OVARIAN CONSERVATION

MARISA ADELMAN, MD
Ovarian conservation vs removal at the time of benign hysterectomy

Marisa R. Adelman, MD; Howard T. Sharp, MD
TRENDS IN OOPHORECTOMY

- Stable rate over last 20 years: 44-47%

- Acute decline following WHI results:
  - Sharpest decline in women 45-49 years old
  - Increased rate for women >50 years old

- Age is the greatest risk factor:
  - 60% for age 45-50 years old
  - 65-70% for age >55 years old

- Associated with PMHx or FHx of breast or ovarian cancer...
  - Even when genetic mutations not identified.
WHERE DOES THE DATA COME FROM?

- Women’s Health Initiative
- Nurses Health Study
- Mayo Clinic Cohort of Oophorectomy and Aging
- Breast Cancer Detection Demonstration Project
- Dutch Breast Cancer Screening Cohort
- Swedish Health Care registers
- English Healthcare Registries
WOMEN’S HEALTH INITIATIVE (OBSERVATIONAL STUDY)

• Population:
  – Postmenopausal women
  – History of hysterectomy with/without BSO

• Purpose: To assess risk of BSO on morbidity and mortality:
  – CVD, hip fracture, cancer, and all-cause mortality.

• Study design: prospective cohort
  – Patients self-reported hospitalizations, then medical records were reviewed.
WOMEN’S HEALTH INITIATIVE (OBSERVATIONAL STUDY)

• Some things to keep in mind:
  – Use of HRT was common (78.6%)
  – Use amongst participants with a history of BSO was 68% at enrollment.
  – Use for at least 10 years amongst participants with a history of BSO was 50.4%.
  – 2,312 participants with a history of BSO (out of 14,254) had no history of HRT.
NURSES’ HEALTH STUDY

• Population:
  – Postmenopausal women (60 years and older)
  – History of hysterectomy with/without BSO

• Purpose: To assess risk of BSO on long-term mortality.
  – CHD, stroke, cancer, and all-cause mortality.

• Study design: Prospective cohort
  – Identified deaths using the National Death Index.
NURSES’ HEALTH STUDY

• Some things to keep in mind:
  – Duration of HRT was 3.3-4.5 years, depending upon age at hysterectomy and BSO status.
  – 75-80% of women having undergone BSO used HRT.
  – Approximately 3,700 participants with a history of BSO (out of approximately 17,000) had no history of HRT.
WHI VS. NHS

<table>
<thead>
<tr>
<th></th>
<th>WHI</th>
<th>NHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants:</td>
<td>~25,000</td>
<td>~30,000</td>
</tr>
<tr>
<td>Age at enrollment:</td>
<td>50-79 years (mean 63 years)</td>
<td>30-55 years</td>
</tr>
<tr>
<td>Years follow-up:</td>
<td>7.6 years</td>
<td>28 years</td>
</tr>
<tr>
<td>HRT use:</td>
<td>70-80% (depending upon BSO status) Mean of 78.6%</td>
<td>30-80% (depending upon age at hysterectomy and BSO status)</td>
</tr>
</tbody>
</table>
# All-Cause Mortality

## Table 1

<table>
<thead>
<tr>
<th>Author</th>
<th>Cohort</th>
<th>Deleterious effect of BSO</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ossewaard et al, 2005</td>
<td>Dutch breast cancer screening cohort</td>
<td>Yes</td>
<td>• 2% Decrease in total mortality per year of delayed menopause</td>
</tr>
<tr>
<td>Rocca et al, 2006</td>
<td>Mayo Clinic Cohort Study of Oophorectomy and Aging</td>
<td>Yes</td>
<td>• Increased risk of mortality with bilateral oophorectomy age &lt;45 y (HR, 1.67; 95% CI, 1.16—2.40)</td>
</tr>
<tr>
<td>Parker et al, 2009</td>
<td>Nurses’ Health Study</td>
<td>Yes</td>
<td>• Oophorectomy associated with increased risk of all-cause death (HR, 1.13; 95% CI, 1.06—1.21)</td>
</tr>
<tr>
<td>Parker et al, 2013</td>
<td></td>
<td></td>
<td>• Even higher risk of all-cause death observed in women who underwent oophorectomy age &lt;50 y, and never used estrogen therapy (HR, 1.41; 95% CI, 1.04—1.92)</td>
</tr>
<tr>
<td>Jacoby et al, 2011</td>
<td>Women’s Health Initiative</td>
<td>No</td>
<td>• BSO not associated with increased risk of death in multivariate analysis (HR, 0.98; 95% CI, 0.87—1.10)</td>
</tr>
<tr>
<td>Gierach et al, 2014</td>
<td>Breast Cancer Detection Demonstration Project</td>
<td>Yes</td>
<td>• Women who underwent BSO by age 35 y had increased risk of death from any cause (HR, 1.20; 95% CI, 1.08—1.34), which progressively decreased when surgery was performed later in life</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• By age 50 y, risk was no longer increased (HR, 1.05; 95% CI, 0.99—1.10)</td>
</tr>
<tr>
<td>Mytton et al, 2017</td>
<td>English Healthcare Registries</td>
<td>Yes</td>
<td>• Ovarian conservation was associated with significantly lower rate of all-cause death (HR, 0.64; 95% CI, 0.55—0.73)</td>
</tr>
</tbody>
</table>

BSO, bilateral salpingo-oophorectomy; CI, confidence interval; HR, hazard ratio; HT, hormone therapy.

ALL-CAUSE MORTALITY

• Vast majority of literature supports a deleterious effect of BSO.
  – Particularly when performed before age 50

• Estrogen appears to mitigate the increase in overall mortality associated with BSO.

• At no age has there been shown to be a survival benefit.
ALL-CAUSE MORTALITY: DECISION ANALYSIS


- Aim: Estimate the optimal strategy for maximizing survival in women of average risk of ovarian cancer
  - What to do with ovaries at the time of benign gynecologic surgery.
  - Considered mortality from CHD, hip fracture, stroke, ovarian cancer, and breast cancer.
ALL-CAUSE MORTALITY: DECISION ANALYSIS

• Followed hypothetical cohorts:
  – Healthy women, who underwent hysterectomy for benign disease, between the ages of 40 and 80.
    • Ovarian conservation with estrogen
    • Ovarian conservation without estrogen
    • Oophorectomy with estrogen
    • Oophorectomy without estrogen
ALL-CAUSE MORTALITY: DECISION ANALYSIS

• Reported results as survival to age 80.

• The base-case analysis considered women undergoing hysterectomy between ages 50 and 54.
  • Ovarian conservation + ET = 62.72%
  • **Ovarian conservation = 62.46%**
  • Oophorectomy + ET = 62.15%
  • **Oophorectomy = 53.88%**
ALL-CAUSE MORTALITY: DECISION ANALYSIS

• For a hypothetical cohort of 10,000 women, oophorectomy without estrogen therapy results confers **858 excess deaths**, compared to ovarian conservation:
  – 838 deaths due to CHD
  – 158 deaths due to hip fracture
  – 47 fewer deaths due to ovarian cancer
ALL-CAUSE MORTALITY: DECISION ANALYSIS

• As age at oophorectomy increases, the risk of dying approaches that of ovarian conservation.
  – Above age 64, the confidence intervals begin to overlap.

• Ovarian conservation confers benefit to long-term survival until age 65.
CANCER RISK AND MORTALITY

• It has been estimated that 1000 cases of ovarian cancer could be prevented annually if every women > 40 years old underwent BSO at the time of hysterectomy.

  – This assumes that all women are good candidates for estrogen replacement therapy, and will be completely compliant with it.
  – Markov decision analysis by Speroff et al. demonstrated a shorter life expectancy in women who underwent oophorectomy prior to age 45, with typical HT rates.
CANCER RISK AND MORTALITY

• What we **know**: oophorectomy reduces the risk of ovarian cancer.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study Type</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacoby et al, 19 2011</td>
<td>Women’s Health Initiative Observational Study</td>
<td>Lower incidence of ovarian cancer with hysterectomy and BSO (0.02%) compared to hysterectomy alone (0.33%)</td>
<td></td>
</tr>
<tr>
<td>Parker et al, 16 2013</td>
<td>Nurses’ Health Study</td>
<td>Decreased risk of ovarian cancer after hysterectomy with BSO (HR, 0.06; 95% CI, 0.02—0.17)</td>
<td></td>
</tr>
<tr>
<td>Chan et al, 24 2014</td>
<td>Kaiser Permanente of Northern California</td>
<td>Decreased risk of ovarian cancer after hysterectomy with BSO (HR, 0.12; 95% CI, 0.05—0.28)</td>
<td></td>
</tr>
</tbody>
</table>
CANCER RISK AND MORTALITY

• What we think we know: premenopausal oophorectomy reduces the risk of breast cancer.

<table>
<thead>
<tr>
<th>Study</th>
<th>Data Source</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parker et al, 2013</td>
<td>Nurses’ Health Study</td>
<td>Lower risk of breast cancer with oophorectomy age &lt;47.5 years</td>
</tr>
<tr>
<td>Robinson et al, 2016</td>
<td>Carolina Breast Cancer Study</td>
<td>Premenopausal hysterectomy and BSO associated with reduced risk of breast cancer (OR, 0.60; 95% CI, 0.47–0.77)</td>
</tr>
<tr>
<td>Mytton et al, 2017</td>
<td>English Healthcare Registries</td>
<td>Ovarian conservation associated with significantly increased rate of admission (HR, 1.34; 95% CI, 1.15–1.55), but significantly decreased rate of death from breast cancer (HR, 0.61; 95% CI, 0.39–0.94)</td>
</tr>
</tbody>
</table>
CANCER RISK AND MORTALITY

• What we **don’t know**: effects of oophorectomy on other cancers.

<table>
<thead>
<tr>
<th>Total cancer</th>
<th>Parker et al,¹⁶ 2013</th>
<th>Nurses’ Health Study</th>
<th>Higher mortality from total cancer associated with oophorectomy (HR, 1.16; 95% CI, 1.05—1.29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaudet et al,²³ 2014</td>
<td>Cancer Prevention Study-II Nutrition</td>
<td>Lower risk of total cancer associated with hysterectomy and BSO (RR, 0.9; 95% CI, 0.85—0.96)</td>
<td></td>
</tr>
<tr>
<td>Altman et al,²² 2016</td>
<td>Swedish Health Care registers</td>
<td>Lower risk of total cancer associated with hysterectomy and BSO (HR, 0.92; 95% CI, 0.87—0.96)</td>
<td>Same risk reduction observed with hysterectomy alone (HR, 0.93; 95% CI, 0.91—0.95)</td>
</tr>
</tbody>
</table>
# Cancer Risk and Mortality

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Study Authors</th>
<th>Study Type</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>Jacoby et al.</td>
<td>Women’s Health Initiative Observational Study</td>
<td>- No significant difference in colorectal cancer risk observed with hysterectomy and BSO</td>
</tr>
<tr>
<td></td>
<td>Parker et al.</td>
<td>Nurses’ Health Study</td>
<td>- Increased mortality from colorectal cancer in patients having undergone hysterectomy with BSO (HR, 1.49; 95% CI, 1.02–2.18)</td>
</tr>
<tr>
<td></td>
<td>Gaudet et al.</td>
<td>Cancer Prevention Study-II Nutrition</td>
<td>- No statistically significant difference in colorectal cancer risk observed with hysterectomy and BSO</td>
</tr>
<tr>
<td></td>
<td>Luo et al.</td>
<td>Meta-analysis</td>
<td>- Increased risk of colorectal cancer with hysterectomy and BSO (pooled RR, 1.22; 95% CI, 1.06–1.40)</td>
</tr>
<tr>
<td></td>
<td>Segelman et al.</td>
<td>Swedish Patient Registry</td>
<td>- 30% Increased risk of colorectal cancer in women who underwent BSO (HR, 2.28; 95% CI, 1.33–3.91)</td>
</tr>
<tr>
<td></td>
<td>Mytton et al.</td>
<td>English Healthcare Registries</td>
<td>- Ovarian conservation associated with significantly decreased rate of death from colon cancer (HR, 0.47; 95% CI, 0.25–0.88)</td>
</tr>
<tr>
<td>Lung</td>
<td>Koushik et al.</td>
<td>Population-based case-control</td>
<td>- Increased risk of lung cancer in women having undergone surgical menopause with BSO (OR 1.90; 95% CI, 1.18–3.06)</td>
</tr>
<tr>
<td></td>
<td>Jacoby et al.</td>
<td>Women’s Health Initiative Observational Study</td>
<td>- No significant difference in lung cancer risk observed with hysterectomy and BSO</td>
</tr>
<tr>
<td></td>
<td>Parker et al.</td>
<td>Nurses’ Health Study</td>
<td>- Increased risk of lung cancer mortality (HR, 1.29; 95% CI, 1.04–1.61) with oophorectomy</td>
</tr>
<tr>
<td></td>
<td>Gaudet et al.</td>
<td>Cancer Prevention Study-II Nutrition</td>
<td>- No statistically significant difference in lung cancer risk observed with hysterectomy and BSO</td>
</tr>
<tr>
<td></td>
<td>Mytton et al.</td>
<td>English Healthcare Registries</td>
<td>- Ovarian conservation associated with significantly decreased rate of admission (HR, 0.66; 95% CI, 0.48–0.91), and no difference in rate of death from lung cancer</td>
</tr>
</tbody>
</table>
CHD RISK AND MORTALITY

• **NHS and WHI disagree**

• **Per NHS:**
  - Women s/p BSO and never treated with estrogen had an increased risk of CHD.
    - Use of estrogen therapy in the early postmenopausal period of surgically menopausal women eliminated the increased risk.
    - Estrogen therapy after natural menopause did not effect risk

• **Per WHI:**
  - BSO is not associated with increased risk of fatal or non-fatal CHD.
CHD RISK AND MORTALITY

**Rate of past or current HT use in WHI was 78.6%.

- Role of oophorectomy on CHD may be time-dependent.
- Proximity to natural menopause may be an important determinant of impact of BSO on CHD.
- HT in the years that follow BSO may partially or completely mitigate the effects on CHD.
## CHD Risk and Mortality

<table>
<thead>
<tr>
<th>Author</th>
<th>Cohort</th>
<th>Deleterious effect of BSO</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colditz et al,</td>
<td>Nurses’ Health Study</td>
<td>Yes</td>
<td>● Increased risk of CHD after BSO in women who were never treated with HT (rate ratio, 2.2; 95% CI, 1.2—4.2)</td>
</tr>
<tr>
<td>(1987)</td>
<td></td>
<td></td>
<td>● Use of HT in early postmenopausal period after BSO eliminated increased risk</td>
</tr>
<tr>
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<td></td>
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</tr>
<tr>
<td>Parker et al,</td>
<td>Nurses’ Health Study</td>
<td>Yes</td>
<td>● Increased risk of CHD at all ages after BSO (HR, 1.17; 95% CI, 1.02–1.35)</td>
</tr>
<tr>
<td>(2009)</td>
<td></td>
<td></td>
<td>● Greater increased risk observed after BSO age &lt;45 y (HR, 1.26; 95% CI, 1.04–1.54)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>● Greatest increased risk observed after BSO age &lt;50 y, and not treated with HT (HR, 1.98; 95% CI, 1.18—3.32)</td>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Rivera et al,</td>
<td>Mayo Clinic Cohort Study of</td>
<td>Yes</td>
<td>● Most dramatic increase in CHD mortality observed with BSO &lt;45 y, either not treated with HT to age 45 y, or interrupted treatment age &lt;45 y (HR, 1.84; 95% CI 1.27—2.68)</td>
</tr>
<tr>
<td>(2009)</td>
<td>Oophorectomy and Aging</td>
<td></td>
<td>● No increase in CHD mortality when women were treated with HT until age 45 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ingelsson et al.</td>
<td>Swedish Health Care registers</td>
<td>Yes</td>
<td>● Hysterectomy with BSO associated with 40% increased risk of CHD in women age &lt;50 y (HR, 2.22; 95% CI, 1.01—4.83)</td>
</tr>
<tr>
<td>(2011)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jacoby et al,</td>
<td>Women’s Health Initiative</td>
<td>No</td>
<td>● BSO not associated with increased risk of CHD in all-comers, or women who never used HT</td>
</tr>
<tr>
<td>(2011)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BSO, bilateral salpingo-oophorectomy; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; HT, hormone therapy.

COGNITIVE FUNCTIONING

• Healthy cell bias theory:
  – Estrogens are neuroprotective of healthy neurons.
  – Estrogens accelerate degeneration of cells that have already undergone pathologic changes.

• Critical time window theory:
  – Initiation of HT around the time of menopause can be beneficial.
  – Initiation of HT in late menopause can be deleterious.
COGNITIVE FUNCTIONING

• Increased risk of cognitive impairment or dementia after surgical menopause:
  – Trend towards increasing risk with younger age at the time of surgery.
  – Association disappears when ET given until age 50.
  – No apparent benefit to the initiation of ET in older postmenopausal women.
COGNITIVE FUNCTIONING

• Earlier age of surgical menopause associated with a steeper slope of cognitive decline and Alzheimer disease neuropathology:
  – Decreased slope of decline observed when HT was initiated within 5 years of menopause, and continued for at least 10 years.
  – No attenuation of decline when HT was initiated more than 5 years after surgical menopause.
SEXUAL FUNCTIONING

- The data is mixed, but by-and-large, BSO at the time of hysterectomy confers a deleterious effect on sexual functioning.

- The effect of hysterectomy alone is unclear.

- There is a complex relationship between abruptness of hormone loss, proximity to menopause, and use of HRT.
SEXUAL FUNCTIONING

• Hormone therapy appears to mitigate some of the physical consequences of oophorectomy, but not necessarily desire, orgasm, or satisfaction.

• BSO at any age confers a risk of HSDD.
  – This is demonstrated most robustly in the population of women age <50 years at the time of surgery.
OSTEOPOROTIC FRACTURE RISK

• There is clear and convincing evidence that estrogen deficiency is associated with bone loss.
  – ≥75% of bone loss occurs during the first 2 decades after menopause.

• The effects of HT on hip fracture risk disappear within 2 years of cessation.

• An increased fracture rate was observed following BSO after natural menopause had occurred.
SUBSEQUENT SURGERY

• In a study of long-term follow-up:
  – The cumulative incidence of subsequent surgery was 9.2% at 30 years post-hysterectomy.
  – The cumulative incidence of subsequent surgery was 7.3% at 30 years in a referent group with intact uterus and ovaries.
OVARIAN CANCER PREVENTION

• A subset of cancers will arise from a background of endometriosis, inflammation, and reactive oxidative species, presumably from retrograde menstruation.

• A subset of cancers will arise from precursor lesions of the fallopian tube.

• Risk reduction can be achieved through hysterectomy and salpingectomy alone.
CONCLUSIONS: OVERALL MORTALITY

• There appears to be a deleterious effect of oophorectomy on overall mortality, particularly when completed prior to age 50.

• While HT may mitigate the increased mortality with oophorectomy, at no age does there appear to be a survival benefit.

• Ovarian conservation may even confer a long-term survival benefit until the age of 65.
CONCLUSIONS: CANCER MORTALITY

- There is a significantly lower rate of ovarian cancer observed after oophorectomy at all ages, and a decreased risk of breast cancer when oophorectomy is completed prior to age 47.5 years.

- The relationship between oophorectomy and all-site cancer, colorectal cancer, and lung cancer is unclear, although the majority of data favor a lower risk with ovarian conservation.
CONCLUSIONS: CHD

- The existing data does not universally implicate BSO in CHD, but there are no data which supports a beneficial effect of oophorectomy on CHD.

- In aggregate, ovarian preservation is associated with an observed benefit to cardiovascular health.
CONCLUSIONS: COGNITIVE FUNCTIONING

• Global cognitive decline, dementia, and Alzheimer’s Disease risk may share a common correlate with estrogen deficiency.

• Surgical menopause appears to confer a risk that is not observed with post-menopausal oophorectomy and natural menopause.
CONCLUSIONS: SEXUAL FUNCTIONING

• Oophorectomy at the time of hysterectomy confers a deleterious effect on sexual functioning.

• Hormone therapy appears to mitigate some of the physical consequences of oophorectomy, but not necessarily desire, orgasm, or satisfaction.
CONCLUSIONS: BMD AND FRACTURE RISK

• Estrogen deficiency following natural or surgical menopause is associated with BMD loss and increased fracture risk.

• HT can halt bone density loss, but the effect is limited to the duration of use, and significant losses can be observed within 2 years of cessation.
CONCLUSIONS: SUBSEQUENT SURGERY

• Routine removal of the ovaries for the purpose of avoiding future surgery is unjustified.
CONCLUSIONS: CANCER PREVENTION

• In the absence of a genetic susceptibility mutation, tubal ligation, salpingectomy, and hysterectomy can provide ovarian cancer risk reduction to women of average risk, without the untoward effects of oophorectomy, and without the need for HT.
REFERENCES


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