.1% compared to hysterectomy alone and 29.2% compared to tubal ligation

• Conclusions
  – Salpingectomy with hysterectomy would reduce ovarian cancer risk at acceptable cost
  – Salpingectomy would be a cost-effective alternative to tubal ligation
  – Opportunistic salpingectomy should be considered for all women undergoing benign hysterectomy or tubal ligation

Kwon, JS. Obstet Gynecol. 2015
Salpingectomy- Technique

• Remove entire tube except the interstitial component
• Remove/cauterize any fimbriated attachments on the ovary
  – BRCA patients with early or pre-cancer (STICs) found at time of prophylactic BSO usually involved the fimbriated end
• Do not interrupt blood supply to the ovary
• Preserve the utero-ovarian ligament

http://memorize.com/lsar-obgyn-pt2/obinno59
Pathologic evaluation of salpingectomy

• In low-risk women- representative sections of the fallopian tube, any suspicious lesions, and entire sectioning of the fimbriae

• In high risk patients (BRCA) the entire fallopian tube is examined
Salpingectomy for Ovarian Cancer Prevention

1. “The surgeon and patient should discuss the potential benefits of the removal of the fallopian tubes during a hysterectomy in women at population risk of ovarian cancer who are not having an oophorectomy.”

2. “When counseling women about laparoscopic sterilization methods, clinicians can communicate that bilateral salpingectomy can be considered a method that provides effective contraception.”

3. “Prophylactic salpingectomy may offer clinicians the opportunity to prevent ovarian cancer in their patients.”

4. “Randomized controlled trials are needed to support the validity of this approach to reduce the incidence of ovarian cancer.”
1. Oral contraceptive use reduces the risk of ovarian cancer
2. Tubal ligation is associated with reduces risk of ovarian cancer
3. RRSO reduces ovarian cancer by 80% in BRCA patients
4. Improved identification of women at inherited high risk of ovarian/breast cancer
5. Salpingectomy as an alternative strategy to other sterilization techniques and opportunistically at the time of hysterectomy or other pelvic surgery to potentially reduce the incidence as well as death rates from ovarian cancer in the general population.
Who is doing opportunistic salpingectomy?

- Feasibility study of postpartum distal salpingectomy
  - 61 women
  - Distal salpingectomy after vaginal delivery or at time of c-section
  - Similar operating times, blood loss and complications compared to historical controls undergoing modified Pomeroy method
  - Feasible and safe
Who is doing opportunistic salpingectomy?

• Survey to determine practice patterns of general OBGYNs regarding salpingectomy at time of hysterectomy
  – 25% response rate
  – 60.7% do counsel patients about potential benefit of salpingectomy
  – Those who counsel patients about salpingectomy are more likely to perform LAVH than vaginal hysterectomy
Summary

• There has been a significant shift in the understanding of the origins of ovarian cancer
• It will be a long time before we can prove a survival advantage of opportunistic salpingectomy
• Regions of Canada and Germany have initiated programs to include opportunistic salpingectomy
• Opportunistic salpingectomy should be discussed with patients undergoing benign surgery or sterilization
• Family history should be reviewed with all patients in order to identify more patients and families at risk
• PREVENTION IS KEY!
Thank you!