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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

M. Jacobson, N. Coakley, M. Bernardini, L. Elit, S.E. Ferguson, R. Kim, and the Gynecologic Guideline Development Group

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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For information about this document, please contact Michelle Jacobson, the lead author, through the PEBC at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

For information about the PEBC and the most current version of all reports, please visit the OH-CCO website at http: https://www.cancercareontario.ca/en/guidelines-advice or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

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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, see Section 2.

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

Risk Reduction Strategies for BRCA1/2 Hereditary Ovarian Cancer Syndromes

Section 2: Guideline – Recommendations and Key Evidence

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, KEY EVIDENCE, AND JUSTIFICATION

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.
Key Evidence for Recommendation 1
• Fifteen papers [1-15] representing 13 individual studies were found. • The four randomized trials found no differences in survival with screening to detect ovarian cancer compared to usual care [5-7,11]. • Only two studies showed a slight benefit in survival [5,12]. • A stage shift was detected in the UK FOCSS study by Rosenthal et al. [12], but there is insufficient evidence that this screening method resulted in a survival benefit.
Justification for Recommendation 1
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 [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.

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 [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.
Key Evidence for Recommendation 3
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 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). • 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 [17].
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 [18-22]. 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) [19].
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.
Women who had not taken HRT after RRSO through at least age 45 had significantly higher mortality due to cardiovascular disease (HR, 1.84; 95% CI, 1.27 to 2.68, p=0.001). Women who took HRT after RRSO had similar outcomes to women not undergoing RRSO (HR, 0.65; 95% CI, 0.30 to 1.41, p=0.28) [19].
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) [20].
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 [22].

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].

Key Evidence for Recommendation 5

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 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 [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].

Key Evidence for Recommendation 6

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 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 *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].

Key Evidence for Recommendation 7

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 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 [16].

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.

Key Evidence for Recommendation 8

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 based on expert opinion.

Justification for Recommendation 8

The Working Group members are confident in their endorsement of the 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 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].

Key Evidence for Recommendation 9

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 primarily comprised of comparative studies.

Justification for Recommendation 9

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.

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.

Risk Reduction Strategies for BRCA1/2 Hereditary Ovarian Cancer Syndromes

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The PEBC is an initiative of the Ontario provincial cancer system, OH (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of GDGs in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of OH (CCO) supported by the OMH. All work produced by the PEBC is editorially independent from the OMH.

JUSTIFICATION FOR GUIDELINE

The previous version of this guideline was out of date and newer clinical options are available. Therefore, the guideline was updated.

GUIDELINE DEVELOPERS

This guideline was developed by the Risk Reduction Strategies for Hereditary Ovarian Cancer GDG (Appendix 1), which was convened at the request of the Gynecologic guideline development group.

The project was led by a small Working Group of the Risk Reduction Strategies for Hereditary Ovarian Cancer GDG, 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 gynecology, genetics gynecologic oncology, genetics, and health research methodology. Other members of the Gynecologic GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [28,29]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [30] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development and to improve the completeness and transparency of reporting in practice guidelines.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original

evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on evidence of the magnitude of the desirable and undesirable effects of an intervention or accuracy of a test, and take into account the certainty of the evidence, the values of key stakeholders (e.g., patients, clinicians, policy makers, etc.), and the potential impact on equity, acceptability and feasibility of implementation. A list of any implementation considerations (e.g., costs, human resources, and unique requirements for special or disadvantaged populations, dissemination issues, etc.) is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine whether any guideline could be endorsed. Evidence-based guidelines with systematic reviews that addressed at least one research question were included. Guidelines were excluded if they were older than three years (published before 2015).

The following sources were searched for guidelines on March 13, 2018 with the search term(s) Ovarian, Ovary, BRCA1 or 2, HBOC, familial, hereditary: National Institute for Health and Care Excellence Evidence Search, Canadian Medical Association Journal Infobase, Scottish Intercollegiate Guidelines Network, American Society of Clinical Oncology, National Health and Medical Research Council – Australia Clinical Practice Guidelines Portal, and Cancer Council Australia – Cancer Guidelines Wiki. MEDLINE/EMBASE were searched for guidelines, on January 7, 2019. The search strategy is reported in Appendix 2. The MEDLINE/EMBASE search yielded 520 hits of which 53 were considered for full-text review. Thirteen guidelines met the inclusion criteria. Of those the group chose the 2018 SOGC guideline to endorse for questions 2 and 3 [16].The group chose this guideline because it was the most current, it is Canadian, and it scored well on the AGREE 2 checklist [30] and answered two out of three research questions. No guidelines were found that answered question 1. The table of excluded guidelines can be found in Appendix 3.

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC RAP, a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey.

DISSEMINATION AND IMPLEMENTATION

The guideline will be published on the OH (CCO) website and may be submitted for publication to a peer-reviewed journal. The Professional Consultation of the External Review is intended to facilitate the dissemination of the guideline to Ontario practitioners. Section 1 of this guideline is a summary document to support the implementation of the guideline in practice. OH (CCO)-PEBC guidelines are routinely included in several international guideline databases including the CPAC Cancer Guidelines Database, the CMA/Joule CPG Infobase database, NICE Evidence Search (UK), and the Guidelines International Network Library.

ACKNOWLEDGEMENTS

The Risk Reduction Strategies for Hereditary Ovarian Cancer GDG would like to thank the following individuals for their assistance in developing this report:

- Sheila McNair, Roxanne Cosby, Emily Vella, Jonathan Sussman, Donna Maziak, W. K. (Bill) Evans, Mark Robson and Melinda Wu for providing feedback on draft versions.
- Faith Maelzer for conducting a data audit.
- Sara Miller for copy editing.

Risk Reduction Strategies for BRCA1/2 Hereditary Ovarian Cancer Syndromes

Section 4: Systematic Review

INTRODUCTION

In 2020, ovarian cancer will account for 4.9% of deaths from cancer in Canada [31]. Approximately 5% to 15% of these cancers will occur in women with the *BRCA1* and *BRCA2* genes [32]. 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%) [33].

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 [12]. 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 developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objectives of this guideline (Section 2), the Working Group derived the research questions outlined below.

RESEARCH QUESTIONS

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, 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 in women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2*?

METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Existing guidelines and Systematic Reviews

A search was conducted for existing guidelines and systematic reviews. Methods for locating and evaluation of existing guidelines and systematic reviews are as follows:

- Databases searched (MEDLINE, EMBASE, Cochrane Database of Systematic Reviews)

- Years covered 2004-July 24, 2020
- Search terms – see Appendix 2
- Selection criteria
  - English language and all included studies in English
  - Directly related to one or more guideline questions
  - At least one original study that meets the inclusion criteria for primary literature

Identified guidelines were evaluated using the AGREE II tool [30]. Identified systematic reviews were evaluated based on their clinical content and relevance. Any identified systematic reviews that addressed the research questions were assessed using A Measurement Tool to Assess Systematic Reviews (AMSTAR 2) [34]. The results of the AMSTAR 2 assessment were used to determine whether any existing review could be incorporated as part of the evidentiary base.

Based on the results of the search for guidelines, systematic reviews were searched for question 1 and part of question 2. Systematic reviews were included if they met the following criteria; evaluated serial U/S, CA125, or ROCA in women to screen for ovarian cancer; reported on the use of HRT, chemoprevention, or risk reduction in women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2*; and were published in English.

Search for Primary Literature

For each outcome per research question, if no guideline or systematic review was included, then a search for primary literature was conducted. For any included systematic review, an updated search for primary literature was performed. If any included systematic review was limited in scope, then a search for primary literature to address the limitation in scope was conducted.

Literature Search Strategy

A search for primary studies was undertaken for question 1. The Cochrane Database of Systematic Reviews, MEDLINE, and EMBASE databases were searched from 2004 to July 24, 2020. Please see Appendix 2 for the primary literature search strategy

Study Selection Criteria and Process

Inclusion Criteria

- English language
- Studies evaluating serial U/S, CA125, or ROCA in women to screen for ovarian cancer.
- Studies evaluating HRT in women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2*.
- RCTs, non-randomized controlled studies, prospective cohort studies, retrospective studies.
- Studies in which n=20 minimally
- No prior oophorectomies

Exclusion Criteria

- Case studies, commentaries, editorials
- Non-English publications,
- Abstracts of non-RCTs

A review of the titles and abstracts was conducted by one reviewer (NC). For studies that warranted full-text review, one reviewer (NC) reviewed each study independently. If uncertainty existed the Working Group was consulted.

Data Extraction and Assessment of Risk of Bias

All included primary studies underwent data extraction by NC independently, with all extracted data and information audited subsequently by an independent auditor. Ratios, including HRs, were expressed with a ratio of <1.0 indicating that the treatment group experienced the better outcome. An HR <1.0 indicates that patients had a lower probability of experiencing an event.

Risk of bias per outcome for each included study was assessed using the Cochrane Risk of Bias tool [35]. This table is reported in Appendix 4.

Synthesizing the Evidence

Meta-analysis was not planned as many of the studies included in this systematic review were quite varied and retrospective.

Assessment of the Certainty of the Evidence

The certainty of the evidence per outcome for each research question, taking into account risk of bias, inconsistency, indirectness, imprecision, and publication bias was assessed using Cochrane Risk of Bias tool [35] and is reported in Appendix 4.

RESULTS

Search for Existing Guidelines and Systematic Reviews

A literature search for guidelines uncovered 523 documents. Of these, 56 underwent full-text review. Fifteen guidelines met the inclusion criteria. Of those the Working Group members chose the 2018 SOGC guideline to endorse for questions 2 and parts of question 3 [16]. The group chose this guideline because it was the most current, it is Canadian, and it scored well on the AGREE 2 checklist [30] and answered two out of three research questions. No guidelines were found that answered question 1. The Working Group was aware of existing systematic reviews that addressed part of question 2 examining the role of HRT in women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2* and therefore this was not endorsed but answered by the systematic reviews found in the search. A table of the excluded guidelines is presented in Appendix 3.

A literature search for systematic reviews for question 1 and part of question 2, uncovered 297 documents. Of these, 19 underwent full-text review and five were retained. The five systematic reviews pertain only to question 2 examining the use of HRT in women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2*. The systematic reviews were retained because their information is more current than that in the endorsed guideline. The systematic review by Vermeulen et al. [22] examined the safety of HRT and the risk of breast cancer. The systematic review by Siyam et al. [36] examined the effects of HRT on QoL and breast cancer risk. The systematic review by Gordhandas et al. examined QoL, cardiovascular and bone health and breast cancer risks [18]. The systematic reviews by Birrer et al. [18] and Marchetti et al. [20] examined breast cancer risk and menopausal symptoms.

Search for Primary Literature

A search for primary literature was conducted for question 1.

Literature Search Results

There were 5791 hits in the primary literature search for question 1. Of these, 124 underwent full-text review of which 15 were retained in the guideline. The Prostate, Lung, Colorectal and Ovarian (PLCO) screening study is represented by three separate papers [1,8,11]. For a summary of the full literature search results, please refer to Appendix 5, which is a flow

diagram depicting the inclusion and exclusion of all studies for this guidance document. A summary of all included studies is reported in Table 4-1.

Table 4-1. Studies selected for inclusion

Reference	Study Type	Population
Jacobson [16] 2018 SOGC	Guideline	Adult women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2* and other ovarian cancer associated genes
Birrer [18] 2018	Systematic Review	Adult women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2* after RRSO
Gordhandas [19] 2019	Systematic Review	Adult women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2* after RRSO
Marchetti [20] 2018	Systematic Review	Adult women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2* after RRSO
Siyam [21] 2017	Systematic Review	Adult women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2* after RRSO
Vermeulen [22] 2019	Systematic Review	Adult women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2* after RRSO
Jacobs [5] 2016 UKCTOCS	RCT	Post-menopausal women aged 50-74 years
Pinsky [11] 2016 **UPDATE OF** PLCO Screening Trial	RCT	Women aged 55-74
Buys [1] 2011 PLCO Screening Trial	RCT	Women aged 55-74
Lai [8] 2015 ABSTRACT (used data from PLCO high-risk menopausal females)	RCT	High-risk menopausal women
Karlan [6] 2014	RCT	Women at high risk for ovarian cancer
Kobayashi [7] 2008 SCSOCS trial	RCT	Asymptomatic postmenopausal women
Cortesi [3] 2017	CCT	Women at high risk for ovarian cancer
Rosenthal [12] 2017 UK FOCSS	CCT	Women whose lifetime ovarian cancer risk was ≥10%

Chen [2] 2014	CCT	*BRCA1/2* carriers or at risk of being a carrier
Nobbenhuis [9] 2011	CCT	Women with a positive family history of ovarian cancer
Van der Velde [14] 2009	Retrospective	Adult women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2*
Van Nagell [15] 2007	CCT	Asymptomatic women with a family history of ovarian cancer
Gaarenstroom [4] 2006	CCT	Women at high risk of hereditary ovarian cancer
Oliver [10] 2006	CCT	Adult women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2* after or at risk of being a carrier
Stirling [13] 2005	CCT	Women at increased risk of ovarian cancer

Abbreviations: BRCA, BReast CAncer gene; CCT, controlled clinical trial; PLCO, Prostate, Lung, Colorectal and Ovarian; RCT, randomized controlled trial; RRSO, risk-reducing salpingo-oophorectomy; SCSOCS, Shizuoka Cohort Study on Ovarian Cancer Screening; SOGC, Society of Obstetricians and Gynaecologists of Canada; UKCTOCS, UK Collaborative Trial of Ovarian Cancer Screening; UK FOCSS, United Kingdom Familial Ovarian Cancer Screening Study

Certainty of the Evidence

Various study designs are included in this guidance document. The guideline being endorsed for questions 2 and 3 [16] was assessed using the AGREE II tool by two independent reviews [30]. A summary of the findings is reported in Table 4-2. The guideline scored well on several domains. Generally, the PEBC considers endorsing guidelines that have scored over 50% on the Rigour portion of the AGREE II tool. Systematic reviews were assessed using the AMSTAR 2 tool [34]. The results are reported in Appendix 6

There were four RCTs for question 1 that were assessed for risk of bias (Appendix 4).

Table 4-2. Agree scores for endorsed guideline

Guideline	Scope and purpose	Stakeholder involvement	Rigour	Clarity of presentation	Applicability	Editorial independence
SOGC #366	92%	56%	76%	94%	54%	25%

Abbreviation: SOGC, Society of Obstetricians and Gynaecologists of Canada

ENDORSEMENT PROCESS

The Working Group members reviewed the guideline in detail, and reviewed each recommendation of that guideline to determine whether it could be endorsed, endorsed with changes, or rejected. This determination was based on the agreement of the Working Group members with the interpretation of available evidence presented in the guideline, and whether it was applicable and acceptable in the Ontario context, and whether new evidence since the guideline was developed might change any of the recommendations.

Outcomes

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?

Fifteen papers [1-15] representing 13 individual studies were represented. Three papers pertained to the PLCO screening study. One was the original result [1], one showed a subset of high-risk patients [8] and the other was an update of the results [11]. There were four randomized clinical trials [5-7,11], eight clinical controlled trials [2-4,9,10,12,13,15], and one retrospective study [14]. The results of these studies are reported in Table 4-3.

Screening vs. usual care/no screening

The four randomized trials found no differences in mortality in screening to detect ovarian cancer compared with usual care or no screening [5-7,11].

Mortality: Annual CA125 and transvaginal ultrasound vs. usual care

In the PLCO trial women aged 55-74 years with no previous diagnosis of lung, colorectal or ovarian cancer were randomized to receive an annual CA125 blood test and TVS or usual care [1]. In the 2016 update to the initial results after 14.7 years of follow-up, when results were measured from date of randomization, survival was similar across arms (p=0.67). In the intervention arm screen-detected cases had borderline significantly improved survival compared to non-screen-detected cases (p=0.04). Survival was 15% higher at five years in screen-detected cases (57.8% vs. 43.1%) but similar at 12 years (25.1% vs. 22.8%) [11]. In the screening arm there were 187 deaths from ovarian cancer. In the usual care arm there were 176 deaths from ovarian cancer (RR, 1.06; 95% CI, 0.87 to 1.30) [11]. Ovarian cancer survival was not different across both arms (p=0.16) [11]. In the Lai et al. abstract, high-risk patients were analyzed. In the screening group 48 were diagnosed with ovarian cancer compared to 44 in the usual care group. Patients in the screening arm diagnosed with cancer experienced significantly improved survival compared to usual care RR for mortality (0.66; 95% CI, 0.47 to 0.93; p=0.016). In addition, 31% of women in the screening arm were diagnosed at stage 1 or 2 compared with 16% in the usual care group (p=0.085) [8].

Mortality: Annual multimodal screening with serum CA125 vs. annual transvaginal ultrasound screening vs. no screening

Only the trial by Jacobs et al. compared different screening approaches to one another [5].The multimodal screening group was comprised of annual screening with serum CA125, which was interpreted with the ROCA. The ROCA scores triaged women to normal, which consisted of annual screening, and an intermediate group, which consisted of a repeat CA125 in three months and if elevated, a repeat CA125 and transvaginal ultrasound in six weeks. The second group in this trial consisted of annual TVS, and the third group had no screening. The reduction in mortality from ovarian cancer was not significant among the groups. There was a mortality reduction over years 0-14 of 15% in the multimodal screening group, and 11% in the TVS group, but this was not significant in the primary prespecified Cox analysis [5].

Incidence of cancer: Annual CA125 and pelvic ultrasound vs. no screening

Asymptomatic postmenopausal women with no history of cancer or bilateral oophorectomy were randomized in the study by Kobayashi et al. to either annual CA125 and pelvic U/S or to no screening. In the screening group, 27 cancers were detected with an additional eight detected outside the screening program. There were 32 cancers in the no screening group. The proportion of cancers found at stage 1 was higher in the screening group

than in the no screening group (63% vs. 38%, p=0.2285) although this was not statistically significant [7].

Incidence of cancer: Screening with CA125 and HE4 vs. screening with CA125

The randomized study by Karlan et al. divided women into three risk groups: women with a variant, women from high-risk families, and women with epidemiologic risk factors or circulating proteins. The women were randomized to receive CA125 and serum HE4 screening or CA125. In both arms if there was a positive result in either test then follow-up imaging was performed. In both arms, a surgical PPV above 25% was demonstrated. There were four cancers detected in each arm of the study. In the whole group surgical consultation was recommended for 37 women (26 in arm 1, n=582; and 11 in arm 2, n=590). On the basis of 12 women with at least two of three tests positive (CA125, HE4, or imaging) an intention to treat analysis showed PPV of 14% in arm 1 and 20% in arm 2. A positive screen was more frequent when HE4 was used, which led to additional follow-up testing and imaging [6].

Non-comparative studies

There were nine single-arm studies in which the patients consisted of women at risk for ovarian cancer. In the Cortesi et al. study of 661 women, 12 cases of ovarian cancer were detected of which half were stage 1 or 2. The screening sensitivity was 70% overall and 73% for women who harboured a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2* [3].

The UK FOCSS study by Rosenthal et al. [12] enrolled patients (n=4383) who had a ≥10% lifetime risk of ovarian or fallopian tube cancer. Screening consisted of ROCA screening every four months with an annual TVS if ROCA was normal and within two months if the ROCA was abnormal. Nineteen patients were diagnosed with invasive ovarian cancer within one year of screening. Thirteen of the cases were detected at the screening visit and six were occult and detected at RRSO. In the screen-detected cancers (n=13), five were stage I to II, and seven were stage IIIb to IV. In the occult cancer-detected cancers during the RRSO, five were stage I to II.

The remaining seven studies had varying results. The study by Chen et al. compared CA125 levels in women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2* at baseline and post-RRSO. In *BRCA1* patients, there was a significant reduction in mean serum concentration levels (p=0.04) while the same was not seen for *BRCA2* carriers [2]. The studies by Nobbenhuis et al. [9], Van der Velde et al. [14], Gaarenstroom et al. [4], Oliver et al. [10], and Stirling et al. [13] all found non-significant results of screening on the stage of cancer detected. The study by Van Nagell Jr et al. screened asymptomatic women and women with a family history of ovarian cancer. Both groups received yearly TVS. If the results were abnormal further testing and screening was completed. Thirty-five primary ovarian cancers were diagnosed; 28 were stage I, eight were stage II, and eight were stage III. TVS had a screening sensitivity of 85.0%, specificity of 98.7%, PPV of 14.01%, and NPV of 99.9% [15].

Table 4-3. Study Results

Reference	Population	Comparison	OC diagnosis	Deaths caused by OC	Other results
Randomized studies					
Jacobs [5] 2016 UKCTOS RCT	Postmenopausal women aged 50-74 years Exclusion criteria were previous bilateral oophorectomy or ovarian malignancy, increased risk of familial ovarian cancer, and active non-ovarian malignancy. Median follow-up 11.1 years	Annual MMS with serum CA125 interpreted with use of the ROCA N=50,640 Annual TVU screening N=50,639 No screening, N=101,359	338 (0.7%) in the MMS group; died 148 (0.29%) 314 (0.6%) in the TVU group, died 154 (0.30%) 630 (0.6%) in the no screening group; died 347 (0.34%)	The primary analysis using a Cox proportional hazards model gave a mortality reduction over years 0-14 of 15% (95% CI -3 to 30; p=0.10) with MMS and 11% (-7 to 27; p=0.21) with USS. At censorship, 649 (0.32%) women had died of ovarian cancer: 347 (0.34%) in the no screening group, 148 (0.29%) in the MMS group, and 154 (0.30%) in the TVU group.	
Pinsky [11] 2016 **UPDATE OF** PLCO Screening Trial RCT	Women 55-74, no previous diagnosis or lung, colorectal or ovarian cancer Median follow-up 14.7 years	Annual CA125 TVS N=34,253 Usual care N=34,304	Measured from start of randomization, survival was similar across arms P=0.67. In the intervention arm screen-detected cases had borderline significantly improved survival compared to non-screen-detected cases P=0.04. Survival was 15% higher at 5 years in screen-detected cases (57.8% vs. 43.1%) but similar at 12 years (25.1% vs. 22.8%).	187 deaths from OC 176 deaths from OC RR 1.06 (95% CI 0.87-1.31)	OC survival not different across trial arms p=0.16
Buys [1] 2011 PLCO Screening Trial RCT	Women 55-74 no previous diagnosis or lung, colorectal or ovarian cancer Median follow-up 12.4 years	Annual CA125 and TVS N=34,253 Usual care N=34,304	212 (5.7 per 10,000 person-years) 176 (4.7 per 10,000 person -years) RR 1.21; 95% CI 0.99 to 1.48	118 (3.1 per 10,000 person-years) 100 (2.6 per 10,000 person -years) Mortality RR 1.18; 95% CI 0.82 to 1.71	False positives N=3285 of these 1,080 (32.9%) underwent surgery and of these 1,080, 163 (15%) experienced a serious complication
Lai [8] 2015	Used data from PLCO high risk menopausal	Annual CA125 and TVS N=11,293	48	Patients in screening arm diagnosed with cancer	31% diagnosed at stage 1 or 2

Reference	Population	Comparison	OC diagnosis	Deaths caused by OC	Other results
ABSTRACT	females (1st degree relative with breast or ovarian cancer)	Usual care N=11,062	44	experienced significantly improved survival compared to usual care RR for mortality 0.66 (95% CI 0.47 to 0.93, p=0.016)	16% diagnosed at Stage 1 or 2 p=0.085
Karlan [6] 2014 RCT	Risk group 1 -women 25-80 years with a deleterious BRCA1/2 mutation, screened semi annually Risk group 2 -women 35-80 years in high risk families, screened semi annually Risk group 3 -women 45-80 years with epidemiologic risk factors or circulating proteins, conferring EOC risk, screened annually	Arm 1 – CA125 and HE4 N=582 Arm 2-CA125 In both arms if screen was + CA125 and HE4 were used to select women for follow-up imaging or clinical follow-up N=590	Both strategies yielded surgical PPV above 25% Surgery performed in 6 women identifying 2 OC yielding PPV in both arms 33% (95% CI 4% to 78%), 25% in Arm 1 and 50% in Arm 2.	Surgical consultation was recommended for 37 women (26 in arm 1 and 11 in arm 2). On the basis if 12 women with at least 2 of 3 tests positive (CA125, HE4 or imaging) an ITT analysis showed PPV of 14% in Arm 1 and 20% in Arm 2. Positive screen more frequent when HE4 was included in the primary screen.	
Kobayashi [7] 2008 SCSOCS trial RCT	Asymptomatic postmenopausal women with no history of cancer and have not had bilateral oophorectomy Japan Mean follow-up of 9.2 years	Annual CA125 and pelvic ultrasound N=41,688 No screening N=40,799	27 (+8 more detected outside the program) 0.31 per 1000 at first screen and 0.38-0.74 per 1000 at subsequent screen for women with abnormal findings 32		Proportion of stage 1 OC 63% 38% p=0.2285
Non-Randomized studies					
Cortesi [3] 2017	Women at risk of developing OC due to family history or gene mutation	N=661 TVU and CA125 Mean follow-up of 112 months	12 OC were detected 2.6 per 1,000 person-years The screening sensitivity was 70%, with 73% for *BRCA1/2* carriers	6 of the cancers were stage 1 or 2	In 41 women who underwent RRSO 2 BRCA1 carriers developed a primary peritoneal cancer
Rosenthal [12] 2017 UK FOCCS	Women with lifetime risk of OC was ≥10% Median follow-up 4.8 years	ROCA screening every 4 months. TVS annually if ROCA was normal or within 2 months if ROCA results were abnormal N=4348	19pts diagnosed with invasive OC/FTC within 1 year or prior screening (13 were detected by screening and 6 at RRSO.	7 (36.8%) of the 19 cancers diagnosed <1 year after prior screen were stage IIIb to IV (95% CI, 16.3% to 61.6%) compared with 17 (94.4%) of 18 cancers	Modeled sensitivity, PPV, and NPV for OC/FTC detection within 1 year were: 94.7% (CI, 74.0% to 99.9%),

Reference	Population	Comparison	OC diagnosis	Deaths caused by OC	Other results
			5 out of 13 screen detected cancers were Stage 1-2. Of the 6 occult cancers 5 were stage 1-2.	diagnosed > 1 year after screening ended (95% CI, 72.7% to 99.9%; P < .001). 18 (94.8%) of 19 cancers diagnosed < 1 year after prior screen had zero residual disease (with lower surgical complexity, P=.16) (95% CI, 74.0%to 99.9%) compared with 13 (72.2%) of 18 cancers subsequently diagnosed (95% CI, 46.5% to 90.3%; P=.09).	10.8% (CI, 6.5% to 16.5%), and 100% (CI, 100% to 100%)
Chen [2] 2014	*BRCA1/2* patients Baseline and post prophylactic RRBSO CA125 levels	N=383	Median baseline CA125 before RRBSO was 9.0 U/ml (range 2-78, mean 13.0)	CA125 immediately pre and post RRBSO in *BRCA1* carriers N=133 there was a significant reduction in mean serum concentrations (mean 15.1 to 12.4; P=0.04) this reduction was not seen in *BRCA2* N=87 carriers 12.8 to 14.6 P=0.5	
Nobbenhuis [9] 2011	Women with a positive family history of ovarian cancer divided into low-, moderate- and high-risk groups	N=545 High N=397 Moderate N=112 Low N=36 Annual serum CA125 and TVU screening The high-risk group was also offered genetic testing	2 cases of OC found. One advanced case on fourth round of screening and one early stage during BSO		Re-call rate for CA125 was High-risk group N=14% Moderate 3% Low 6% Re-call rate for TVU was High-risk group N=25% Moderate 6% Low 17% BSO because of abnormal test High-risk N=7 Moderate risk N=1

Reference	Population	Comparison	OC diagnosis	Deaths caused by OC	Other results
Van der Velde [14] 2009 Retrospective	*BRCA1/2* mutation carriers	N=241 Annual pelvic examination, TVU and CA125	3 cancers detected PPV 20% for pelvic examination, 33% for TVU and 6% for CA125	NPV 99.4% for pelvic examination, 99.5% for TVU and 99.4% for CA125	All detected cancers were at an advanced stage.
Van Nagell [15] 2007	Asymptomatic women ≥ 50 years and asymptomatic women ≥ 25 with a family history of ovarian cancer	N=25,327 Patients received yearly TVS. If abnormal repeat in 4-6 weeks. If abnormal the CA125 and Colour Doppler flow sonography. Then either referred to surgery or repeat TVS in 6mo	N=364 who had persisting ovarian tumour on TVS who underwent exploratory laparoscopy or surgery. N=35 primary Ovarian cancers 9 = serous of low malignancy 7 = metastatic to ovary	28= stage 1 8= stage 2 8= stage 3 9 developed OC within 12 months of a negative screen (false-negative)	TVS had screening sensitivity of 85.0%, specificity of 98.7% and PPV of 14.01% and NPV of 99.9% After 107,276 screening years, N= 7 ovarian cancer deaths in the annually screened population and N=3 ovarian cancer deaths among noncompliant women. Excluding patients with nonepithelial or borderline ovarian malignancies, the survival of patients with ovarian cancer in the annually screened population was 89.9%±10.1% at 2 years and 77.2%±22.8% at 5 years.
Gaarenstroom [4] 2006	N=269 women at high risk of hereditary ovarian cancer. A total of 113 (42%) BRCA1/2 mutation, and 127 (47%) underwent salpingo-oophorectomy	Screening was performed using TVU and serum CA125 testing.	Mean follow-up was 26 months No occult cancers were found.	In N=8 with elevated CA125 levels and abnormal ultrasound, a malignancy found. 4 of these (1 borderline, 1 stage Ia, 1 stage IIIb, and 1 stage IIIc ovarian or peritoneal cancer) were detected at first screening. 1 stage IIIb and 1 stage IIIc cancer were detected at the second screening after 12	No peritoneal carcinoma was found among those 114 women who underwent BSO with normal or benign pathology results.

Reference	Population	Comparison	OC diagnosis	Deaths caused by OC	Other results
				months, and two interval stage IIIc and IV cancers were detected 8 and 10 months after the first screening visit.	
Oliver [10] 2006	N= 132 BRCA1 and N=20 BRCA2 N= 72 HBOC N= 88 HBC	Clinical data collected in consecutive women at Amsterdam Hospital	In 10 women with elevated CA125 level and a positive TVU, 3 screening carcinomas (one FIGO stage IC, one stage IIIB and one stage IV) and one interval carcinoma (stage IV) were detected. Five occult ovarian/fallopian tube carcinomas (two stage IA, one stage IC, one stage IIIB and one stage IV) after prophylactic BSO have been found in 152 women.	Five occult ovarian/fallopian tube carcinomas (two stage IA, one stage IC, one stage IIIB and one stage IV) after prophylactic BSO have been found in 152 women.	The sensitivity, specificity, PPV and NPV of the combination of CA125 and TVU were the highest (40%, 99%, 40% and 99%) followed by CA125 alone (50%, 96%, 13% and 99%), pelvic exam (40%, 98%, 21% and 99%) and TVU, separately (40%, 90%, 6% and 99%).
Stirling [13] 2005	Women from 3 cancer genetics centres in the UK	Pre-symptomatic women N=1,110 at increased risk and N= 553 at moderate-risk, N=557 high-risk TVU and CA125	13 epithelial ovarian malignancies (12 invasive and one borderline) 10 tumors were detected at screening: three (FIGO) stage I (including borderline), two stage II, four stage III, and one stage IV. Of the three cancers not detected by screening, two were stage III and one was stage IV	29 women underwent diagnostic surgery but were found not to have ovarian cancer.	

Abbreviations: BSO, bilateral salpingo-oophorectomy; CI, confidence interval; EOC, epithelial ovarian cancer; FTC, fallopian tube cancer; FIGO, International Federation of Gynecology and Obstetrics; FOCSS, Familial Ovarian Cancer Screening Study; HE4, human epididymis 4 gene; ITT, intention to treat; MMS, multimodal screening; NPV, negative predictive value; OC, ovarian cancer; PPV, positive predictive value; PLCO, Prostate, Lung, Colorectal and Ovarian; RCT, randomized controlled trial; ROCA, risk of ovarian cancer algorithm; RR, risk ratio; RRBSO, risk-reducing bilateral salpingo-oophorectomy; RRSO, risk-reducing salpingo-oophorectomy; SCSOCS, Shizuoka Cohort Study on Ovarian Cancer Screening; TVS, transvaginal sonography; TVU, transvaginal ultrasound; UKCTOCS, UK Collaborative Trial of Ovarian Cancer Screening

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?

The guideline produced by the SOGC [16] was retained from the guideline search as it sufficiently addressed the issue of the optimal strategy to prevent ovarian cancer and was therefore endorsed by the Risk Reduction Strategies for Heredity Ovarian Cancer Working Group. Only certain sections of the guidelines are being endorsed. In this guideline, the following sections are being endorsed (see page 1498 of the Jacobson et al. SOGC clinical practice guideline) [16].

- Risk-reducing surgery according to established guidelines is the most effective way to reduce the risk of ovarian cancer in women with a hereditary predisposition or risk (strong, low).
- RRSO should be offered to women who harbour a pathogenic or likely pathogenic variant in *BRCA1* between 35 and 40 years of age and *BRCA2* from between 40 and 45 years for ovarian/tubal/peritoneal carcinoma risk reduction.
- For women diagnosed as pathogenic variant carriers postmenopausally, RRSO should be offered upon diagnosis.
- RRSO should be considered for breast cancer risk reduction in women who harbour a pathogenic or likely pathogenic variant in *BRCA2* younger than 50 years.
- After a breast cancer diagnosis, RRSO for breast cancer mortality reduction should be considered within two years to women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and for *BRCA2* as part of their breast cancer treatment if considered appropriate by their oncologist.
- All RRSO for women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2* should be performed by a skilled gynecologist/gynecologic oncologist familiar with the technique described. It is imperative that specimens be examined by an experienced pathologist familiar with optimal specimen processing and diagnostic criteria. Should an invasive or occult carcinoma be found, patients should be referred to a gynecologic oncologist.

The use of HRT in women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2* who have had RRSO was evaluated by five systematic reviews [18-22]. The systematic reviews used in this guidance document were assessed using the AMSTAR 2 tool [34]. The included systematic reviews' scores varied from scoring well to moderately low on those items that were applicable. They provided a priori design, and explained their selection of the study designs for inclusion in the review. Three studies conducted duplicate study selection and data extraction. While the studies performed literature searches the details were lacking. The reviews did not provide information on the risk of bias of the studies, funding source of each study or provide a reference list of excluded studies. This information is reported in Appendix 6.

The systematic review by Siyam et al. assessed QoL of HRT on menopausal symptoms. There were six studies in the analysis. These six studies were a mixture of cross-sectional surveys and prospective cohort designs. The studies used several QoL questionnaires: the FACT-ES; MSL, MENQOL-I, and the MRS. Three studies showed an improvement in QoL and three studies showed no change [21].

The systematic review by Siyam et al. reported on vasomotor symptoms and found that in four studies assessing this symptom the use of HRT reduced the symptoms of hot flashes. This systematic review also accessed sexual function in five studies. The following

questionnaires were used: MENQOL and FACT-ES, or the Sexual Activity Questionnaire, Female Sexual Function index, or Female Sexual Distress Scale – revised. An improvement in sexual function while using HRT was seen in two studies that used the sexual domain of MENQOL. One feature of sexual activity that improved with HRT use across the studies was discomfort/pain. The facets of sexual activity, such as pleasure, habit, satisfaction and libido showed no improvement [21]. Four studies evaluated the effect on vulvovaginal atrophy. Two studies included vaginal dryness as a component of sexual function. They found that HRT improved vaginal dryness and lubrication difficulty with intercourse. In two studies the effect of HRT on vulvovaginal atrophy was measured separately from sexual function and the studies did not show improvement [21].

The systematic review by Birrer et al. found that in women who underwent an RRSO, hormone replacement alleviated menopausal symptoms. One study found that hot flashes, cold sweats, and night sweats were decreased but there was no statistically significant difference between groups concerning other menopausal symptoms, such as vaginal dryness, bleeding or irritation, headache, mood swings, weight gain, and breast sensitivity [18]. 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 ($p=0.027$) [19]. Bone health was assessed in three studies in the Gordhandas et al. systematic review. The studies demonstrated that in patients who used HRT the OR was 1.2 (95% CI, 0.4 to 3.7) for bone disease. 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 systematic review by Siyam et al. reported on the prevention of bone loss in women who took HRT. This was reported in three studies. It showed that the women who took HRT had less bone loss compared to women who did not use HRT [21].

The systematic review by Gordhandas et al. also reported on cardiovascular health and cognitive function. One meta-analysis showed that the pooled effect of RRSO increased the risk of cardiovascular disease compared with women who were premenopausal (RR, 2.62; 95% CI, 2.05 to 3.35). The pooled effect on cardiovascular disease was 4.55 (95% CI, 2.56 to 8.01) for women who underwent RRSO before age 50 compared with bilateral salpingo-oophorectomy after age 50. Another study demonstrated that in the general population, women who underwent an RRSO before the age of 45 had an increase in mortality related to cardiovascular disease compared to women who had not had an oophorectomy (HR, 1.44; 95% CI, 1.01 to 2.05; $p=0.04$). Women who had not taken HRT after RRSO through at least age 45 had significantly higher mortality due to cardiovascular disease (HR, 1.84; 95% CI 1.27 to 2.68; $p=0.001$).Women who took HRT after RRSO were not statistically different than women not undergoing RRSO (HR, 0.65; 95% CI, 0.30 to 1.41; $p=0.28$) [19].

The effects on cognitive function were demonstrated by the Mayo Clinic Cohort of Oophorectomy and Aging study. This study showed that bilateral oophorectomy before menopause had an increased risk of cognitive impairment or dementia compared to those without oophorectomy (HR, 1.46; 95% CI, 1.13 to 1.90) [31]. The risk was higher for women undergoing RRSO before age 49 that were not treated with estrogen until age 50 (HR, 1.89; 95% CI, 1.27 to 2.83; $p=0.002$). In women who took estrogen until age 50, risk of cognitive impairment or dementia was not significantly different (HR, 0.79; 95% CI, 0.25 to 2.54; $p=0.69$) [19].

The risk of developing breast cancer was assessed by three systematic reviews. 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 was performed. There were n=326 who used estrogen alone and n=114 who used estrogen plus progesterone for a mean of 3.3 years. The difference was not significant 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) and in prospective studies only (OR, 0.53; 95% CI 0.25 to 1.15) [20].

The systematic review by Siyam et al. included four studies. However, one study was an update of a previous study. All four of the studies demonstrated that breast cancer risk did not change with HRT use. There were two studies that discussed the type of HRT used. In one study, three women taking estrogen only developed breast cancer (OR, 0.48; 95% CI, 0.1 to 2.1), and no cases were seen in women taking estrogen and progesterone. The duration of the effect of HRT on breast cancer risk was reported in one study. Compared to women who have never used HRT the risk of breast cancer did not change with more than three years of HRT use after RRSO [21].

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 (2.8-4.3 years) was associated with increase in breast cancer risk [22].

3. What is the optimal post-surgical management protocol to address the sequelae of RRSO in women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2*?

The guideline produced by the SOGC [16] was retained from the guideline search as it sufficiently addressed the issue of the optimal strategy to prevent ovarian cancer and was therefore endorsed by the Risk Reduction Strategies for Heredity *BRCA1/2* Ovarian Cancer Working Group. Only certain sections of the guidelines are being endorsed. In this guideline, the following sections are being endorsed (see page 1498 of the Jacobson et al. SOGC clinical practice guideline) [16].

- Post-oophorectomy care should be administered in an individualized manner, ensuring optimal QoL, bone health, and cardiovascular risk amelioration.
- Following RRSO, it is not recommended to do surveillance for peritoneal cancer in *BRCA* mutation carriers.

Ongoing, Unpublished, or Incomplete Studies

Table 4-4. Ongoing, Unpublished, or Incomplete Studies Randomized Phase 3 Studies

ClinicalTrials.gov Identifier	Title	Brief summary
NCT00039559	Clinical Trial to Screen Participants Who Are at High Genetic Risk for Ovarian Cancer	Screening trial to determine the significance of cancer antigen 125 (CA125) levels in detecting ovarian cancer in participants who have a high genetic risk of developing ovarian cancer.
NCT01696994	Screening for Ovarian Cancer in Older Patients (PLCO Screening Trial)	This clinical trial studies whether screening methods used to diagnose cancer of the prostate, lung, colon, rectum, or ovaries can reduce deaths from these cancers. Screening tests may help doctors find

ClinicalTrials.gov Identifier	Title	Brief summary
		cancer cells early and plan better treatment for ovarian cancer. The ovarian cancer screening tests are part of a trial that addresses the screening of four cancer sites, each with their own results record: prostate (NCT00002540), lung (NCT01696968), colorectal (NCT01696981), and ovarian (NCT01696994).
NCT01907789	Prophylactic Salpingectomy With Delayed Oophorectomy	The goal of this clinical research study is to compare ovarian cancer screening, risk-reducing salpingo-oophorectomy (RRSO), and prophylactic salpingectomy with delayed oophorectomy (PSDO). The safety of RRSO and PSDO will also be studied.
NCT02227654	Evaluating the Performance of Morphology Index in Surgical Decision-Making for Ovarian Tumors	The present investigation will prospectively evaluate whether serial transvaginal ultrasonography with Morphology Index (MI) can further reduce false positive results by more accurately distinguishing benign from malignant ovarian tumors. If there is no change in the detection of true positive cases, the result will be an increase in the positive predictive value of ovarian cancer screening.
NCT01187602	Short Non-coding RNA Biomarkers of Predisposition to Ovarian Cancer (sncRNA)	The purpose of this study is to create new tests to identify biomarkers for ovarian cancer so that a screening test can be developed. For patients who have a diagnosis of ovarian Cancer, researchers will use blood samples before and after treatment to see if disease status can be determined by measuring the amount of biomarker.
NCT00327925	Blood Test for Ovarian Cancer Associated Antibodies (CAAb)	Blood is collected from patients and cultured in a CimTube (a test tube with stimulation media) for several days. Following the culture step, the supernatant fluid is tested for the presence of CAAb on experimental test kits. Null Hypothesis: There is no relationship between the presence or absence of ovarian cancer (OC) and the CAAb i.e. d=0. Alternative Hypothesis: The expectation of the CAAb in the cancer population differs from that of the control population, i.e. m1 is not equal to m2. Since the sign of the difference is not important, the test will be two-sided.
NCT02296307	DOvEE - Diagnosing Ovarian & Endometrial Cancer Early (DOvEE)	This study hopes to improve early detection of ovarian and endometrial cancers. It will determine if women with bloating, abdominal distension, abdominal/pelvic pain, increased urinary frequency and/or

ClinicalTrials.gov Identifier	Title	Brief summary
		early satiety, benefit from earlier surgery after screening by CA-125 ovarian cancer biomarker and transvaginal ultrasound.
NCT03150121	Biomarkers for Early Detection of Ovarian Cancer Using Uterine Lavage (BEDOCA)	Screening programs for high-grade ovarian carcinoma failed to reduce disease-specific mortality, since they do not offer early enough detection of the disease. Most cases of high grade ovarian cancer develop in the fallopian tubes, hence the universal recommendation for high-risk populations (e.g., BRCA1/2 mutation carriers) is to undergo risk-reducing bilateral salpingo-oophorectomy (RRBSO) around the age of 40. The aims of this trial are: (1) to identify novel early-stage disease biomarkers using liquid biopsies obtained through uterine lavage, and (2) to optimize the technique a of uterine lavage and the processing of the samples for ultimate implementation as a routine diagnostic test for high risk populations.
NCT00155740	Mesothelin as a New Tumor Marker for Ovarian Cancer	Mesothelin is a 40-kDa glycosylphosphatidylinositol-linked glycoprotein. In normal tissues, the expression of mesothelin has subsequently been shown to be largely restricted to mesothelial cells, although immunoreactivity has also been reported in epithelial cells of the trachea, tonsil, fallopian tube, and kidney. Mesothelin has been shown to be over-expressed in pancreatic carcinomas, gastric carcinoma and ovarian carcinoma, and it seems that mesothelin may be utilized as a new tumour marker for ovarian carcinoma. We will evaluate that if mesothelin can be a new potential tumor marker for ovarian cancer in this proposal.
NCT02288676	DOvEEgene: Diagnosing Ovarian and Endometrial Cancer Early Using Genomics (DOvEEgene)	This study aims to develop and validate a test for diagnosing ovarian and endometrial cancers early. It relies on detecting somatic mutations that are associated with these cancers in a biofluids sample taken from the cervix and the uterine cavity.
NCT03480776	ASA in Prevention of Ovarian Cancer (STICs and STONEs)	The standard or usual treatment for women with a high risk gene mutation, BRCA1 or BRCA2, is to have risk-reducing surgery to remove the fallopian tubes and ovaries (bilateral salpingo-oophorectomy or bilateral salpingectomy inclusive of fimbria) after they have decided not to have more children naturally.

ClinicalTrials.gov Identifier	Title	Brief summary
		Acetylsalicylic Acid (ASA) is a safe, well tolerated drug taken by mouth. ASA has been available for over 100 years and has been used mainly to relieve fever and pain, but also as an anti-inflammatory medication in order to reduce inflammation (swelling).

DISCUSSION

Women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2* are faced with difficult decision making surrounding risk reduction for tubal/ovarian/peritoneal cancer. The development of a screening modality for high-grade serous carcinoma is a priority; thus far, no studies have demonstrated reliable screening regimens. Though the UK FOCSS study is promising in its results, as the ROCA has been previously, the stage shift demonstrated was not entirely associated with women undergoing screening, but also by women who chose to undergo RRSO during the screening interval. Furthermore, for a screening test to be recommended, it must show survival benefit, and we do not have the evidence from this study to show survival benefit from the documented stage shift. Further studies are needed to develop a reliable screening regimen for tubal/ovarian/peritoneal cancer akin to the well-developed breast screening programs in which these patients enrol. Similarly, postoperative surveillance is effectively screening for peritoneal cancer after the removal of fallopian tubes and ovaries. Given that no screening method exists for identification of early stage cancers when the risk is relatively high, and that the risk of developing postoperative peritoneal cancer is low, postoperative surveillance for peritoneal cancer is unlikely to be effective.

In addition to screening, the option of salpingectomy alone for risk reduction or salpingectomy with delayed oophorectomy to delay the onset of surgical menopause is appealing. At present, there are several ongoing studies evaluating the efficacy of two-step surgery for tubal/ovarian/peritoneal cancer risk reduction. Salpingectomy with delayed oophorectomy has already been shown to be acceptable to women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2* by the TUBA group [37]; furthermore, Harmsen's mathematical model study is interesting in that tubal/ovarian/peritoneal cancer mortality does not statistically seem to be affected by a delayed oophorectomy when the surgeries are performed at the recommended ages [38]. The results of the ongoing studies for ovarian cancer risk reduction from salpingectomy with delayed oophorectomy will take more than 15 years to determine if this regimen is appropriate for risk reduction.

The primary deterrent to risk-reducing surgery is premature menopause. Despite reassuring evidence that HRT does not significantly increase the risk of breast cancer in carriers above baseline risk, there is still less than a 50% uptake of HRT in unaffected carriers. It is reassuring that the systematic reviews analyzed in this paper demonstrate that HRT is both safe and effective for menopausal symptoms and long-term health complications. It is imperative that surgeons offering RRSO are comfortable providing menopausal hormone therapy to women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2* who have no contraindications to the treatment. The majority of the HRT used in the Kotsopoulos et al. paper on breast cancer risk and HRT after RRSO included conjugated estrogens and medroxyprogesterone acetate [23]. Although conjugated estrogen alone has been shown in the 20-year follow-up of the Women's Health Initiative to be associated with less breast cancer in all-comers, medroxyprogesterone acetate has been associated with a small but significant increased risk of breast cancer, and is not the endometrial-protective agent of choice when offering HRT to women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and

BRCA2. The advent of newer hormone therapies since the Women's Health Initiative has given prescribers a broader armamentarium of options to choose from when prescribing HRT [39].

In addition to treatment of QoL symptoms of menopause and sexual functioning, HRT has clearly been shown in the reviews above to decrease cardiovascular and bone-related complications of premature menopause and is important to be offered to the patients at the average age of menopause, or at minimum 45 years of age. Where this notion continues to be a challenge is in the young carriers affected by a breast cancer diagnosis. When they undergo premature surgical menopause, HRT is typically not offered, even in hormone receptor-negative, early stage breast cancer treated with bilateral mastectomy. Further studies are needed to determine if it is acceptable to treat these women with HRT, thereby minimizing the sequelae of premature menopause and improving the acceptability of risk-reducing surgery.

CONCLUSIONS

Treatment of women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2* should follow the recommendations outlined in Section 1. Fifteen studies including four randomized trials demonstrated that currently no screening method that shows a survival benefit for ovarian, tubal, or primary peritoneal cancer [1-15]. The most effective way for women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2* to reduce the risk of ovarian cancer is to have an RRSO. Women should be offered HRT until age 51 if they have the RRSO. This was demonstrated by five meta-analyses [18-22]. Women who have had RRSO should have individualized post-oophorectomy care taking into account QoL, bone health, and cardiovascular risks [16]. It is not recommended to do peritoneal surveillance after a RRSO [16].

Risk Reduction Strategies for BRCA1/2 Hereditary Ovarian Cancer Syndromes

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC RAP (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the 14 members of the GDG Expert Panel, 11 members voted and two abstained, for a total of 78% response in May 2020. Of those who voted, all approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. In women with a personal history of breast cancer, does the second bullet refer to using systemic hormone therapy beyond age 51 for vasomotor symptom management? It's a bit confusing whether you are referring to the premenopausal or postmenopausal women. In my family practice I have a couple of premenopausal early stage triple negative *BRCA1/2* patients, bilateral mastectomy and premature menopause since RRSO on HRT. Should that be acknowledged in this recommendation or that further study is still needed	We have changed the recommendation for clarity. Although it would seem to make sense that negative effects of hormonal replacement should correlate with hormonal receptor status the literature does not support that. There do not seem to be any long-term data in the mastectomy population and we presume that many family doctors are prescribing HRT.
2. Recommendation 4 Women with a personal history of breast cancer should not be offered HRT. Should there be a qualifying statement regarding hormone receptor status for these women, or is this irrelevant in this context?	We have changed the recommendation for clarity.
3. I would advise, however, that over the long term, there are many non-academic health centres where this work is being done and it would be very significant for the leaders in such centres to be involved in drafting revision, etc, and being recognized as contributors.	We have not modified the document, but will take the suggestions for other versions.
4. Change in the whole document to: women carriers of *BRCA 1/2* mutations	We have modified the document.

instead of : women who are *BRCA1/2* carriers.	
5. Minor edits in the tables and document	The document has been modified for clarification.
6. A comment was made about Recommendation 5: "After a breast cancer diagnosis, RRSO for breast cancer mortality reduction should be considered within two years to women who harbour a pathogenic or likely pathogenic variant in *BRCA1* and *BRCA2* as part of their breast cancer treatment if considered appropriate by their oncologist"	This recommendation is endorsed from another guideline and no changes were made. The working group felt it was clear.
7. A comment was made asking for clarification on the risk of dementia in women who take HRT on page 24.	We have modified the document.

RAP Review and Approval

Three RAP members reviewed this document in February and March 2020. The RAP approved the document on March 16, 2020. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from RAP.

Comments	Responses
1. Can further comment be made about safe length of time for HRT? There is a statement that it seems to have the most benefit with least detriment from 35-50. This infers it is "bridging" the period of premature menopause in women who have surgery and resultant surgical menopause. The studies only reported for around five years. Perhaps this should be more explicitly documented. The reason I ask is that in the women's health study there was detriment to long-term HRT, albeit in healthy women after menopause	The document has not been changed. The challenge is that there are no data available especially in women with *BRCA* mutations.
2. Minor clarifications and typographical errors	We have modified the document accordingly.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Nine targeted peer reviewers from Ontario who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Two agreed to be the reviewers (Appendix 1). Two responses were received. Results of the feedback survey are summarized in Table 5-3. The main comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=2)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				1	1
2. Rate the guideline presentation.					2
3. Rate the guideline recommendations.			1		1
4. Rate the completeness of reporting.					2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?				1	1
6. Rate the overall quality of the guideline report.					
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.				1	1
8. I would recommend this guideline for use in practice.				1	1
9. What are the barriers or enablers to the implementation of this guideline report?	Dissemination to genetic counselling programs and medical oncologists, in addition to gynecologists and gynecologic oncologists, will be important. The major challenge here is distribution of the recommendations to busy clinicians in an easily digestible way. It would be helpful to have some way on assessing adherence to guideline-based care in the future.				

Table 5-4. Summary of the Working Group's responses to comments from targeted peer reviewers.

Comments	Responses
1. Regarding recommendation 1, the accompanying systematic review addresses annual screening versus usual care. However, six-monthly pelvic U/S with or without CA-125 is commonly observed, which is not specifically discussed in the supporting evidence cited in the systematic review.	There is unfortunately no evidence for screening every six months and indeed this has been taken out of the American guideline's 2017 rewrite. The only study with some support for screening (UK FOCSS) is discussed but since only a stage shift and no survival benefit was demonstrated we note in this article that no U/S and CA-125 screening can currently be recommended.
Under Key Evidence for Recommendation 4, supporting literature specific to breast cancer risk and long term use of HRT (beyond a median of 3.3 years) is not provided, which can be important for women undergoing RRSO at age	The studies we included addressed breast cancer risk in the specific carrier population. We do not have longer-term studies looking at breast cancer risk with HRT. A direct quote from the 2017 North American Menopause Society position statement

35.	with regards to premature menopause states "Results of the WHI studies in older women do not apply to women with early menopause, and observational evidence suggests benefit with HRT taken to the average age of menopause." [40] Although the current studies in carriers regarding length of HRT use are reassuring, we extrapolate from the non-carrier literature that the benefits of HRT outweigh the risks for iatrogenic premature menopause to the average age of menopause in carriers without contraindications.
Accompanying a recommendation for HRT (estrogen alone or estrogen plus progesterone) use in women who carry *BRCA1/2* mutation and are post RRSO, it may be useful to identify that medroxyprogesterone acetate is not commonly preferred in this group, as stated in the systematic review discussion. This may be clinically relevant to the end-user of this guideline.	There are several studies including randomized control data suggestive that conjugated estrogen (CE) only (WHI and 2020 WHI update [39]) confers a lower risk of breast cancer than non-users. The same RCTs showed a small but significant increased risk of breast cancer in medroxyprogesterone acetate (MPA) and CE users. Large prospective studies in non-carriers (i.e., E3N) suggest that progesterone is not associated with an increased breast cancer risk, but synthetic progestins such as MPA are [41]. In carriers, the Kotsopoulos et al. paper from 2019 [42] shows a non-significant association with a trend to higher breast cancer rates in combined HRT, most of which was synthetic progestin containing. The reviewer is correct in the association between medroxyprogesterone acetate and other synthetic progestins and breast cancer in carriers. We have changed the document to include the statement that "Where combination HRT is used, it is prudent to choose progesterone over synthetic progestins, or the TSEC" (See the SMART trials) which uses no progestins in carriers [18].
2. Generally excellent. I do take issue with the section of Recommendation 5 where there is an implication that RRSO done two to three years after diagnosis has an impact on breast cancer mortality in both *BRCA1* and *BRCA2*. I understand that this is derived from a prior guideline and you feel that you cannot change it, but the main study on which this is based has a major ascertainment bias and, as a breast oncologist, I seriously question the strength of the evidence supporting this recommendation. Otherwise, the guidelines are sound and indeed excellent.	The Working Group has decided to change the wording from "should" to "can" and as follows: After a breast cancer diagnosis, RRSO for breast cancer mortality reduction can be considered within two years for women who harbour a pathogenic or likely pathogenic variant in *BRCA*1 if younger than the recommended age range for ovarian cancer risk reduction. RRSO before age 40 and specifically for breast cancer treatment in *BRCA*2 should be considered only if recommended by their breast cancer oncologist.
3. It may be visually helpful to organize recommendations with labelled sub-points 4a, 4b, 4c etc.	We have added bullet points for clarity.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. General gynecologic and radiology clinicians, genetic counsellors and risk reduction clinics, and primary care physicians in the PEBC database were contacted by email to inform them of the survey. One hundred seventy-four members in Ontario were contacted. Eleven (6.3%) responses were received. One hundred sixty-three stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from 11 people are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

	Number 11 (6.3%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.				3	8
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	1			4	6
3. I would recommend this guideline for use in practice.				2	9
4. What are the barriers or enablers to the implementation of this guideline report?	• Who will be included in the implementation of this guideline? Family physicians to be included? Rural communities? How will they be impacted? • Barriers - patient awareness and safety of use of HRT in *BRCA*1 and 2 carriers post RRSO Enablers - If proven to be safe in long term studies that salpingectomy is an effective measure of risk reduction, I believe that it would be readily embraced as a choice of surgery in many *BRCA*1 and 2 patients, either as definitive or as a first step followed by bilateral salpingectomy. • Enabler - filling current knowledge gap. Multi-stakeholder involvement. • Widespread effective communication is required to ensure appropriate implementation. Emphasis should be made that evidence-based guidelines should replace experience-based practices. • Dissemination of educational material to primary care. • Small population of applicable patients. Recent CMAJ Sept 2019 Management of Ovarian cancer risk in women with BRCA1/2 suggests beneficial role of				

	acetylsalicylic acid low dose with ongoing prospective Canadian trial. Such an overview sends mixed messages to primary care although ongoing results are realized. • It is complex and will require management by the family physician and various specialists. It will be difficult to nail down the relative risk and mortality benefit of these recommendations to patients. • *BRCA*1/2 patients do not have access to Cancer Centre expertise before cancer. Such valuable information should be available at high-risk Ontario Breast Screening Program centres or focused high-risk virtual consults. There are no barriers with virtual medicine for rare disorders. • Constant feedback from practitioners after implementation is crucial to highlight strengths and weaknesses of the process

Table 5-6. Summary of the Working Group's responses to comments from professional consultants.

Comments	Responses
1. The clear messages would be welcomed in a CMAJ article to increase educational dissemination for primary care.	This guideline will be published and we can look at publishing in the CMAJ
2. AGREE is not in the acronym list.	The document has been modified
3. Can SHRT be used as an acronym for systemic replacement hormone therapy?	This is not typically an acronym we use. The working group has decided not to make any changes to the document.
4. In recommendation 3: It is written "It is premature to recommend ASA." Why not just say: "ASA is not recommended."	The Working Group chose this wording to reflect that the evidence for this recommendation is not yet mature. No changes were made in the document.
5. #4: Is really two recommendations. I do not see a reference for the statement of no hormone therapy at any time for a patient with a mutation and a personal history of breast cancer.	All the recommendations in Recommendation 4 pertain to hormone therapy and are therefore together.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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Appendix 1: Affiliations and Conflict of Interest Declarations

Members of the Risk Reduction Strategies Hereditary Ovarian Cancer Syndromes Working Group

Name	Affiliation	Declarations of interest
Working Group members		
Michelle Jacobson Working Group Chair Gynaecologist	Women's College Hospital, Toronto, Ontario	Consult and speaker for Pfizer, Duchesnay, Allergan and Biosyent. PI for the Stics and Stones study
Nadia Coakley Health Research Methodologist	Program in Evidence-Based Care McMaster University Hamilton, Ontario	None declared
Kelly Anne Branco Patient Representative		Received travel expenses and honorarium to speak at conference about my journey with ovarian cancer.
Marcus Bernardini Gynaecologic Oncologist	Division Head of Gynaecologic Oncology at UHN and Mount Sinai Hospital, Toronto Ontario Associate Professor Department of Obstetrics and Gynecology Gynaecologic Oncology, University of Toronto, Toronto, Ontario Clinician Investigator, Princess Margaret Cancer Centre Cancer Clinical Research Unit (CCRU), Princess Margaret Cancer Centre	Advisory Board Member for Astra Zeneca, Proctor and Minogue Medical

Name	Affiliation	Declarations of interest
Laurie Elit Gynaecologic Oncologist	Division Head for Gynecologic Oncology at Hamilton Health Sciences Centre-Juravinski Cancer Centre, Hamilton, Ontario Professor, Department of Obstetrics and Gynecology, McMaster University, Hamilton Ontario	None declared
Sarah Ferguson Gynaecologic Oncologist	Associate Professor Department of Obstetrics and Gynecology Gynaecologic Oncology, University of Toronto, Toronto, Ontario Director of Research for the Division of Gynecologic Oncology at the University Health Network, Toronto, Ontario Ontario Gynecologic Cancers Lead for Cancer Care Ontario, Toronto, Ontario	None declared
Raymond Kim Medical Geneticist	Princess Margaret Cancer Centre Medical Director, Familial Cancer Clinic Department of Medicine, Division of Medical Oncology University of Toronto Assistant Professor	None declared
RAP panel		

Name	Affiliation	Declarations of interest
Jonathan Sussman	Scientific Director, Program in Evidence-Based Care, Cancer Care Ontario Chair, Department of Oncology McMaster University, Hamilton Ontario	None declared
Donna Maziak	Department of Surgery, University of Ottawa Division of Thoracic Surgery, Ottawa Hospital - General Campus Surgical Oncology Ottawa Ontario	None declared
W. K. (Bill) Evans	Professor Emeritus, Department of Oncology, McMaster University Hamilton, Ontario	None declared
Expert Panel		
Lisa Allen General Gynecologist	Sinai Health System Toronto, ON	Author on the guideline that is being endorsed
Leah Jutzi Gynaecologic Oncologist	Royal Victoria Regional Health Centre Barrie, ON	Received support for a local Continuing medical education event from Astra Zeneca and Roche.
Anna Plotkin Gynaecologic Oncologist	Trillium Health Partners Mississauga, ON	None declared
Laura Sovran General Gynecologist	London Health Science Centre London, ON	None declared
Andrea Simpson General Gynecologist	St. Michael's Hospital Toronto, ON	None declared
Romy Nitsch General Gynecologist	Kingston Health Sciences Centre Kingston, ON	None declared
Matthew Cesari Pathologist	Trillium Health Partners Mississauga, ON	AstraZeneca provided support for validation studies ($5,000 or more in a single year) to the

Name	Affiliation	Declarations of interest
		laboratory where I am currently Program Chief.
Tanya Chawla Radiologist	Sinai Health System Toronto, ON	None declared
Marla Ash Primary Care Physician	North York General Hospital Toronto, ON	None declared
Jacob MacGee Gynaecologic Oncologist	London Health Science Centre London, ON	Serve on Drug Advisory Board for Astra Zeneca and Merck. Received travel and speaker fees from Astra Zeneca
Julie-Ann Francis Gynaecologic Oncologist	Lakeridge Health Oshawa, ON	None declared
Joan Murphy Gynaecologic Oncologist	Trillium Health Partners Mississauga, ON	None declared
Margaret Anthes Radiation Oncology	Thunder Bay Regional Health Sciences Centre Thunder Bay, ON	None declared
J. Wylam Faught Gynaecologic Oncologist	The Ottawa Hospital Ottawa, ON	None declared
Targeted Peer Reviewers		
Mark Robson	Clinical Genetics Research Laboratory, Memorial Sloan-Kettering Cancer Center, New York, NY, USA	Received $500 or more in a single year to act in a consulting capacity from Change Healthcare. Received funds from AstraZeneca, Merck and Pfizer for travel and editorial support. Received grants and research support from AstraZeneca, Merck, AbbVie, Tesaro, Medivation and Pfizer. Currently in uncompensated advisory relationships with AstraZeneca, Merck, Epic

Name	Affiliation	Declarations of interest
		Sciences, Daiichi-Sankyo and Pfizer.
Melinda Wu	Women's College Hospital Toronto, ON	None declared

Appendix 2: Literature Search Strategy

Medline

1. exp ovarian neoplasms/
2. (ovar$ adj5 (neoplasm$ or cancer$ or carcin$ or tumo$ or metasta$ or malig$)).tw.
3. 1 or 2
4. hereditar$.tw.
5. (Hereditary Breast and Ovarian Cancer Syndrome).mp.
6. HBOC.mp.
7. (gene$ adj5 mutation$).mp.
8. hereditar$.mp.
9. BRCA?.mp.
10. risk reduction.mp.
11. bilateral salpingo oophorectomy.mp.
12. screening.mp.
13. chemoprevention.mp.
14. hormone replacement therapy.mp.
15. hrt.mp.
16. familial ovarian cancer.mp.
17. 4 or 5 or 6 or 7 or 8 or 9 or 16
18. 3 and 17
19. (ovar$ adj5 (neoplasm$ or cancer$ or carcin$ or tumo$ or metasta$ or malig$)).mp.
20. 3 or 19
21. 17 and 20
22. (systematic adj (review: or overview:)).mp.
23. (meta-analy: or metaanaly:).mp.
24. (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.
25. (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
26. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.
27. (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
28. (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.
29. (stud: adj1 select:).ab.
30. (28 or 29) and review.pt.
31. or/22-27
32. 30 or 31
33. consensus development conference/
34. practice guideline/
35. *consensus development/ or *consensus/

36. *standard/
37. (guideline: or recommend: or consensus or standards).kw.
38. (guideline: or recommend: or consensus or standards).ti.
39. or/33-38
40. (editorial or note or letter or short survey).pt. or abstract report/ or letter/ or case study/
41. (32 or 39) not 40
42. exp animal/ not human/
43. 41 not 42
44. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
45. randomization/ or single blind procedure/ or double blind procedure/
46. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
47. or/44-46
48. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
49. 48 and random$.tw.
50. (clinic$ adj trial$1).tw.

EMBASE
1. exp ovarian neoplasms/
2. (ovar$ adj5 (neoplasm$ or cancer$ or carcin$ or tumo$ or metasta$ or malig$)).tw.
3. 1 or 2
4. hereditar$.tw.
5. (Hereditary Breast and Ovarian Cancer Syndrome).mp.
6. HBOC.mp.
7. (gene$ adj5 mutation$).mp.
8. hereditar$.mp.
9. BRCA?.mp.
10. risk reduction.mp.
11. bilateral salpingo oophorectomy.mp.
12. screening.mp.
13. chemoprevention.mp
14. hormone replacement therapy.mp.
15. hrt.mp.
16. familial ovarian cancer.mp.
17. 4 or 5 or 6 or 7 or 8 or 9 or 16
18. 3 and 17
19. (ovar$ adj5 (neoplasm$ or cancer$ or carcin$ or tumo$ or metasta$ or malig$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
20. 3 or 19
21. 17 and 20
22. (systematic adj (review: or overview:)).mp.

23. (meta-analy: or metaanaly:).mp.
24. (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.
25. (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
26. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.
27. (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
28. (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.
29. (stud: adj1 select:).ab.
30. (28 or 29) and review.pt.
31. or/22-27
32. 30 or 31
33. consensus development conference/
34. practice guideline/
35. *consensus development/ or *consensus/
36. *standard/
37. (guideline: or recommend: or consensus or standards).kw.
38. (guideline: or recommend: or consensus or standards).ti.
39. or/33-38
40. (editorial or note or letter or short survey).pt. or abstract report/ or letter/ or case study/
41. (32 or 39) not 40
42. exp animal/ not human/
43. 41 not 42
44. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
45. randomization/ or single blind procedure/ or double blind procedure/
46. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
47. or/44-46
48. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
49. 48 and random$.tw.
50. (clinic$ adj trial$1).tw.
51. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
52. placebo/
53. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
54. (allocated adj2 random).tw.
55. or/50-54
56. 47 or 49 or 55
57. (editorial or note or letter or short survey).pt. or abstract report/ or letter/ or case study/
58. 56 not 57
59. animal/ not human/
60. 58 not 59
61. 21 and 43

62. 21 and 60

Appendix 3: Excluded Guidelines

Guideline	Reason for exclusion
U. S. Preventive Services Task Force et al. (2018). "Screening for Ovarian Cancer: US Preventive Services Task Force Recommendation Statement." JAMA **319**(6): 588-594.	Screening for women not to be high risk.
Salvador, S., et al. (2017). "No. 344-Opportunistic Salpingectomy and Other Methods of Risk Reduction for Ovarian/Fallopian Tube/Peritoneal Cancer in the General Population." Journal of Obstetrics & Gynaecology Canada: JOGC **39**(6): 480-4	Reviews the potential benefits of opportunistic salpingectomy.
Expert Panel on Women's, Imaging. (2017). "ACR Appropriateness Criteria Ovarian Cancer Screening." Journal of the American College of Radiology **14**(11S): S490-S499	Only covered imaging
Daly, M. B., et al. (2017). "NCCN Guidelines Insights: Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2017." Journal of the National Comprehensive Cancer Network **15**(1): 9-20.	Very difficult to endorse these guidelines
Daly, M. B., et al. (2017). "Genetic/familial high-risk assessment: Breast and ovarian, version 2.2017: Featured updates to the NCCN guidelines." JNCCN Journal of the National Comprehensive Cancer Network **15**(1): 9-20.	Very difficult to endorse these guidelines
American College of Obstetricians and Gynecologists; Society of Gynecologic Oncology. (2017). "Practice Bulletin No 182: Hereditary Breast and Ovarian Cancer Syndrome." Obstetrics & Gynecology **130**(3): e110-e126.	A very good guideline, but not as new as the guideline we chose to endorse
Basta, A., et al. (2017). "Recommendations of the Polish Gynecological Oncology Society for the diagnosis and treatment of ovarian cancer; Zalecenia Polskiego Towarzystwa Ginekologii Onkologicznej dotyczace diagnostyki i leczenia raka jajnika." Current Gynecologic Oncology **15**(1): 5-2	More of an Ovarian Cancer treatment guideline

Paluch-Shimon, S., et al. (2016). "Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening." Annals of Oncology **27**(suppl 5): v103-v110.	There is current evidence not included in these guidelines
Morgan, R. J., et al. (2016). "Ovarian cancer, version 1.2016: Clinical practice guidelines in oncology." JNCCN Journal of the National Comprehensive Cancer Network **14**(9): 1134-1163.	There is current evidence not included in these guidelines
Walker, J. L., et al. (2015). "Society of Gynecologic Oncology recommendations for the prevention of ovarian cancer." Cancer **121**(13): 2108-2120.	There is current evidence not included in these guidelines
Singer, C. F., et al. (2015). "Clinical Practice Guideline for the prevention and early detection of breast and ovarian cancer in women from HBOC (hereditary breast and ovarian cancer) families." Wiener Klinische Wochenschrift **127**(23-24): 981-986.	There is current evidence not included in these guidelines
Llort, G., et al. (2015). "SEOM clinical guidelines in Hereditary Breast and ovarian cancer." Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societes & of the National Cancer Institute of Mexico **17**(12): 956-961.	There is current evidence not included in these guidelines
Lancaster, J. M., et al. (2015). "Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions." Gynecologic Oncology **136**(1): 3-7.	There is current evidence not included in these guidelines
Committee on Gynecologic, Practice. (2015). "Committee opinion no. 620: Salpingectomy for ovarian cancer prevention." Obstetrics & Gynecology **125**(1): 279-281.	There is current evidence not included in these guidelines
Gonzalez-Santiago S, Ramon y Cajal T, Aguirre E, Ales-Martinez JE, Andres R, Balmana J, et al. SEOM clinical guidelines in hereditary breast and ovarian cancer (2019). Clinical and Translational Oncology. 2020;22(2):193-200.	No new evidence

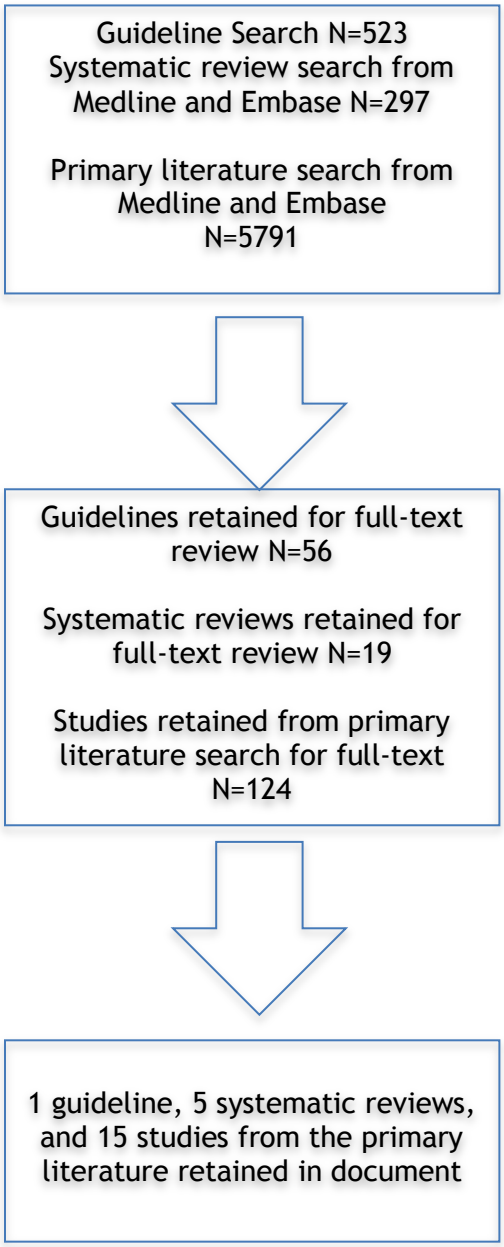
Dullens B, De Putter R, Lambertini M, Toss A, Han S, Van Nieuwenhuysen E, et al. Cancer Surveillance in Healthy Carriers of Germline Pathogenic Variants in BRCA1/2: A Review of Secondary Prevention Guidelines. Journal of Oncology. 2020;2020 (no pagination)(9873954).	Reviews other guidelines
Rees M, Angioli R, Coleman RL, Glasspool R, Plotti F, Simoncini T, et al. European Menopause and Andropause Society (EMAS) and International Gynecologic Cancer Society (IGCS) position statement on managing the menopause after gynecological cancer: focus on menopausal symptoms and osteoporosis. Maturitas. 2020;134:56-61.	Not much information on HBOC

Appendix 4: Cochrane Risk of Bias

Study	Comparison	Randomization method	Blinding	Incomplete outcome data	Selective reporting	Other sources of bias
Jacobs 2016 UKCTOCS	MMS - annual multimodal screening with serum CA125 interpreted with use of the risk of ovarian cancer algorithm N=50,640 TVS - annual transvaginal ultrasound screening N= 50,639 or no screening N=101,359	Low risk Use of computer to randomize each successive volunteer to one of three groups.	Low risk for ovarian cancer diagnosis and deaths caused by ovarian cancer	Low risk 1.12% lost to follow-up	Low risk Primary outcome - Ovarian cancer diagnosis	Low risk
Buys 2011 PLCO Screening Trial	Annual CA125 and transvaginal ultrasound N=34,253 Usual care N=34,304	Low risk Stratified by partial centre	Low risk ovarian cancer mortality and diagnosis	High risk - Initially patients with oophorectomy were excluded, but a protocol change 3 years later allowed them to participate. - By 5th and 6th screening 25% of population was not compliant	Low risk Primary outcome - Ovarian cancer mortality	Low risk
Karlan 2014	Arm 1 – CA125 and HE4 Arm 2=CA125 In both arms if screen was + CA125 and HE4 were used to select women for follow-up imaging or clinical follow-up	Low risk Randomized by blocks by risk group and study site	Low risk for ovarian cancer diagnosis	Low risk 2.7% of participants dropped out of the trial	Low risk Primary outcome diagnosis of ovarian cancer	Low risk
Kobayashi 2008 SCSOCS trial	Annual CA125 and pelvic ultrasound N=41,688 No screening N=40,799	Low risk Assigned to groups by computer	Low risk for ovarian cancer diagnosis	Moderate risk - Details not clear about number of women lot to follow-up in final analysis	Moderate risk Primary outcome not clearly defined	Low risk

Abbreviations: CA125, cancer antigen 125; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; HE4, human epididymis protein 4; ITT, intention to treat; MMS, multimodal screening; PFS, progression-free survival; PLCO, Prostate, Lung, Colorectal and Ovarian; SCSOCS, Shizuoka Cohort Study on Ovarian Cancer Screening; TVS, transvaginal ultrasound; UKCTOCS, UK Collaborative Trial of Ovarian Cancer Screening

Appendix 5: PRISMA Flow Diagram



Appendix 6: AMSTAR 2 tool.

Evaluation of included systematic reviews using AMSTAR 2.

ITEM	Birrer	Gordhandas	Marchetti	Siyam	Vermeulen
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y	Y	Y	Y	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	PY	N	N	PY	N
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Y	Y	Y	Y	Y
4. Did the review authors use a comprehensive literature search strategy?	N	N	PY	PY	N
5. Did the review authors perform study selection in duplicate?	N	N	Y	Y	Y
6. Did the review authors perform data extraction in duplicate?	N	N	Y	Y	Y
7. Did the review authors provide a list of excluded studies and justify the exclusions?	N	N	N	N	N
8. Did the review authors describe the included studies in adequate detail?	N	PY	PY	PY	PY
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	N	N	N	N	N
10. Did the review authors report on the sources of funding for the studies included in the review?	N	N	N	N	N
11.If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N	N	N	N	N
12 If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N	N	N	N	N
13 Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	N	N	N	N	N
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	N	N	N	N	N
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N	N	N	N	N
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	N	Y	Y	Y	Y

Abbreviations: N=no; PY=Partial yes; Y=yes

Appendix 7: Guideline Document History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original 2004	1966 -2004	Full Report	Peer review publication. Web publication.	N.A.
Reviewed October 2014	2004-2013	New data added to original Full Report	Updated web publication.	2004 recommendations require an update
Version 2 2020	2013-2020	Full Report	Updated web publication.	New recommendations