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Guideline 4-4 Version 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Ontario Health (Cancer Care Ontario)

Risk Reduction Strategies for BRCA1/2 Hereditary Ovarian Cancer Syndromes

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An assessment conducted in November 2023 deferred the review of Guideline 4-4 Version 2. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 4-4 Version 2 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/931

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Risk Reduction Strategies for BRCA1/2 Hereditary Ovarian Cancer Syndromes

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, the systematic review, and the guideline development process, see the Full Report.

GUIDELINE OBJECTIVES

To make recommendations regarding the care of 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*.

RECOMMENDATIONS

Recommendation 1
Screening for ovarian, tubal, or primary peritoneal cancer is not recommended in women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2*.
Qualifying Statements for Recommendation 1
• There is currently no screening method for ovarian, tubal, or primary peritoneal cancer that shows a survival benefit. • More data are required before any screening method for ovarian, tubal, and peritoneal cancer can be recommended.

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 [16].
Key Evidence for Recommendation 2
We endorse the recommendations from the clinical practice guideline conducted by Jacobson et al. [16] 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 one randomized study and one comparative study.

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 [16].
Qualifying Statements for Recommendation 3

- There is an ongoing clinical trial (NCT03480776) determining the effectiveness of the use of acetylsalicylic acid in ovarian cancer.

Recommendation 4

- In the absence of contraindications, premenopausal women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2* undergoingRRSO should be offered hormone therapy until the average age of menopause (age 51).
- Systemic hormone replacement therapy, 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) [17].

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 *BRCA*2 should be considered only if recommended by their breast cancer oncologist.

This is endorsed from Jacobson et al. 2018 [16].

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, RRSO had a significant reduction in breast cancer incidence when it was performed before the age of 50 years (HR, 0.18; 95% CI, 0.05 to 0.63) [23].

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 women who 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 [16]

Qualifying Statements for Recommendation 6

- A 2016 Dutch study examined mathematical models for ovarian cancer risk following two-step surgery in women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *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 [24].

Recommendation 7

All RRSO for women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *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 FIMbriated 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 [16].

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 [16].

Qualifying Statements for Recommendation 8

- Because of the increased risk of osteoporosis following premature 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.

Recommendation 9

Following RRSO, it is not recommended to do surveillance for peritoneal cancer in women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2*.
This is endorsed from Jacobson et al. 2018 [16].

Qualifying Statements for Recommendation 9

- Following the 90% risk reduction in ovarian/tubal cancer afforded by bilateral RRSO, the risk of peritoneal cancer is low (3.89% lifetime risk in *BRCA1*, 1.9% in *BRCA2*). No surveillance is recommended for women who have undergone RRSO [25-27].

GLOSSARY OF TERMS

AGREE – Appraisal of Guidelines for Research and Evaluation
BRCA – BReast CAncer gene
CA125 - Cancer Antigen 125
CCO – Cancer Care Ontario
CI – Confidence Interval
FACT–ES - Functional Assessment of Cancer Therapy-Endocrine Score
GDG - Guideline Development Group
HBOC – Hereditary Breast Ovarian Cancer
HE4 - Human Epididymis Protein 4
HRT - Hormone Replacement Therapy
HR – Hazard Ratio
MENQOL-I - Menopause-Specific Quality of Life-Intervention Tool
MSL - Menopause Symptoms List
MRS - Menopause Rating Scale
NPV – Negative Predicted Value
OH – Ontario Health
OMH – Ontario Ministry of Health
OR – Overall Response
PEBC - Program in Evidence-Based Care
PPV – Positive Predictive Value
QoL – Quality of Life
RAP – Report Approval Panel
RCT – Randomized Clinical Trial
ROCA – Risk of Ovarian Cancer Algorithm
RR – Relative Risk
RRSO - Risk-Reducing Salpingo-Oophorectomy
SOGC - Society of Obstetricians and Gynaecologists of Canada
TSEC - Tissue Selection Estrogen Complex
TVS – Transvaginal Sonography
TVU - Transvaginal Ultrasound
UK FOCSS – United Kingdom Familial Ovarian Cancer Screening Study
U/S – Ultrasound