REVIEW

Risk reduction strategies for BRCA1/2 hereditary ovarian cancer syndromes: a clinical practice guideline

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Abstract

Objective: The purpose of this guideline is to make recommendations regarding the care of women who harbour a pathogenic or likely pathogenic variant in BRCA1 and BRCA2.

Methods: Draft recommendations were formulated based on evidence obtained through a systematic review of RCTs, comparative retrospective studies and guideline endorsement. The draft recommendations underwent an internal review by clinical and methodology experts, and an external review by clinical practitioners.

Results: The literature search yielded 1 guideline, 5 systematic reviews, and 15 studies that met the eligibility criteria.

Conclusions: In women who harbour a pathogenic or likely pathogenic variant in BRCA1 and BRCA2, screening for ovarian cancer is not recommended. Risk-reducing surgery is recommended to reduce the risk of ovarian cancer. In the absence of contraindications, premenopausal women undergoing RRSO should be offered hormone therapy until menopause. Systemic hormone replacement therapy, is not recommended for women who have had a personal history of breast cancer. RRSO should be considered for breast cancer risk reduction in women younger than 50 years. After a breast cancer diagnosis, RRSO for breast cancer mortality reduction can be considered within two years to women who harbour a pathogenic or likely pathogenic variant in BRCA1 if younger than the recommended age range for ovarian cancer risk reduction. RRSO before the age of 40 and specifically for breast cancer treatment in BRCA2 should be considered only if recommended by their breast cancer oncologist. Following RRSO, it is not recommended to do surveillance for peritoneal cancer.

Keywords: Cancer Care Ontario, Surgery, Systemic treatment, Ovarian cancer, BRCA1/2, HBOC, RRSO, Screening, Guideline recommendations

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Introduction
In 2020, ovarian cancer will account for 4.9% of deaths from cancer in Canada [1]. Approximately 5 to 15% of these cancers will occur in women with the BRCA1 and BRCA2 genes [1]. In women with a hereditary ovarian cancer syndrome the cumulative chance of developing ovarian cancer to the age of 80 years is 44% for BRCA1 and 17% for BRCA2 carriers. This is significantly greater than the general population (1.7%) [2].

Many women at risk of ovarian cancer are recommended to undergo RRSO. However, this surgery causes infertility, premature menopause, and risks for early cardiovascular disease, cognitive decline, and osteoporosis if done before menopause [3]. Screening modalities described are mostly comprised of a CA125 blood test, and TVU. However, it is not known if these screening modalities actually help to detect cancer earlier or what the optimal timing should be for high-risk women. A viable ovarian cancer screening protocol is needed.

This systematic review has been registered on the PROSPERO website (International prospective register of systematic reviews) with the following registration number CRD42018110541. Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=110541.

The Working Group members of the Risk Reduction for Hereditary Ovarian Cancer Syndromes GDG (Guideline Development Group) developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objectives of this guideline, the Working Group derived the research questions outlined below.

1. In women who harbour a pathogenic or likely pathogenic variant in BRCA1 and BRCA2 and are at increased risk for epithelial ovarian, fallopian tube, or primary peritoneal cancer, does screening with either serial U/S, CA125 or ROCA (Risk of Ovarian Cancer Algorithm), decrease their risk of ovarian cancer?
2. In women who harbour a pathogenic or likely pathogenic variant in BRCA1 and BRCA2 and are at increased risk for epithelial ovarian, fallopian tube, or primary peritoneal cancer, what is the optimal strategy to prevent these cancers?
3. What is the optimal post-surgical management protocol to address the sequelae of RRSO (Risk-Reducing Salpingo-Oophorectomy) in women who harbour a pathogenic or likely pathogenic variant in BRCA1 and BRCA2?

Target population
These recommendations apply to women who harbour a pathogenic or likely pathogenic variant in BRCA1 and BRCA2.

Intended users
This guideline is targeted for: clinicians involved in the care of women who harbour a pathogenic or likely pathogenic variant in BRCA1 and BRCA2.

Development of recommendations
The Program in Evidence-based Care (PEBC) produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [4, 5]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts, patient and caregiver review, and external review by Ontario clinicians and other stakeholders.

The project was led by a small Working Group of the Gynecologic GDG members, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in surgical oncology, medical oncology, genetics and health research methodology.

Literature search results
Search for existing guidelines, systematic reviews and primary literature
As a first step in developing this guideline, a search for existing guidelines and systematic reviews was undertaken to determine if an existing guideline or systematic review could be adapted or endorsed. To this end, practice guideline databases, guideline developer websites along with Medline, the Cochrane Database of Systematic reviews and EMBASE (2004-2020) were searched. Identified guidelines were evaluated using the AGREE II tool [6]. Any identified systematic reviews that addressed the research questions were assessed using A Measurement Tool to Assess Systematic Reviews (AMSTAR 2) [7]. The results of the AMSTAR 2 assessment were used to determine whether or not any existing review could be incorporated as part of the evidentiary base.

The search for guidelines and systematic reviews uncovered 6611 documents, of these, 119 underwent full-text review. One guideline, five systematic reviews and 15 studies from the primary literature were retained.

The Working Group members reviewed the guidelines in detail and reviewed each recommendation of that
A stage shift was detected in the UK FOCSS study by Rosenthal et al. Only two studies showed a slight benefit in survival [3, 13]. The four randomized trials found no differences in survival with screening to detect ovarian cancer compared to usual care [14–16, 19]. Only two studies showed a slight benefit in survival [3, 13]. A stage shift was detected in the UK FOCSS study by Rosenthal et al.

The Working Group members weighed the benefits and harms and determined that mortality was a key outcome. The evidence does not show a benefit for survival in screening for ovarian cancer.

Recommendation 2
Risk-reducing surgery is recommended to reduce the risk of ovarian cancer in women with a hereditary predisposition or risk. This is endorsed from Jacobson et al. 2018 [23].

Key Evidence for Recommendation 2
We endorse the recommendations from the clinical practice guideline conducted by Jacobson et al. [23] on behalf of the SOGC (The Society of Obstetricians and Gynaecologists of Canada). This guideline scored well on the AGREE II scale. The scores are reported in Table 4–3 in Section 4 of this document. The evidence underpinning the recommendations is comprised of one randomized study and one comparative study.

Justification for Recommendation 2
The Working Group members are confident in their endorsement of this recommendation. The source had adequate quality ratings, there is an excellent alignment with research questions of interest to the Working Group, methods and evidence and synthesis are convincing, and the treatments and patients included in the evidence base are generalizable to the Ontario context.

Recommendation 3
It is premature to recommend acetylsalicylic acid for ovarian cancer prophylaxis in women who harbour a pathogenic or likely pathogenic variant in BRCA1 and BRCA2. This is endorsed from Jacobson et al. 2018 [23].

Qualifying Statements for Recommendation 3
• There is an ongoing clinical trial (NCT03480776) determining the effectiveness of the use of acetylsalicylic acid in ovarian cancer.

Key Evidence for Recommendation 3
We endorse the recommendations from the clinical practice guideline conducted by Jacobson et al. [23] on behalf of the SOGC. This guideline scored well on the AGREE II scale. The scores are reported in Table 4–3 in Section 4 of this document. The evidence underpinning the recommendations is comprised of 12 population-based case-control studies.

Justification for Recommendation 3
The Working Group members are confident in their endorsement of this recommendation. The source had adequate quality ratings, there is an excellent alignment with research questions of interest to the Working Group, methods and evidence and synthesis are convincing, and the treatments and patients included in the evidence base are generalizable to the Ontario context.

Recommendation 4
In the absence of contraindications, premenopausal women who harbour a pathogenic or likely pathogenic variant in BRCA1 and BRCA2 undergoing RRSO should be offered hormone therapy until the average age of menopause (age 51).
Recommendations, key evidence, and interpretation of evidence (Continued)

• Systemic HRT, at any age, is not recommended for women who harbour a pathogenic or likely pathogenic variant in BRCA1 and BRCA2 who have had a personal history of breast cancer. These women can be offered non-hormonal alternatives for vasomotor symptom management.
• Symptoms related to the genitourinary syndrome of menopause should be treated with moisturizers, lubricants, and local low-dose estrogen therapy as needed.

Qualifying Statements for Recommendation 4
• The treatment of symptoms relating to the genitourinary syndrome of menopause in the third bullet point is based on accepted general practice and not BRCA-carrier-specific evidence.
• Where combination HRT is used, it is prudent to choose progesterone over synthetic progestins, or the TSEC (Tissue-Selective Estrogen Complex) [24].

Key Evidence for Recommendation 4

Five meta-analyses concerning HRT use in women who harbour a pathogenic or likely pathogenic variant in BRCA1 and BRCA2 were found [25–29]. The systematic review by Gordhandas et al. evaluated five studies that demonstrated that women who used HRT reported fewer endocrine symptoms (p < 0.05) and had similar levels of sexual functioning when compared to women without HRT after RRSO. Women had less discomfort (p = 0.001) and HRT reduced dyspareunia (p = 0.027) [26]. In the Gordhandas et al. systematic review bone health was assessed by three studies. The studies demonstrated that in women who used HRT the OR for bone disease was 1.2 (95% CI, 0.4 to 3.7). Another study showed that women who had been deprived of estrogen for greater than two years had a higher prevalence of bone loss compared with women who took HRT.

The risk of developing breast cancer was assessed by three systematic reviews. All three reviews showed that taking HRT was not associated with an increase in breast cancer diagnosis. The systematic review and meta-analysis by Marchetti et al. included three studies. The risk of breast cancer associated with HRT use after RRSO was 1.01 (95% CI, 0.16 to 1.54). When limited to prospective trials, the risk of breast cancer in women who harbour a pathogenic or likely pathogenic variant in BRCA1 and BRCA2 who used HRT did not have a negative impact (HR, 0.98; 95% CI, 0.63 to 1.52). A subgroup analysis on the type of HRT showed no significant difference in breast cancer risk for women who used estrogen alone compared to estrogen and progesterone. However, the breast cancer risk was lower for women who used estrogen alone versus estrogen and progesterone in the overall population (OR, 0.62; 95% CI, 0.29 to 1.31) [27].

The systematic review by Vermeulen et al. also examined the risk of breast cancer in women taking HRT following RRSO. Seven studies were evaluated and none of the studies showed that short-term use (2.8 to 4.3 years) was associated with an increase in breast cancer risk [28].

Recommendation 5
• RRSO should be offered to women who harbour a pathogenic or likely pathogenic variant in BRCA1 after the age of 35 and BRCA2 from between 40 and 45 years for ovarian/tubal/peritoneal carcinoma risk reduction.
• For women diagnosed as pathogenic variant carriers after menopause, RRSO should be offered upon diagnosis.
• RRSO should be considered for breast cancer risk reduction in women younger than 50 years who harbour a pathogenic or likely pathogenic variant in BRCA2.
• After a breast cancer diagnosis, RRSO for breast cancer mortality reduction can be considered within two years to women who harbour a pathogenic or likely pathogenic variant in BRCA1 if younger than the recommended age range for ovarian cancer risk reduction. RRSO before the age of 40 and specifically for breast cancer treatment in BRCA2 should be considered only if recommended by their breast cancer oncologist.

This is endorsed from Jacobson et al. 2018 [23].

Qualifying Statements for Recommendation 5
• In a Canadian cohort study, 3722 unaffected women who harboured a pathogenic or likely pathogenic variant in BRCA1 and BRCA2 who had undergone only RRSO were followed until breast cancer diagnosis, prophylactic bilateral mastectomy, or death. In BRCA1 carriers, HRs of breast cancer after RRSO were not significant at 0.96 (95% CI, 0.73 to 1.26), nor were they significant in BRCA2 carriers (HR, 0.65; 95% CI, 0.37 to 1.16). However, when the latter group was stratified by age, RRHSO had a significant reduction in breast cancer incidence when it was performed before the age of 50 years (HR, 0.18; 95% CI, 0.03 to 0.63) [30].

Key Evidence for Recommendation 5

We endorse the recommendations from the clinical practice guideline conducted by Jacobson et al. [23] on behalf of the SOGC. This guideline scored well on the AGREE II scale. The scores are reported in Table 4–3 in Section 4 of this document. The evidence underpinning the recommendations is primarily comprised of a guideline from 2017 and comparative studies.

Justification for Recommendation 5

The Working Group members are confident in their endorsement of this recommendation. The source had adequate quality ratings, there is an excellent alignment with research questions of interest to the Working Group, methods and evidence and synthesis are convincing, and the treatments and patients included in the evidence base are generalizable to the Ontario context.

Recommendation 6
• Bilateral salpingectomy alone for ovarian/tubal/peritoneal cancer risk reduction in women who harbour a pathogenic or likely pathogenic variant in BRCA1 and BRCA2 is still under investigation and should only be offered as an alternative to RRSO under a research protocol or if RRSO is an unacceptable choice for the patient.
• Bilateral salpingectomy is an option for women who harbour a pathogenic or likely pathogenic variant in BRCA1 and BRCA2 who are younger than the recommended age for RRSO and do not wish to conceive further pregnancies (without assisted reproductive technologies).
• The inclusion of hysterectomy with RRSO for harbour a pathogenic or likely pathogenic variant in BRCA1 and BRCA2 should be individualized, taking into account risk factors for uterine cancer, other uterine pathology, and tamoxifen use.
• There are insufficient data to routinely recommend hysterectomy to reduce the risk of papillary serous uterine cancer in women who harbour a pathogenic or likely pathogenic variant in BRCA1. This is endorsed from Jacobson et al. 2018 [23].

Qualifying Statements for Recommendation 6
• A 2016 Dutch study examined mathematical models for ovarian cancer risk reduction following two-step surgery in women who harbour a pathogenic
Recommendations, key evidence, and interpretation of evidence (Continued)

or likely pathogenic variant in \( \text{BRCA1} \) and \( \text{BRCA2} \). The investigators determined that whether salpingectomy offers (at its worst) a 35% risk reduction in ovarian cancer or (at its best) performs at the level of RRSO, an interval salpingectomy followed by bilateral oophorectomy five years later within the recommended window for preventive surgery affords risk reduction similar to that with RRSO alone [31].

Key Evidence for Recommendation 6

We endorse the recommendations from the clinical practice guideline conducted by Jacobson et al. [23] on behalf of the SOGC. This guideline scored well on the AGREE II scale. The scores are reported in Table 4–3 in Section 4 of this document. The evidence underpinning the recommendations is primarily comprised of a guideline from 2017 and comparative studies.

Justification for Recommendation 6

The Working Group members are confident in their endorsement of this recommendation. The source had adequate quality ratings, there is an excellent alignment with research questions of interest to the Working Group, methods and evidence and synthesis are convincing, and the treatments and patients included in the evidence base are generalizable to the Ontario context.

Recommendation 7

All RRSO for women who harbour a pathogenic or likely pathogenic variant in \( \text{BRCA1} \) and \( \text{BRCA2} \) should be performed by a skilled gynecologist. It is imperative that specimens be examined by an experienced pathologist familiar with the Sectioning and Extensively Examining the FIMbred End technique and diagnostic criteria. Should an invasive or occult carcinoma be found, patients should be referred to a gynecologic oncologist. This is endorsed from Jacobson et al. 2018 [23].

Key Evidence for Recommendation 7

We endorse the recommendations from the clinical practice guideline conducted by Jacobson et al. [23] on behalf of the SOGC. This guideline scored well on the AGREE II scale. The scores are reported in Table 4–3 in Section 4 of this document. The evidence underpinning the recommendations is primarily comprised of comparative studies and one clinical practice guideline from 2015.

Justification for Recommendation 7

The Working Group members are confident in their endorsement of this recommendation. The source had adequate quality ratings, there is an excellent alignment with research questions of interest to the Working Group, methods and evidence and synthesis are convincing, and the treatments and patients included in the evidence base are generalizable to the Ontario context.

Recommendation 8

Post-oophorectomy care should be administered in an individualized manner, ensuring optimal QoL, bone health, and cardiovascular risk amelioration. This is endorsed from Jacobson et al. 2018 [23].

Qualifying Statements for Recommendation 8

- Because of the increased risk of osteoporosis following pre-mature menopause, undergoing dual x-ray absorptiometry scan one year following RRSO is suggested, then determining the future frequency based on those results.
- Cardiovascular disease risk should be followed and ameliorated by the primary care practitioner or internist, while encouraging healthy lifestyle choices for these women.

Related guidelines

Tinmouth J, Zwaal C, Gryfe R, Carroll JC, Baxter N, McCurdy BR, Ferguson SE. Cancer Screening for Persons at Risk for or Affected with Lynch Syndrome Evidence. Toronto (ON): Cancer Care Ontario; 2018 October 22. Program in Evidence-Based Care Guideline No.: 15-16es.

Review and update

Guidelines developed by the PEBC are reviewed and updated regularly. Please visit the CCO Web site (http://www.cancercare.on.ca) for the full evidence-based series report and subsequent updates.

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Several studies have shown that CA125 levels are elevated in patients with ovarian cancer. For example, a study by Chen et al. (2014) showed that CA125 levels were significantly higher in patients with ovarian cancer compared to those with benign conditions.

Other studies have also demonstrated the usefulness of CA125 in the diagnosis of ovarian cancer. For instance, a study by Buys et al. (2014) found that CA125 levels were predictive of ovarian cancer risk in women with a family history of the disease.

In addition to CA125, other markers have also been studied for their potential role in the early detection of ovarian cancer. For example, a meta-analysis by Higgins and Green (2011) found that the use of CA125 combined with other markers, such as HE4, could improve the accuracy of ovarian cancer screening.

Despite these findings, the use of CA125 in clinical practice remains controversial. Some studies have shown that CA125 levels may not be as reliable as initially thought, and that they may not be able to distinguish between benign and malignant conditions in all cases.

In conclusion, while CA125 remains a widely used marker for the detection of ovarian cancer, its limitations should be recognized, and other markers, such as HE4, should be considered in combination with CA125 to improve the accuracy of ovarian cancer screening.

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