Where does ovarian cancer come from?
The fallopian tube?
And why the gynecologist cares!

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I have no conflict of interests to disclose

Time to Consider: Removing the fallopian tubes

- For women who are young and carry a BRCA mutation and desirous of continued ovarian function
- At the time of routine hysterectomy or pelvic surgery post-childbearing
- Instead of tubal ligation for contraception

Timeline: Origin of serous cancer in the FT

1993
BRCA1

1997
F-ICA assoc with BRCA

2001
Tubal dysplasia in RRSO

2004
Progression of p53 signature to STIC

2007
70% of PSC involve tube

2010
P53 mutations match, molecular genetics match

Today:
Clinical Implications of FT origin

Bowtell et al, Nat Rev Can 2011
Crum, Clin Med 2007
Kurman et al, Human Path 2011
Classic thinking....

- Germ Cell (3%-5%)
- Sex Cord-Stromal (2%-3%)
- Secondary (Metastatic) (5%)
- Epithelial (EOC) (90%)


Serous Pelvic Cancer: Old school

Ovarian Cancer

Early Stage Ovarian Cancer

Ovarian Cancer Risk Reduction in average risk women and mutation carriers

- OCPs – 50% reduction in ovarian cancer risk
- BTL – up to 40% reduction in ovarian cancer risk
- Hysterectomy- 36% reduction in ovarian cancer risk for 15 years.
- Increased risk with PID

Risk Reducing salpingo-oophorectomy for BRCA mutation carriers

80-90% effective in reducing ovarian cancer
50% reduction in breast cancer if performed before age 50
Increase life expectancy 6.6-11.7 years for combined BSO, mastectomy

Microsectioning the tubes and ovaries

Sectioning of RRSO Specimens

Pathology Review of 163 RRSO Cases from UCSF

<table>
<thead>
<tr>
<th>Age</th>
<th>Surgical specimen pathology</th>
<th>Staging surgery</th>
<th>Adjuvant treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44 OSC, 0.1 cm</td>
<td>benign</td>
<td>none</td>
<td>recurrent peritoneal CA @ 19 months</td>
</tr>
<tr>
<td>2</td>
<td>40 bilateral OSC, 3.5 cm &amp; TSC, 0.5 cm</td>
<td>staged at RRSO, Stage IIC ovarian CA</td>
<td>Taxol/Carboplatin x6</td>
<td>NED @ 47 months</td>
</tr>
<tr>
<td>3</td>
<td>67 STIC Stage IIC tubal CA, washings (+)</td>
<td>Taxotere/Carboplatin x6</td>
<td>NED @ 7 months</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>52 TSC, 0.23 cm</td>
<td>Stage I tubal CA, washings (+)</td>
<td>Taxotere/Carboplatin x6</td>
<td>NED @ 90 months</td>
</tr>
<tr>
<td>5</td>
<td>52 STIC, 0.13 cm</td>
<td>benign</td>
<td>none</td>
<td>NED @ 7 months</td>
</tr>
<tr>
<td>6</td>
<td>52 OSC, 0.08 cm</td>
<td>not performed</td>
<td>none</td>
<td>recurrent peritoneal CA @ 81 months</td>
</tr>
<tr>
<td>7</td>
<td>50 STIC, 1.1 cm</td>
<td>Stage I tubal CA, washings (+)</td>
<td>Taxotere/Carboplatin x6</td>
<td>NED @ 132 months</td>
</tr>
<tr>
<td>8</td>
<td>52 OSC, 0.1 cm</td>
<td>STIC, 0.3 cm</td>
<td>benign</td>
<td>NED @ 78 months</td>
</tr>
<tr>
<td>9</td>
<td>60 STIC, 0.1 cm</td>
<td>not performed</td>
<td>none</td>
<td>NED @ 64 months</td>
</tr>
<tr>
<td>10</td>
<td>60 STIC, 0.2 cm</td>
<td>not performed</td>
<td>none</td>
<td>NED @ 64 months</td>
</tr>
<tr>
<td>11</td>
<td>52 STIC, 0.1 cm</td>
<td>not performed</td>
<td>none</td>
<td>NED @ 66 months</td>
</tr>
</tbody>
</table>

14 RRSO series: 95 of 132 occult cancers (71%) originated in the fallopian tube.

Reitma et al, Euro J Cancer, 2013
Mingels et al, Gyn Onc, 2012
Powell et all, Int J Gyn Onc 2011
Manchanda et al, BJOG, 2011
Finch et al, Gynecol Oncol 2006
Leeper et al, Jynecol Oncol 2002
Oliver et al, Br J Cancer 2004
Callahan et al, J Clin Oncol
Hermens et al Int J Cancer 2006
Laki et al, Cancer 2007
Lu et al, J Clin Oncol 2000

RRSO summary of literature

OSC = ovarian serous carcinoma
TSC = tubal serous carcinoma
STIC = serous tubal in situ carcinoma or non-invasive tubal serous carcinoma
STIC and cancer in proximity

Stepwise Progression: Precursor Lesions

Evidence compelling that HGPSC originates in the fallopian tube

- Consistent with epidemiology
- Precursor lesion in tube
- Mullerian molecular markers: PAX8, not calretinin
- Molecular markers match, P53 mutation in >80%
- STIC or tube involved in 70% of PSC in sporadic and BRCA related cancer.
- Mouse model
New Model of Serous Carcinogenesis


Serous Pelvic Cancer

Fallopian tube
peritoneal
ovarian

Salpingectomy in women with BRCA mutations

If a young woman is not ready for menopause

What about removing the tube first and removing the ovaries at a later time?

NCCN Guidelines for BRCA mutation carriers: Removal of tubes and ovaries

- After children or age 35-40
- Uptake of RRSO: 60-70%
- Median age of RRSO = 44-51
- Cardiovascular mortality increased for age 40-45
- Many of these women will not be eligible for estrogen
At Age 30, Risk of Ov Cancer

<table>
<thead>
<tr>
<th>AGE</th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>2.2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>50</td>
<td>8.7%</td>
<td>1.9%</td>
</tr>
<tr>
<td>60</td>
<td>22%</td>
<td>7.4%</td>
</tr>
</tbody>
</table>

Chen et al, JCO 2007

Salpingectomy in mutation carriers

**Pros**
- Some cancer risk reduction
- Avoid premature menopause
- Maintain option for IVF pregnancy
- Option for those unwilling to have BSO

**Cons**
- Two stages to surgery
- Delay of removing the ovaries
- May not be as effective
- No Breast cancer risk reduction

Oophorectomy reduces Breast Cancer Risk

- **BRCA1**
  - $\leq 40$: OR 0.36, CI 0.20-0.64
  - 41-50: OR 0.50, CI 0.27-0.92
  - $>50$: OR 0.66, CI 0.21-2.09

- **BRCA2**
  - $\leq 40$: OR 0.69, CI 0.25-1.95
  - 41-50: OR 0.44, CI 0.15-1.24
  - $>50$: OR 1.00, CI 0.06-16.1

Eisen et al, J Clin Oncol, 2005

Cost Effectiveness Model

<table>
<thead>
<tr>
<th></th>
<th>Average Discounted Costs (Can $)</th>
<th>Avg Life Expectancy Gain</th>
<th>Avg QALY Expectancy Gain</th>
<th>Incremental C-E Ratio (cost per QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSO @ 40</td>
<td>$25,987</td>
<td>21.15</td>
<td>17.56</td>
<td>---</td>
</tr>
<tr>
<td>Tubes @ 40</td>
<td>$38,208</td>
<td>20.74</td>
<td>18.17</td>
<td>$20,050</td>
</tr>
<tr>
<td>Tubes @ 40, Ov @ 50</td>
<td>$41,577</td>
<td>20.83</td>
<td>18.26</td>
<td>$37,805</td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSO @ 40</td>
<td>$16,932</td>
<td>22.62</td>
<td>18.87</td>
<td>---</td>
</tr>
<tr>
<td>Tubes @ 40</td>
<td>$33,150</td>
<td>22.08</td>
<td>19.51</td>
<td>$25,658</td>
</tr>
<tr>
<td>Tubes @ 40, Ov @ 50</td>
<td>$37,686</td>
<td>22.14</td>
<td>19.56</td>
<td>$88,680</td>
</tr>
</tbody>
</table>

Delayed oophorectomy with the greatest QALY

Kwon et al, Obstet Gynecol 2013
Why leave the tube in women at average risk?

In US 30% women undergo hysterectomy, 50% have ovaries and fallopian tube left in situ

~20% of women who develop ovarian cancer have had a prior hysterectomy
Up to 20% of ovarian cancer patients have had a tubal ligation
24% of ovarian cancer patients have germ-line mutations

Walsh et al, PNAS 2011
Davis et al, J La Soc 2003

When to consider removing the fallopian tube in average risk women?

Remove FT even if preserving ovaries at time of hysterectomy
Consider in place of tubal ligation
Perform salpingectomy with pelvic surgery

Removal of the tube at hysterectomy

• No detrimental effect on:
  ovarian function
  hormonal levels
  blood supply to the ovary
• If tube is left in situ, incidence of hydrosalpinx: 28%, requiring surgery 7.8%


Salpingectomy Instead of tubal ligation or at time of any pelvic surgery

Pros
• Decreased tubal pathology
• Decreased ectopic rate
• Improved sterilization efficacy
• Potential cancer risk reduction

Cons
• Requires surgery
• May be difficult to access tube
• Potential for bleeding
• May require additional equipment/incision/cost
• Uncommon cancer
Technique

BRCA 1 or 2 mutation
• Inspect entire abdomen
• Peritoneal cytology
• Remove adjacent ovarian capsule (fimbria ovarica)
• Remove all the tube
• Place in an endoscopic bag
• Pathology: microsectioning entire tubes

No known genetic risk
• Preserve the utero-ovarian ligament
• Remove or cauterize any attachments to the ovary
• If the entire fallopian tube cannot be removed, consider removing the tubal fimbrial end
• Pathology: examine the fimbriae in 2-3 cassettes.

Removal of tube vs tube and ovary

Removal of tube vs tube and ovary
Caution: Limited data on impact of Salpingectomy

• In average risk women: none
• In BRCA mutation carriers:
  Greene et al, Editorial (Am J Ob/Gyn 2011)
  Dietl et al, Opinion (Hum Reprod 2011)
  LeBlanc et al, feasibility of “radical fimbrectomy” (Gynecol Oncol 2011)
  Kwon et al, Markov model (ObGyn 2013)
  Holman et al, FORCE survey (SGO 2013)
  Clinical trial currently enrolling/proposed

Time to Consider: Removing the fallopian tubes

• For women who are young and carry a BRCA mutation and desirous of continued ovarian function
  Standard of care is risk reducing salpingo-oophorectomy

• At the time of routine hysterectomy or pelvic surgery post-childbearing
  Use judgement in vaginal hysterectomy, poor access, low visibility, high risk.

• Instead of tubal ligation for contraception
  In office procedures are lower cost.
  Use judgement in PPTL, at caesarian section.