Ovarian Cancer Prevention in High-Risk Patients

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Disclosures

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No. 366-Gynaecologic Management of Hereditary Breast and Ovarian Cancer

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HEREDITARY BREAST AND OVARIAN CANCER

Bottom Line: Breast cancer is relatively common in the general population (12% lifetime risk) and the majority of cases occur sporadically. About 5-10% of breast cancer is due to an inherited gene change. Mutations in the genes BRCA1 or BRCA2 are the most common cause of hereditary breast and ovarian cancer (HBOC) and BRCA1 and BRCA2
Over 3100 Canadian women are diagnosed with ovarian cancer every year.

Second most common gynecologic malignancy.

Most lethal gynecologic malignancy, and the fifth ranking cause of cancer death for women.

45% survival
How to manage that risk?

- Ovarian Cancer
- Surgical Complications
- Cardiovascular Disease
- Bone Health
- Cognition
- Quality of Life
- Sexual Health

Gaba 2022 J Med Genetics
In 2023 Genetic Testing ➡️ Prevention

You only find what you look for.

You only diagnose what you know.
Hereditary Ovarian Cancer is more than BRCA 1 & 2
Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial


Summary
Background Ovarian cancer has a poor prognosis, with just 40% of patients surviving 5 years. We designed this trial to establish the effect of early detection by screening on ovarian cancer mortality.

Methods In this randomised controlled trial, we recruited postmenopausal women aged 50–74 years from 13 centres in National Health Service Trusts in England, Wales, and Northern Ireland. Exclusion criteria were previous bilateral oophorectomy or ovarian malignancy, increased risk of familial ovarian cancer, and active non-ovarian malignancy. The trial management system confirmed eligibility and randomly allocated participants in blocks of 32 using comput-
OCP and Ovarian Cancer Risk

Schrijver 2020; Cibula 2018; Huber 2020; *the lancet* Vol 371, 2008

OCP in *BRCA* carriers
- 2855 breast cancer cases
- 1503 ovarian cancer cases
- RR 0.50 (0.33-0.75)
- 36% reduction in ovarian cancer with each additional 10 years of use
- Breast cancer risk data is heterogeneous
Risk-reducing Bilateral Salpingo-Oophorectomy (RRBSO) to Prevent Ovarian Cancer

Figure 5 Forest plots of relative risk (RR) estimates for risk reduction of ovarian cancer associated with risk-reducing salpingo-oophorectomy in BRCA 1 (a) and BRCA 2 (b) mutation carriers.
10 cohort studies
8087 participants (2936 surgery and 5151 control participants)
BRCA1 and BRCA2
RRSO versus no RRSO
Follow-up period ranged from 0.5 to 27.4 years.

Overall survival was longer with RRSO (HR 0.32, 95% CI 0.19 to 0.54; P < 0.001)
HGSC cancer mortality (HR 0.06, 95% CI 0.02 to 0.17; I² = 69%; P < 0.0001)
Breast cancer mortality (HR 0.58, 95% CI 0.39 to 0.88; I² = 65%; P = 0.009)
None of the studies reported bone fracture incidence.
Ovarian cancer risk perception quality of life (MD 15.40, 95% CI 8.76 to 22.04; P < 0.00001)
BRCA2 c. 6065 C > G
35-40y for BRCA1
40-45y for BRCA2
45-50y for RAD51C
45-50y for RAD51D
45-50y for BRIP1
> 45y for PALB2

Recommended Timing
Pathologic Review of Fallopian Tubes

SEE FIM Protocol
Practical Approach to RRSO

Timing
- BRCA 1 or 2
- Work around
  - breast cancer recovery
  - mastectomy/reconstruction
  - Personal considerations

Pathologic processing of specimens

Unexpected findings at OR
- occult pre-invasive findings
- overt cancer

Role of hysterectomy
The Role of Hormone Replacement Therapy

- Mitigates many adverse health effects associated with premature surgical menopause:
  - Prevents bone mineral density loss and fractures
  - Reduces the risk of cardiovascular disease
  - Decreases risk of all cause mortality

- **Johansen (2020)** → HRT users had lower total cholesterol and waist circumferences, suggesting lower rates of metabolic syndrome
  - **Hickey (2021)** → waist and hip ratios significantly increased following RRBSO and this increase was prevented by HRT use

- **Kotsopoulos et al (2019)** → HRT use after premenopausal RRBSO was associated with reduced bone loss compared to non-users
  - (-2.00% vs -4.69%, p=0.02 lumbar spine) (-1.38% vs. -3.21%, p=0.04 total hip)

- **Challberg et al (2011)** → prevalence of reduced bone mass was much greater among women who had over 24 months of estrogen deprivation compared to those who used HRT.
  - Osteoporosis 13% HRT users vs. 3% non users

- **Jiang et al. (2021)** → HRT use mitigated the loss of bone density with RRBSO
HRT Safety in High-Risk Patients

- **Rebbeck et al. (2005)**: RRBSO was associated with reduced breast cancer (BC) risk (HR 0.40 [95% CI 0.18, 0.92]) compared to BRCA carriers without RRBSO or HRT use.

- **Eisen et al. (2008)**: Decreased odds of BC risk associated with HRT use (OR 0.58 [95% CI 0.35, 0.96]).

- **Domchek et al. (2011)**: HRT use following RRBSO was not associated with an increase in risk of BC in BRCA1 carriers (HR 0.52 [95% CI 0.30, 0.92]) and BRCA2 carriers (HR 0.24 [95% CI 0.05, 1.03]).

- **Kotsopoulos et al. (2016)**: HRT use regardless of formulation was not associated with BC (OR 0.80 [95% CI 0.55, 1.16]).

- **Kotsopoulos et al. (2018)**: HRT use after RRBSO was not associated with an increased risk of BC (HR 0.97 [95% CI 0.62, 1.52]). After 10 years of follow-up, the cumulative incidence of BC was significantly lower among ET users compared to EPT users.

- **Michaelson-Cohen et al. (2021)**: RRBSO < 45 years: HRT did not increase the odds of BC (OR 0.8 [95% CI 0.3, 1.9]).

Review Manchanda 2022
Mainstreaming of Genetic Testing
Personalized care is essential

Ongoing clinical relationships are essential

Alternatives to oophorectomy need research
Gynecologic Oncology Survivorship Clinic
Personalized Gynecologic Cancer Prevention & Survivorship

The Division of Gynecologic Oncology is launching a new clinic to serve patients in BC with high hereditary risk for gynecologic cancer. The mission of this clinic is to improve the quality of peri-operative care, education and hormone therapy support for patients embarking on preventative gynecologic surgery.

Referrals  kate.fang@vch.ca  605 875 4111 ext 20153. Fax 604 875 5807
Optional Slides for Discussion
How to find people at high risk?

- All ovarian patients need genetic testing
- Ask about family history
  - Young breast
  - ANY ovarian
  - Multiple cancers in one person
  - Limited paternal female relatives
  - Ashkenazi Jewish ancestry
- Support carriers in family communication
Family History Factors to Consider

• Limited paternal history
• Few women in the family
• Adopted
• Ashkenazi Jewish Ancestry 1/40

Actual population rates are higher than previously thought 1.64% in large studies*

*Couch NEJM CARRIERS Study 2021
Cancer Genetics is Evolving

• Genetic testing changed
• Access to testing is improving
• Value of genetic information for patients is expanding i.e. parp inhibitor
• highly effective
• Many new genes to consider
Should hysterectomy be done at the time of RRSO?

<table>
<thead>
<tr>
<th>Disadvantages</th>
<th>Benefits</th>
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<tr>
<td>OR time</td>
<td>Simplifies post surgery HRT</td>
</tr>
<tr>
<td>Recovery time</td>
<td>? Risk of serous endometrial cancer *</td>
</tr>
<tr>
<td>Complication Rate</td>
<td>Eliminates endometrial cancer risk if on tamoxifen</td>
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</tbody>
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* Prophylactic specimens 1083 BRCA 1 carriers
  Incidental uterine cancer in 8 patients

Who to refer?

- Patients having risk reducing gynecologic surgery due to a known mutation in BRCA1&2, BRIP1, RAD51C, RAD51D, PALB2 or Lynch Syndrome.

- Patients with uninformative genetic testing (no mutation OR variant of uncertain significance) and concerns about family cancer history.

- Patients requiring complex post-surgical menopause care.

- Patients requesting individualized assessment and advice regarding hereditary risk and prophylactic surgery options.

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