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

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Key Words: BRCA, hereditary breast ovarian cancer (HBOC), familial ovarian cancer, genetic cancer syndrome, BRCA1, BRCA2

KEY MESSAGES

1. BRCA variant status is not a contraindication to hormone therapy.
2. There is no validated screening for ovarian cancer in high-risk patients.
3. Pathology for risk-reducing salpingo-oophorectomy specimens must be conducted by a pathologist trained in the Sectioning and Extensively Examining the Fimbria protocol.
4. Salpingectomy alone for risk reduction should only be conducted in research settings.
5. Optimal risk-reducing salpingo-oophorectomy is performed in women aged 35 to 40 in BRCA1 and 40 to 45 in BRCA2.

Abstract

Objective: This Committee Opinion outlines the gynaecologic management recommendations for women diagnosed with hereditary breast and ovarian cancer syndrome (HBOC) with respect to screening, contraception, chemoprophylaxis, fertility considerations, risk-reducing surgery, and post-oophorectomy care.

Intended Users: This Committee Opinion is designed for gynaecologic oncologists, general gynaecologists, family physicians, genetic

counsellors, registered nurses, nurse practitioners, residents, and health care providers.

Target Population: Adult women (18 years and older) with a pathogenic germline variant in the BRCA1, BRCA2, and other ovarian cancer–associated genes.

Evidence: While reviewing evidence, databases searched include Medline, Cochrane, and PubMed. Medical Subject Heading search terms used include BRCA AND gynaecology management, hormone replacement therapy, risk reduction, chemoprophylaxis, fertility from 01/2010 and 10/2017. Literature search was begun 07/2017 and finalized 10/2017. In total 183 studies were identified, and 101 were used.

Validation Methods: The content and recommendations were drafted and agreed upon by the principal authors. The Board of the Society of Obstetricians and Gynaecologists of Canada approved the final draft for publication. The quality of evidence was rated using the criteria described in the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology framework (Table 1). The interpretation of strong and conditional (weak) recommendations is described in Table 2. The Summary of Findings is available upon request.

Benefits, Harms, and Costs: We may expect a risk reduction of up to 90% in women predisposed to HBOC who undergo risk-reducing bilateral salpingo-oophorectomy. The harms of iatrogenic premature menopause are offset by the benefits of risk reduction. By minimizing potential tubal/ovarian/peritoneal cancers, we can expect savings to the health care system.

Guideline Update: Evidence will be reviewed 5 years after publication to decide whether all or part of the opinion should be updated. However, if important new evidence is published prior to the 5-year cycle, the review process may be accelerated for a more rapid update of some recommendations.

Sponsors: This guideline was developed with resources funded by the Society of Obstetricians and Gynaecologists of Canada.

Recommendations:

1. Patients identified by their gynaecologist, primary care physician, medical geneticist, or oncologist as being at high risk for hereditary breast ovarian cancer according to the National Comprehensive Cancer Network or their respective provincial criteria should be offered genetic counselling and assessment. Patients should be thoroughly counselled on the results and implications of their testing by an expert in genetics (strong, high).
2. Patients with a strong clinical suspicion for hereditary breast ovarian cancer and uninformative or variant of unknown clinical significance testing should be seen every 5 years by genetics (strong, moderate).
3. There is currently insufficient data to support ovarian/tubal/peritoneal cancer screening.
4. Risk-reducing surgery according to established guidelines (Table 3) is the most effective way to reduce the risk of ovarian cancer in women with a hereditary predisposition or risk (strong, low).
5. Breastfeeding appears to be protective in BRCA1 carriers. There are insufficient data for BRCA2 (conditional, moderate).
6. Optimal breast screening is delayed by lactational changes, and decisions on duration of breastfeeding should be made on an individualized basis (strong, high).
7. BRCA carriers of pathogenic variants undergoing gonadotoxic or hormone-based breast cancer treatment should have an urgent consultation with reproductive endocrine and infertility specialists if fertility is a concern and child-bearing is not complete (strong, high).
8. BRCA1 carriers are recommended to undergo risk-reducing salpingo-oophorectomy during child-bearing age and should consider this when family planning (strong, high).
9. BRCA mutation carriers affected by infertility can safely undergo fertility treatments (strong, moderate).
10. The option to screen preimplantation for embryos harbouring a pathogenic variant is available in Canada and should be discussed with all carriers, regardless of fertility (strong, high).
11. Combined hormonal contraceptive use is an effective method of chemoprevention for ovarian/tubal/peritoneal cancer in the general population and women with BRCA1/2 (strong, high).
12. The use of CHCs in young BRCA1 variant carriers should be individualized, taking into account the risks and benefits (strong, moderate).
13. It is premature to recommend ASA for ovarian cancer prophylaxis in the BRCA carrier population (conditional, low).
14. Risk-reducing salpingo-oophorectomy should be offered to BRCA1 carriers between 35 and 40 years of age and BRCA2 carriers from between 40 and 45 years for ovarian/tubal/peritoneal carcinoma risk reduction (strong, high).
15. For women diagnosed as pathogenic variant carriers postmenopausally, risk-reducing salpingo-oophorectomy should be offered upon diagnosis (strong, high).
16. Risk-reducing salpingo-oophorectomy should be considered for breast cancer risk reduction in BRCA2 mutation carriers under 50 years (strong, moderate).
17. After a breast cancer diagnosis, risk-reducing salpingo-oophorectomy for breast cancer mortality reduction should be considered within 2 years to BRCA1 carriers, and for BRCA2 carriers as part of their breast cancer treatment if considered appropriate by their oncologist (strong, high).
18. Bilateral salpingectomy alone for ovarian/tubal/peritoneal cancer risk reduction in BRCA variant carriers is still under investigation and should only be offered as an alternative to risk-reducing salpingo-oophorectomy under a research protocol or if risk-reducing salpingo-oophorectomy is an unacceptable choice for the patient (strong, low).
19. Bilateral salpingectomy is an option for BRCA variant carriers who are younger than the recommended age for risk-reducing salpingo-oophorectomy and do not wish to conceive further pregnancies (without assisted reproductive technologies) (strong, high).
20. The inclusion of hysterectomy with risk-reducing salpingo-oophorectomy for BRCA variant carriers should be individualized, taking into account risk factors for uterine cancer, other uterine pathology, and tamoxifen use (strong, moderate).
21. There are insufficient data to routinely recommend hysterectomy to reduce the risk of papillary serous uterine cancer in BRCA1 mutation carriers (conditional, low).
22. All risk-reducing salpingo-oophorectomy for BRCA variant carriers should be performed by a skilled gynaecologist/gynaecologic 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 gynaecologic oncologist (strong, high).
23. In the absence of contraindications, premenopausal BRCA1/2 carriers undergoing risk-reducing salpingo-oophorectomy should be offered hormone therapy until the average age of menopause (strong, high).
24. Women with a history of breast cancer can be offered nonhormonal alternatives for vasomotor symptom management (strong, moderate).
25. Local vaginal estrogen therapy can be considered in all women suffering from genitourinary syndrome of menopause, but nonhormonal alternatives are recommended first in women with a personal history of breast cancer, especially those on aromatase inhibitors (strong, moderate).
26. Post-oophorectomy care should be administered in an individualized manner, ensuring optimal quality of life, bone health, and cardiovascular risk amelioration (strong, moderate).
27. Following RRSO, it is not recommended to do surveillance for peritoneal cancer in BRCA mutation carriers (conditional, moderate).

SUMMARY

This Committee Opinion is designed to guide clinicians in the gynaecologic management of women with HBOC. HBOC refers to women who harbour a pathogenic germline variant in the BRCA1 or BRCA2 genes or have a strong family history that increases their risk for breast, epithelial ovarian, fallopian tube, and peritoneal cancer (ovarian cancer). Although other pathogenic germline variants have recently been implicated in hereditary ovarian cancer, including mismatch repair genes (Lynch syndrome), BRIP1, RAD51C, RAD51D, and STK11,[1] this review will focus on HBOC. It is likely that additional genes may be implicated as more data are gathered on this patient population. This paper accompanies the American College of Obstetricians and Gynecologists Practice Bulletin number 182, Hereditary Breast and Ovarian Cancer Syndrome, updated in September 2017, and makes recommendations for the care of Canadian women with HBOC.[2] In this paper we summarize the risks of HBOC as they pertain to gynaecologic malignancy and address the full spectrum of care, from screening to contraceptive care and family planning to chemoprophylaxis and risk-reducing surgery. We then summarize the data on management of premature menopause in HBOC. Special consideration is given for women with a personal history of breast cancer (Tables 1 and 2).

Table 1. Key to Grading of Recommendations, Assessment, Development, and Evaluation (GRADE)

Strength of the Recommendation	Definition
Strong	Highly confident of the balance between desirable and undesirable consequences (i.e., desirable consequences outweigh the undesirable consequences; or undesirable consequences outweigh the desirable consequences).
Conditional (weak)[a]	Less confident of the balance between desirable and undesirable consequences.
Quality level of a body of evidence	**Definition**
High/++++	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate/+++0	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low/++00	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low/+000	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a] Conditional (weak) recommendations should not be misinterpreted as weak evidence or uncertainty of the recommendation.

INTRODUCTION

Germline pathogenic variants in the BRCA1 and BRCA2 genes are responsible for the majority of hereditary breast and ovarian cancer. The prevalence of a mutation in either gene in the general population is 1/300 to 1/800, with founder mutations present more frequently in Ashkenazi Jewish, French Canadian, Icelandic, Dutch, Swedish, Norwegian, German, French, and Spanish families.[3,4] It is estimated that approximately 10% to 15% of all women with serous epithelial ovarian cancer and 5% to 10% of women with breast cancer develop their tumour based on inherited germline mutations, most commonly in the BRCA1 or BRCA2 gene.[5–9]

ABBREVIATIONS

ASA	acetylsalicylic acid
CA	125 cancer antigen 125
CHC	combined hormonal contraceptive
CI	confidence interval
GSM	genitourinary syndrome of menopause
HBOC	hereditary breast ovarian cancer
HR	hazard ratio
HT	hormone therapy
IVF	in vitro fertilization
NCCN	National Comprehensive Cancer Network
OR	odds ratio
PGD	pre-implantation genetic diagnosis
RCT	randomized controlled trial
RRSO	risk-reducing salpingo-oophorectomy
TVUS	transvaginal ultrasound
VUS	variant of unknown clinical significance

Ovarian/Tubal/Peritoneal Carcinoma

Women with a pathogenic BRCA1 variant face a 36% to 53% lifetime risk of developing ovarian cancer, while those with a pathogenic BRCA2 variant have an 11% to 25% risk.[10,11] The lifetime risk of developing ovarian cancer in the general population is 1.5% to 1.8%; thus the risk of ovarian cancer in BRCA carriers is over 20 times higher. The lifetime risk of developing ovarian cancer in BRCA1 carriers at age 35 years matches that of the general population and increases to 3.8% by age 40. In BRCA2 carriers, the risk approaches 5% by age 50.[12] On the basis of a cohort of 491 women, BRCA carriers with a personal

Table 2. Judgement and interpretation of strong and conditional recommendations[1]

Judgement/interpretation	Strong recommendation "We recommend. . ..."	Conditional recommendation "We suggest. . .."
Judgement by guideline panel	It is clear to the panel that the net desirable consequences of a strategy outweighed the consequences of the alternative strategy.	It is less clear to the panel whether the net desirable consequences of a strategy outweighed the alternative strategy.
Implications for patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
Implications for clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual to arrive at a management decision consistent with his or hervalues and preferences.
Implications for policy makers	The recommendation can be adopted as policy in most situations.	Policy making will require substantial debate and involvement of various stakeholders.

Table 3. Risks and recommendations for gynaecologic management of BRCA1 and BRCA2 deleterious variants

Risk and recommendation	BRCA1	BRCA2
Ovarian cancer	36%–53%	11%–25%
Breast cancer	65%–80%	45%–85%
Recommended age for risk-reducing oophorectomy	35–40 y	40–45 y
Risk of ovarian cancer after breast cancer diagnosis	12.7%	6.8%
20-year risk of primary peritoneal cancer after oophorectomy	3.9%	1.9%

history of breast cancer have a subsequent risk of developing ovarian cancer of 12.7% for BRCA1 and 6.8% for BRCA2[13] (Table 3).

Breast and Other Cancers

Breast cancer rates and histologies in BRCA carriers vary between the 2 genes. In BRCA1, the estimated lifetime risk of breast cancer to age 70 is 65% to 80%, and tumours are frequently triple negative; in BRCA2, the lifetime risk of breast cancer is 45% to 85%, and tumours are often estrogen and progesterone receptor positive.[5,14] Male BRCA1 carriers are at elevated risk for aggressive prostate cancer, while male BRCA2 carriers are at elevated risk for male breast cancer, prostate cancer, pancreatic cancer, and melanoma.[1]

GENETIC COUNSELLING

Recommendations for genetic testing for HBOC vary by province/territory. Provincial/territorial eligibility criteria for testing can be found on the respective ministry of health's website. Genetic counselling can help determine whether a patient is eligible for provincially funded testing. The NCCN also has broader guidelines with eligibility criteria for HBOC testing. Their recommendations are summarized in Table 4.[1]

The outcomes of genetic counselling are complex and require detailed and thorough explanation by a qualified genetics counsellor.

Proband Testing – A true positive is defined by a germline pathogenic variant detected on molecular genetic analysis of a given gene (e.g., BRCA1/2). This is usually conducted on the first individual to be tested in a family (proband). Ideal probands are those who fulfill the local genetic testing criteria and have been diagnosed with the disease of interest.

When no pathogenic variants are detected, this is referred to as a negative or uninformative result. A negative or uninformative result in the proband may be the result of a technical limitation of the genetic test or another gene causing the family's cancer diagnoses, or the cancer may not be hereditary.

Predictive Genetic Testing – This is the practice of offering genetic testing to family members after another family member receives a true-positive result. Predictive testing is typically done on patients who are not affected by cancer to predict their cancer risk(s) after counselling and informed consent. A true negative in predictive testing occurs when a patient undergoes predictive testing for the familial pathogenic variant and is found not to harbour the variant.

Variant of Unknown Significance – A VUS occurs when there is a variant within the assayed gene but there is inadequate information to know whether this genomic variant causes disease.[15] Patients with a strong clinical suspicion of HBOC and an uninformative or VUS result should be seen periodically by the genetics team or counsellor

because the information and library of deleterious mutations are dynamic.

The process of informed genetic testing has evolved with the recognition of moderately penetrant ovarian cancer contributing genes on multigene panels. This is beyond the scope of this article, but genetic variants in these emerging cancer-causing genes should be done in conjunction with the most up-to-date data, and with a genetics expert.

Recommendations

1. Patients identified by their gynaecologist, primary care physician, medical geneticist, or oncologist as being at high risk for hereditary breast ovarian cancer according to the National Comprehensive Cancer Network or their respective provincial criteria should be offered genetic counselling and assessment. Patients should be thoroughly counselled on the results and implications of their testing by an expert in genetics (strong, high).
2. Patients with a strong clinical suspicion for hereditary breast ovarian cancer and uninformative or variant of unknown clinical significance testing should be seen every 5 years by genetics (strong, moderate).

OVARIAN/TUBAL/PERITONEAL CARCINOMA SCREENING

While excellent screening options for breast cancer in BRCA mutation carriers exist by way of magnetic resonance imaging and mammography, options for ovarian cancer screening have not been proven effective, and risk-reducing surgery is the only proven way to reduce mortality in women with genetic predisposition to ovarian cancer.

Ovarian cancer is the gynaecologic cancer with the highest mortality. The U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results Program data describe the majority of patients (60%) being diagnosed at an advanced stage with 5-year survival of approximately 28%.[16] There is currently no screening regimen that would be considered effective for ovarian cancer in the general or high-risk populations.[17,18] In the large United Kingdom Familial Ovarian Cancer Screening Study, 202 638 women were followed for a median 11 years and were allocated to annual screening by TVUS, CA 125 blood test augmented with TVUS, or no screening. The primary outcome of death due to ovarian cancer was not statistically significantly different among groups. Future analysis and more frequent testing are being explored to determine whether test frequency improves early stage disease identification,[19] although the low incidence of early stage cancers likely indicates that the challenge with screening is not related to the test but to the early peritoneal dissemination of disease.

Table 4. National Comprehensive Cancer Network clinical practice guidelines for high-risk assessment: breast and ovarian cancer

Anyone with a family history within 3 generational pedigrees of 1 or more of the following:
• A blood relative with a known mutation in a gene that increases cancer risk
• A blood relative with 2 or more primary breast cancers
• Two or more relatives with breast cancer on the same side of the family with at least 1 diagnosed before age 50
• A blood relative with ovarian cancer
• A close blood relative with breast cancer before age 45
• A blood relative with male breast cancer
Anyone of Ashkenazi Jewish (at least 1 Ashkenazi Jewish grandparent) ancestry with breast, ovarian, or pancreatic cancer at any age.
Anyone with a cancer diagnosis and 1 or more of the following:
• A blood relative with a known mutation in a gene that increases cancer risk
• Breast cancer at or before the age of 50
• Triple-negative breast cancer at or before the age of 60
• Ovarian, fallopian tube, or primary peritoneal cancer at any age
• Male breast cancer at any age
Anyone with breast cancer at any age and 1 or more of the following:
• A blood relative with a known mutation in a gene that increases cancer risk
• An Ashkenazi Jewish ancestor
• A close blood relative with breast cancer before age 50
• A close blood relative with ovarian cancer
• A second primary breast cancer
Two or more close blood relatives with breast cancer with at least 1 diagnosed before age 50
Anyone with a personal or family history of 3 or more of the following, especially if any of the cases are diagnosed before age 50:
• Pancreatic cancer
• Prostate cancer
• Melanoma
• Sarcoma
• Adrenal cancer
• Brain tumors
• Leukemia
• Uterine cancer
• Thyroid cancer
• Kidney cancer
• Diffuse gastric cancer
• Colon cancer

The same authors of the United Kingdom Familial Ovarian Cancer Screening Study examined the high-risk population in a separate study (UKFOCSS). The phase 2 results of this trial involved 4348 women having a CA 125 blood test every 4 months and an ultrasound scan once a year. CA 125 results were analyzed using the Risk of Ovarian Cancer Algorithm. Of 13 women in the study group who were diagnosed with cancer, 5 (38%) had stage 1 to 2 disease. Upon completion of screening, 18 further cases were diagnosed, 1 of which (5%) was in the early stages. The results were underpowered to detect survival benefit, but the authors concluded that 4 monthly screenings with the Risk of Ovarian Cancer Algorithm and TVUS may diagnose earlier stage disease.[20]

The recent publication from the Modena study group examined 661 high-risk women who were followed with TVUS and CA 125, 127 of whom were BRCA1 or BRCA2 carriers.[19,21] After 112 months, 12 ovarian/tubal/peritoneal cancer cases were found, 6 (50%) of which were early stage disease. One woman was diagnosed under the age of 40, and 9 (75%) of the women who were diagnosed with cancer were over 50 years. In both the Modena trial and the UKFOCSS trial, the median age of initial participation was significantly higher than the recommended ages for prophylactic risk-reducing surgery, so very little can be concluded from either of these 2 studies to guide the management of younger women awaiting prophylactic surgery.

Recommendations

3. There is currently insufficient data to support ovarian/tubal/peritoneal cancer screening.
4. Risk-reducing surgery according to established guidelines (Table 3) is the most effective way to reduce the risk of ovarian cancer in women with a hereditary predisposition or risk (strong, low).

FAMILY PLANNING CONSIDERATIONS

Pregnancy and Lactation

Pregnancy and lactation appear to have a protective effect on the risk of BRCA1-associated breast cancer, particularly in women who have breastfed for more than 1 year, as seen in a cohort study of 1600 matched pairs of carriers (OR 0.68; 95% CI 0.52−0.91).[22] No such reduction was found for BRCA2 mutation carriers. One case-control study looking only at parity found an increased risk of breast cancer (OR 1.53; 95% CI 1.01−2.32) in BRCA2 mutation carriers with 2 or more children.[23]

Because of lactational changes in the breast during pregnancy and postpartum, breast screening is not optimally performed during these times.[24] The risk-benefit analysis of suboptimal imaging versus prolonged breastfeeding seems to favour breastfeeding in BRCA1 carriers, while more data are required to make conclusions about the effects on BRCA2 carriers.

Recommendations

5. Breastfeeding appears to be protective in BRCA1 carriers. There are insufficient data for BRCA2 (conditional, moderate).
6. Optimal breast screening is delayed by lactational changes, and decisions on duration of breastfeeding should be made on an individualized basis (strong, high).

Fertility Considerations

There have been multiple reports in the literature suggesting that BRCA1/2 carriers may have a decreased ovarian reserve.[25,26] Indeed, in a matched case-control study from 2013, Finch et al. showed that BRCA1/2 pathogenic variant carriers entered the climacteric earlier than controls (48.8 and 49.2 years vs. 50.3 years, respectively), but there were no fertility sequelae associated with this earlier menopause.[25] BRCA1 mutation carriers also appear to have a lower circulating antimüllerian hormone on average compared with BRCA2 carriers and controls.[27] Turan et al. in 2017 showed that BRCA1/2 mutation carriers with a personal history of breast cancer have a decreased response to controlled ovarian hyperstimulation and produce fewer oocytes (16.4 ± 7.7 vs. 11.0 ± 8.0, $P = 0.015$) and embryos (8.2 ± 4.7 vs. 5.1 ± 4.4, $P = 0.013$) compared with controls.[28]

BRCA pathogenic variant carriers also frequently face a host of iatrogenic fertility issues. Bilateral RRSO or salpingectomy renders a patient infertile; oocyte cryopreservation and IVF, respectively, become her only options for fertility.[29] Women exposed to gonadotoxic chemotherapy may become temporarily or permanently menopausal. Valentini et al. undertook a multicentre study of 1954 BRCA1/2-mutated breast cancer patients, 1426 of whom underwent adjuvant chemotherapy.[30] The likelihood of primary ovarian insufficiency was significantly higher for older BRCA2 carriers (46.8%) versus BRCA1 carriers (32.7%); ($P < 0.001$), regardless of tamoxifen use. Overall there was no significant increase in the number of carriers who became menopausal following chemotherapy compared with non-carrier controls (35.6% vs. 49%, $P = 0.18$).[30] Women who have HT for breast cancer treatment (tamoxifen, aromatase inhibitors) cannot conceive during treatment, and the

ongoing Pregnancy Outcome and Safety of Interrupting Therapy for Women With Endocrine Responsive Breast Cancer (POSITIVE) trial will help to determine the safety of interruption of endocrine therapy to conceive after breast cancer.[31–35]

Recommendations

7. BRCA carriers of pathogenic variants undergoing gonadotoxic or hormone-based breast cancer treatment should have an urgent consultation with reproductive endocrine and infertility specialists if fertility is a concern and child-bearing is not complete (strong, high).

8. BRCA1 carriers are recommended to undergo risk-reducing salpingo-oophorectomy during child-bearing age and should consider this when family planning (strong, high).

IVF and Pre-implantation Genetic Diagnosis

For BRCA pathogenic variant carriers the option to undergo IVF and screen for mutated embryos (PGD) exists.[36] In 2008, a group from Toronto's Women's College Hospital performed a case-control study of 1380 matched pairs of carriers to determine whether a history of infertility, the use of fertility medications, or IVF was associated with elevated breast cancer risk in carriers. They found that carriers who had undergone fertility treatment were not at significantly increased risk for breast cancer (OR 1.21; 95% CI 0.81–1.82).[37] A small retrospective cohort study of 62 carriers undergoing IVF for PGD or fertility preservation (i.e., normal fertility potential) demonstrated a normal stimulation response compared with non-carriers.[38]

The acceptability for the use of PGD among carriers has been evaluated in several qualitative surveys. Carriers are more inclined to consider PGD if they have a personal history of breast or ovarian cancer.[39] One study on decision making in patients with BRCA mutations showed only 4 of 18 (22.2%) carriers chose to undergo PGD. None of the couples intended to terminate a BRCA mutation–positive pregnancy.[40] In another survey, 37.5% would have considered PGD if it had been available before they had completed child-bearing.[41]

Recommendations

9. BRCA mutation carriers affected by infertility can safely undergo fertility treatments (strong, moderate).

10. The option to screen preimplantation for embryos harbouring a pathogenic variant is available in Canada and should be discussed with all carriers, regardless of fertility (strong, high).

OVARIAN/TUBAL/PERITONEAL CARCINOMA RISK REDUCTION

Chemoprophylaxis

Combined hormonal contraceptives

The use of CHCs for ovarian cancer prophylaxis is well-described in the literature. In the general population, a 40% to 50% risk reduction in ovarian cancer has been reported, and this has been found to be consistent in BRCA1/2 mutation carriers.[42–45] A meta-analysis of 3 case-control studies resulted in a 43% risk reduction in ovarian cancer associated with any past CHC use (OR 0.57; 95% CI 0.93–0.97).[43]

Concerns around a possible association between CHC and breast cancer development in BRCA variant carriers have made the choice for reliable contraception and ovarian cancer prophylaxis complex. The risk of breast cancer in variant carriers associated with CHC has been examined in a large case-control study of 1311 matched pairs of BRCA1/2 variant carriers, where the case group had a personal history of breast cancer. In this study, CHC use for 5 years or more was associated with an 33% increased risk of breast cancer in BRCA1 variant carriers (OR 1.33; 95% CI 1.11–1.6) Other risk factors included use of CHC before age 30 (OR 1.29; 95% CI 1.09–1.52), breast cancer diagnosis before age 40 (OR 1.38; 95% CI 1.11–1.72), and those who used CHC before 1975 (1.42; 95% CI 1.17–1.75).[44] In a 2011 meta-analysis, no significant increase in breast cancer with CHC use in carriers could be found, apart from the aforementioned cohort of BRCA1 variant carriers. There has been no association of breast cancer with CHC use in BRCA2 variant carriers, despite the majority of their breast cancers being estrogen and progesterone receptor positive.[43] Findings were similar though not statistically significant for breast cancer concerns in a 2013 meta-analysis, where 14 studies were included. The OR for ovarian cancer in CHC use was 0.58 (95% CI 0.46–0.73), and a statistically nonsignificant association with breast cancer was found (OR 1.21; 95% CI 0.93–1.58).[46]

Non-steroidal anti-inflammatories

The use of ASA and other analgesics (non-steroidal anti-inflammatory drugs and acetaminophen) has been studied to determine their effects on ovarian cancer incidence in the general population. The Ovarian Cancer Association Consortium analyzed the use of ASA and non-steroidal anti-inflammatory drugs in 12 population-based case-

control studies totalling 7776 ovarian cancer cases. The Consortium found that ASA use was associated with a significantly reduced risk of ovarian cancer (OR 0.91; 95% CI 0.84–0.99). Low-dose ASA (<100 mg) and daily use were found to yield the lowest ORs.[47] A large Danish case-control study of 4103 ovarian cancer cases showed similar findings, where continuous use of low-dose ASA was associated with an OR of 0.56 (95% CI 0.32–0.97), particularly in nonserous epithelial ovarian cancer.[48] There is an ongoing clinical trial to determine the utility of ASA for ovarian cancer prophylaxis in BRCA1/2 variant carriers.[49]

Recommendations

11. Combined hormonal contraceptive use is an effective method of chemoprevention for ovarian/tubal/peritoneal cancer in the general population and women with BRCA1/2 (strong, high).

12. The use of CHCs in young BRCA1 variant carriers should be individualized, taking into account the risks and benefits (strong, moderate).

13. It is premature to recommend ASA for ovarian cancer prophylaxis in the BRCA carrier population (conditional, low).

Surgical Risk Reduction

Risk-reducing bilateral salpingo-oophorectomy

RRSO is the most effective method of prevention for ovarian/tubal/peritoneal carcinoma. In BRCA1/2 mutation carriers, RRSO reduces the risk of ovarian cancer by 80% to 90%.[50] Although older literature also suggests that RRSO confers a 50% reduction in breast cancer development in BRCA1/2 carriers, a more recent study suggests that only premenopausal BRCA2 carriers have a 50% risk reduction in breast cancer rates from RRSO.[50–52] In this Canadian cohort study, 3722 unaffected BRCA1/2 carriers who had undergone RRSO but not preventive breast surgery 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 0.73–1.26), nor were they significant in BRCA2 carriers (HR 0.65; 95% CI 0.37–1.16). However, when the latter group was stratified by age, RRSO had a significant reduction in breast cancer incidence when performed before age 50 (HR 0.18; 95% CI = 0.05–0.63).[51]

Women undergoing premenopausal RRSO are concerned about their quality of life, sexuality, and long-term cardiovascular, bone, and cognitive function as a result of premature menopause.[53,54] They can be reassured by the findings of several large cohort studies, totalling more than 8500 BRCA1/2 carriers, that RRSO leads to a significant reduction not only in mortality from ovarian cancer but also in all-cause mortality of 60% to 77%.[55]

Recommendations for timing of RRSO vary by mutation. To minimize the incidence of ovarian cancer to near–general population rates, the most appropriate age to perform RRSO is between 35 and 40 years for a BRCA1 carrier and between 40 and 50 years for a BRCA2 carrier [R]. Given that BRCA2 carriers also benefit from breast cancer risk reduction from RRSO when performed before age 50, the consensus according to NCCN is to perform RRSO in these women between ages 40 and 45 years.[1,51] In women who are diagnosed as pathogenic variant carriers postmenopausally, there appears to be benefit for risk reduction throughout the lifetime because the ovarian cancer risk continues to increase beyond age 70.[56]

For BRCA1 carriers with breast cancer, there appears to be a significant benefit to RRSO performed shortly after diagnosis, regardless of age. In the Canadian prospective cohort study from 2015 conducted by Metcalfe et al., RRSO significantly reduced breast cancer mortality by 62%, and by 73% when performed within 2 years of breast cancer diagnosis.[57] A subgroup analysis by tumour receptor status revealed that mortality was especially reduced by 93% for triple-negative breast cancers. For BRCA2 mutation carriers, there does not seem to be a clear breast cancer mortality benefit to RRSO after diagnosis. However, 1 treatment for premenopausal estrogen receptor–positive breast cancer includes chemical or surgical oophorectomy and aromatase inhibitors; thus RRSO may be considered among these options.[34,57] The results reported by Metcalfe et al. are similar to those of a number of studies, where the reduction in breast cancer mortality after oophorectomy ranged from 70% to 85% in BRCA1 mutation carriers, with improved mortality benefit in triple-negative cancer.[55,58,59]

Recommendations

14. Risk-reducing salpingo-oophorectomy should be offered to BRCA1 carriers between 35 and 40 years of age and BRCA2 carriers from between 40 and 45 years for ovarian/tubal/peritoneal carcinoma risk reduction (strong, high).

15. For women diagnosed as pathogenic variant carriers postmenopausally, risk-reducing salpingo-oophorectomy should be offered upon diagnosis (strong, high).

16. Risk-reducing salpingo-oophorectomy should be considered for breast cancer risk reduction in BRCA2 mutation carriers under 50 years (strong, moderate).

17. After a breast cancer diagnosis, risk-reducing salpingo-oophorectomy for breast cancer mortality reduction should be considered within 2 years to BRCA1 carriers, and for BRCA2 carriers as part of their breast cancer treatment if considered appropriate by their oncologist (strong, high).

Two-stage surgery/salpingectomy alone

There is a mounting body of evidence to support a precursor lesion of serous carcinoma in the fimbrial ends of the fallopian tubes.[60,61] Pathologic studies obtained from BRCA1/2 mutation carriers undergoing prophylactic RRSO surgery have demonstrated high-grade serous intraepithelial precursor lesions/carcinomas in the fimbria: these lesions have been associated with an increased risk of peritoneal cancer.[62–64] On the basis of such findings, many centres are investigating whether salpingectomy alone or a 2-step RRSO with interval salpingectomy may be a viable option for young BRCA mutation carriers. The Dutch Early Salpingectomy (Tubectomy) With Delayed Oophorectomy in BRCA1/2 Gene Mutation Carriers (TUBA) nonrandomized controlled trial is currently ongoing, as are 2 other non-randomized controlled trials in Texas and France.[65] Although salpingectomy seems like an ideal solution to balance ovarian cancer risk reduction with the risks of premature menopause, data supporting or refuting this approach are still in their infancy.

It has been suggested that opportunistic bilateral salpingectomy may significantly reduce the risk of ovarian cancer in the general population by 35%.[66] A 2016 Dutch study looked at mathematical models for ovarian cancer risk following 2-step surgery in BRCA variant carriers. 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 5 years later within the recommended window for preventive surgery affords risk reduction similar to that with RRSO alone.[67]

Recommendations

18. Bilateral salpingectomy alone for ovarian/tubal/peritoneal cancer risk reduction in BRCA variant carriers is still under investigation and should only be offered as an alternative to risk-reducing salpingo-oophorectomy under a research protocol or if risk-reducing salpingo-oophorectomy is an unacceptable choice for the patient (strong, low).

19. Bilateral salpingectomy is an option for BRCA variant carriers who are younger than the recommended age for risk-reducing salpingo-oophorectomy and do not wish to conceive further pregnancies (without assisted reproductive technologies) (strong, high).

RRSO with hysterectomy

There is no clear evidence on the inclusion of prophylactic hysterectomy with RRSO in BRCA1/2 mutation carriers. Arguments for hysterectomy include the ability to remove the intramural portion of the tube, to decrease the risk of subsequent uterine carcinoma (especially if tamoxifen is being used for breast cancer treatment or prophylaxis), to simplify the administration of HT, and to be used in the setting of preexisting uterine/cervical pathology (dysplasia, large fibroids, prolapse, etc.).[67,68] Some papers report a higher rate of papillary serous uterine cancer in BRCA1 carriers, although the overall rate of uterine cancer was no higher than that in the general population.[69,70] Arguments against hysterectomy include longer operating time, more hospital resources, and a higher rate of surgical morbidity/operative complications. After reviewing the available data in 2014, Vyarvelska et al. recommended against routine hysterectomy with RRSO but suggested that each decision be made on an individualized basis taking risk factors for uterine cancer into account.[71]

Recommendations

20. The inclusion of hysterectomy with risk-reducing salpingo-oophorectomy for BRCA variant carriers should be individualized, taking into account risk factors for uterine cancer, other uterine pathology, and tamoxifen use (strong, moderate).

21. There are insufficient data to routinely recommend hysterectomy to reduce the risk of papillary serous uterine cancer in BRCA1 mutation carriers (conditional, low).

Technical components of RRSO

Laparoscopic RRSO should be performed in the absence of contraindications or surgical morbidity. Pelvic washings should be undertaken and sent for cytologic examination.[72] The upper abdominal organs, liver, diaphragm surface, paracolic gutters, and appendix should be inspected. The tubal transection should occur within the intramural portion of the cornua and the remnant cauterized. The infundibulopelvic ligament should be skeletonized and transected

2 cm distal from the ovary, with care taken not to injure the ureter.[73] The specimens should be removed carefully without contaminating the incision and in an endoscopic bag if a laparoscopic approach is used, to avoid port-site seeding of occult malignancy.[2,74]

Histopathologic examination

Occurrence of occult carcinoma of the tube or ovary in prophylactic surgery specimens has been reported as between 2% and 9% in larger series (>100 cases).[74,75] Although the majority of tubal cancers are found in the fimbrial ends of the tube, there have been cases of fallopian tube cancers/precursor lesions isolated from the mid/distal tube.[76] All RRSO specimens must be processed following published guidelines for what is commonly known as the Sectioning and Extensively Examining the Fimbria protocol. Use of this protocol, which optimizes histologic examination of both fallopian tubes and ovaries, has significantly improved the detection of occult cancers in the distal fallopian tube,[77] from 2.5% to 17% when the Sectioning and Extensively Examining the Fimbria protocol is used.[78] Processing of histologic sections should include sections for immunohistochemistry in addition to routine hematoxylin and eosin sections. Diagnosis and reporting of occult cancers and significant precursor lesions (serous tubal intraepithelial carcinoma) should follow published criteria to improve diagnostic reproducibility. Many occult high-grade serous tubal invasive carcinomas and intraepithelial carcinomas/lesions have been detected through this ultrasensitive pathologic examination, and some may have been missed when examined in the usual fashion.[79]

Recommendation

22. All risk-reducing salpingo-oophorectomy for BRCA variant carriers should be performed by a skilled gynaecologist/gynaecologic 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 gynaecologic oncologist (strong, high).

Management of premature menopause in BRCA mutation carriers

The majority of unaffected carriers undergoing RRSO at the recommended age (BRCA1 35 to 40 years and BRCA2 40 to 45 years) will be rendered surgically prematurely menopausal. Deleterious or negative effects include quality of life disturbances such as vasomotor symptoms, GSM, sexual dysfunction, and mood changes, among others.[54] Long-term sequelae include cardiovascular disease, osteoporosis, and premature cognitive decline.[54,80] Current guidelines recommend that in the absence of contraindications, women from the general population with premature menopause take HT until the average age of menopause and use local vaginal hormonal therapies for GSM.[80] The BRCA mutation carrier population is unique in that iatrogenic menopause occurs in the unaffected carrier as early as 35 years, and there is an already heightened concern about breast cancer development. Even more challenging are the BRCA mutation carriers who have developed breast cancer at a young age and are now menopausal because of RRSO, chemotherapy, or ovarian suppression with endocrine therapy.

The use of HT in BRCA1/2 carriers has been investigated in a number of prospective studies. There is a paucity of RCT data on which to base recommendations. In 1999, Guidozzi et al. conducted an RCT to determine whether HT after ovarian cancer is associated with a shortened disease-free survival period. They found no difference in mortality or disease-free survival.[81] In 2006, a prospective cohort study found no association between HT and the development of ovarian cancer in BRCA1/2 mutation carriers (OR 0.93; 95% CI 0.56−1.56).[82]

With regard to breast cancer risk and HT, 2 cohort studies suggested that HT is not correlated with an increased risk of breast cancer in the unaffected BRCA population who have undergone RRSO but not prophylactic mastectomy. Eisen et al. studied 472 BRCA1 mutation carriers who took HT and found that the OR for breast cancer associated with ever use of HT was 0.58 (95% CI 0.35−0.96).[83] Similarly, Kotsopoulos et al. studied 432 matched pairs of women with BRCA1 mutation for a mean duration of 4 years and found that the OR for breast cancer in HT ever users was 0.80 (95% CI 0.55−1.16).[84] Should there indeed be a significant risk reduction in breast cancer due to RRSO, Rebbeck et al. demonstrated that the reduction is not lessened by the introduction of menopausal HT.[85]

HT has been shown to be effective in the improvement of vasomotor symptoms in BRCA1/2 mutation carriers.[86,87] With regard to sexual functioning, RRSO is associated with more vaginal dryness (28%), dyspareunia (35%), less pleasure, and less satisfaction.[88] Carriers were twice as likely to have hypoactive sexual desire disorder.[89] One study found that sexual activity returns to baseline with HT after 1 year.[89,90] Finch et al. concluded, based on their cohort, that HT does not completely ameliorate decline in sexual functioning.[86]

BRCA1/2 mutation carriers who undergo RRSO premenopausally are at increased risk for cardiovascular disease, metabolic syndrome, obesity, elevated blood glucose, and hypertension.[91,92] In the general population these risks are somewhat mitigated by HT, but this has not been studied specifically in the BRCA population. Similarly, BRCA1/2 mutation carriers have a 30% higher chance of osteopenia/osteoporosis without HT compared with women who took HT.[93] There is an ongoing study examining the effects of RRSO on cognition in BRCA1/2 mutation carriers.

On the basis of the results of 2 RCTs from Sweden examining the use of HT after breast cancer, we cannot recommend systemic HT for any patients with a personal history of breast cancer.[94,95] Their symptoms can be improved with local vaginal therapies for GSM and selective serotonin or serotonin/norepinephrine reuptake inhibitors, gabapentin, clonidine, and cognitive behavioural therapy for vasomotor symptoms.[96,97] Local estrogen can be used in women with a personal history of breast cancer, but because of the potential risks of increasing serum estradiol concentration, it should be prescribed after a trial of nonhormonal alternatives.[80]

Recommendations

23. In the absence of contraindications, premenopausal BRCA1/2 carriers undergoing risk-reducing salpingo-oophorectomy should be offered hormone therapy until the average age of menopause (strong, high).

24. Women with a history of breast cancer can be offered nonhormonal alternatives for vasomotor symptom management (strong, moderate).

25. Local vaginal estrogen therapy can be considered in all women suffering from genitourinary syndrome of menopause, but nonhormonal alternatives are recommended first in women with a personal history of breast cancer, especially those on aromatase inhibitors (strong, moderate).

Management after prophylactic surgery

Because of the increased risk of osteoporosis following premature menopause, undergoing dual x-ray absorptiometry scan 1 year following RRSO is suggested, then determining the future frequency on the basis of 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

26. Post-oophorectomy care should be administered in an individualized manner, ensuring optimal quality of life, bone health, and cardiovascular risk amelioration (strong, moderate).

Surveillance following bilateral RRSO/screening for peritoneal carcinoma

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% BRCA2).[98–100] No surveillance is recommended for women who have undergone RRSO.

Recommendation

27. Following RRSO, it is not recommended to do surveillance for peritoneal cancer in BRCA mutation carriers (conditional, moderate).

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