REVIEW CPD

Management of ovarian cancer risk in women with *BRCA1/2* pathogenic variants

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Ovarian cancer has the highest mortality of all female reproductive cancers, largely owing to the absence of early symptoms and lack of effective screening, resulting in diagnosis at an advanced stage. Hereditary breast and ovarian cancers include specifically identified genetic variants that greatly increase the lifetime risk of breast and ovarian cancer. *BRCA1* and *BRCA2* (*BRCA 1/2*) pathogenic germline variants account for most hereditary breast and ovarian cancer syndromes.

Given the substantial lifetime risk and high mortality of ovarian cancer in women with *BRCA1/2* pathogenic variants, risk reduction is a priority, and a risk-reducing salpingo-oophorectomy can decrease the lifetime risk of ovarian cancer by about 80%.[1] Gynecologic management associated with reducing the risk of ovarian cancer in this population includes medical and surgical prophylaxis, important contraception and fertility considerations, and the management of iatrogenic premature menopause, as detailed in the recently published Society of Obstetrician and Gynaecologists of Canada (SOGC) clinical practice guideline.[1] We discuss the gynecologic management of women with a *BRCA1/2* pathogenic variant who are at high risk of ovarian cancer, based on evidence outlined in Box 1. These women with a *BRCA1/2* pathogenic variant are also at substantially increased risk of breast cancer and require specific management,[5,6] but this is outside the scope of this review and will not be covered.

Box 1: Evidence used in this review

We searched PubMed from 2014 to 2019 for articles with "*BRCA*" and "risk reduction," and selected randomized controlled trials, systematic reviews, meta-analyses and observational studies (final search date Feb. 20, 2019). We screened 135 abstracts and reviewed 46 articles. We also reviewed relevant organizational guidelines on the management of women with hereditary breast and ovarian cancer syndromes, including the Society of Obstetrician and Gynaecologists of Canada guideline (and its 100 references),[2] in addition to the Royal College of Obstetricians and Gynaecologists[3] and the American College of Obstetricians and Gynecologists.[4]

KEY POINTS

- Women who meet criteria for *BRCA1/2* testing should undergo counselling and assessment by health professionals with genetics expertise.
- There is no effective screening protocol shown to reduce mortality from ovarian cancer, including in women at high risk, who carry *BRCA1/2* pathogenic variants.
- The only strategy shown to reduce ovarian cancer mortality in such women is a risk-reducing salpingo-oophorectomy, which should be done at age 35–40 years in women with *BRCA1* and age 40–45 in women with *BRCA2*.
- Women who undergo risk-reducing salpingo-oophorectomy (who do not have a personal history of breast cancer) should consider hormone replacement therapy until the average age of menopause to help mitigate the substantial risks associated with surgical premature menopause, as hormone replacement therapy in *BRCA1/2* mutations carriers with no personal history of breast cancer is not associated with an increased risk of breast cancer.

What are *BRCA 1/2* pathogenic variants?

Pathogenic germline variants in *BRCA1/2* substantially increase a woman's lifetime risk of breast and ovarian cancer, in addition to other cancers such as prostate and pancreatic cancer and melanoma. *BRCA1/2* genes code for tumour suppressor proteins that function to maintain DNA integrity. *BRCA1/2* pathogenic variants are inherited in an autosomal dominant fashion, and the prevalence in the general population ranges from 1/400 to 1/800, but can be as high as 1/40 in women of Ashkenazi Jewish descent.[7,8] Women with *BRCA1* and *BRCA2* pathogenic variants have a cumulative lifetime risk of ovarian cancer of 39%–44% and 11%–17%, respectively,[9,10] and this is greatly increased above the 1.4% lifetime risk of ovarian cancer in the average Canadian woman.[11] The risk of ovarian cancer begins to rise above the population risk after age 40 years in women with *BRCA1*, and after age 50 in women with *BRCA2*; this finding forms the basis for the approach to risk reduction outlined below. Given the histopathologic similarity between high-grade serous

carcinoma of the ovary, fallopian tube and peritoneum, the term "ovarian cancer" in this review is used to refer to the entire spectrum of disease.

Who should be tested for *BRCA1/2* pathogenic variants?

Indications for testing, as well as the interpretation of results, should be done with the guidance of a genetic counsellor, geneticist or other health professional with expertise in genetics. According to the National Comprehensive Cancer Network's guidance on *BRCA1/2* screening (Box 2),[12] patients who meet criteria for *BRCA1/2* testing should be referred for risk assessment and pretest counselling, followed by determination of family status. If a familial *BRCA1/2* pathogenic variant is known, the patient should undergo genetic testing for that specific variant. If no familial *BRCA1/2* variant is known, comprehensive *BRCA1/2* testing or multigene testing for the hereditary breast and ovarian cancers panel should be considered, ideally with the affected individual (or family member with the highest likelihood of harbouring the variant).[12]

In 1915 unselected women given a diagnosis of advanced-stage ovarian cancer, *BRCA1/2* pathogenic variants were found in 15%.[13] As such, consideration of *BRCA1/2* testing is recommended in all women who have received a diagnosis of high-grade serous ovarian cancer, because as many as 40% of these women have no family history suggestive of hereditary breast and ovarian cancers.[4,14] Beyond the enormous implications of this knowledge for family members, *BRCA1/2* status may directly influence treatment, as polymeric adenosine diphosphate ribose (ADP-ribose) polymerase inhibitors for *BRCA1/2*–positive ovarian cancers have recently been shown to prolong progression-free survival.[15]

Can we screen for ovarian cancer?

Given the increased risk of ovarian cancer (and the often poor prognosis after diagnosis), in addition to the health implications and adverse effects of risk-reducing salpingo-oophorectomy, this population would greatly benefit from a reliable screening test

Box 2: National Comprehensive Cancer Network® (NCCN®) indications for testing for BRCA1/2 pathogenic or likely pathogenic variants

- Individual from a family with a known BRCA1/2 pathogenic or likely pathogenic variant
- Personal history of breast cancer and 1 or more of:
  - Diagnosed at age 45 yr or younger
  - Diagnosed at age 46–50 yr with:
    - An additional breast cancer primary at any age
    - One or more close blood relatives with breast cancer at any age
    - One or more close blood relatives with high grade prostate cancer
    - Unknown or limited family history
  - Diagnosed at age 60 yr or younger with triple negative breast cancer
  - Diagnosed at any age with:
    - One or more close blood relatives with any 1 of:
      Breast cancer diagnosed at age 50 yr or younger
      Ovarian cancer
      Male breast cancer
      Metastatic prostate cancer
      Pancreatic cancer
    - Two or more additional diagnoses of breast cancer at any age in patient or close blood relatives
  - Ashkenazi Jewish ancestry
- Personal history of ovarian cancer
- Personal history of pancreatic cancer
- Personal history of male breast cancer
- Personal history of metastatic prostate cancer
- Personal history of high-grade prostate cancer at any age with any of:
  - One or more close blood relatives with ovarian cancer, pancreatic cancer, or metastatic prostate cancer at any age, or breast cancer at age 50 yr or younger
  - Two or more close blood relatives with breast or prostate cancer at any age
  - Ashkenazi Jewish ancestry
- BRCA1/2 pathogenic variant detected by tumour profiling
- An individual who does not meet the criteria but has 1 or more first- or second- degree blood relatives who meet the criteria.*

Note: Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast and OvarianV.3.2019.[12] © 2019 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations therein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available.

*There are limitations for testing an unaffected individual.

for ovarian cancer. Unfortunately, to date, no screening test or algorithm has been shown to reduce mortality. Proposed screening for ovarian cancer relies on serial transvaginal ultrasound and serum cancer antigen 125 (CA-125). Transvaginal ultrasound for adnexal masses carries a high false-positive rate, leading to potential anxiety, unnecessary surgical intervention and subsequent iatrogenic ovarian insufficiency or menopause.[16] Cancer antigen 125 may be elevated in several benign gynecological conditions, especially in premenopausal women, making interpretation of elevated levels challenging. In all cases, the theorized underlying pathogenesis of ovarian cancer, with shedding of malignant cells from the tubal fimbriated end into the abdominopelvic cavity,[17] likely leads to rapid disease progression between serial screening opportunities, which hampers the development of an effective screening protocol.

Several large, high-quality randomized controlled trials have found no survival benefit of screening for ovarian cancer in the general population. Both the US Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer study[16] and the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) study[18] together randomized almost 280 000 women at average risk to screening with CA-125 and transvaginal ultrasound, and found no effect on ovarian cancer mortality. In addition, one-third of women had unnecessary surgical intervention from a false-positive screen, which was associated with a 15% risk of serious surgical complications.[16]

In women at high risk, several large prospective studies have not shown an effect of screening on ovarian cancer mortality. The large, phase II multicentre prospective UK Familial Ovarian Cancer Screening Study screened 4348 women at high risk using the Risk of Ovarian Cancer Algorithm–based interpretation of CA-125 results every 4 months, and annual transvaginal ultrasound (more frequently if Risk of Ovarian Cancer Algorithm score was abnormal).[19] Similarly, the MODENA study prospectively screened 661 women with *BRCA1/2* pathogenic variants using CA-125 and transvaginal ultrasound every 6 months.[19] Screening in both studies was associated with diagnosis of earlier stage (stage I or II) disease, but this did not translate into a reduction in ovarian cancer mortality.[19] As such, screening should not replace surgery for primary prevention, and women at high risk should be aware of the limitations of screening.

What can be done to reduce the risk of ovarian cancer in women at high risk?

Surgical risk reduction

Salpingo-oophorectomy

In the absence of an effective screening program, surgery offers the best protection against the development of ovarian cancer in women at high risk. Risk-reducing salpingo-oophorectomy is the current standard of care[2–4,20] and reduces the lifetime risk of ovarian cancer by about 80%.[1] In a recent Cochrane review of 8087 women with *BRCA1/2* pathogenic variants, where 2936 underwent risk-reducing salpingo-oophorectomy and 5151 did not, this procedure decreased all-cause mortality (hazard ratio [HR] 0.32, 95% confidence interval [CI] 0.19–0.54), ovarian cancer mortality (HR 0.06, 95% CI 0.02–0.17) and breast cancer mortality (HR 0.58, 95% CI 0.39–0.88).[21] Although outside the scope of this review, the benefit of risk-reducing salpingo-oophorectomy on breast cancer mortality is substantial as well, given the major lifetime risk of breast cancer in women with *BRCA1/2* pathogenic variants (72% and 69%, respectively),[9] a finding that supports the strong recommendation for oophorectomy in this population.

Timing of risk-reducing salpingo-oophorectomy in women with *BRCA1/2* is established based on the age when the risk of ovarian cancer begins to surpass that of the baseline population. For women with *BRCA1* and *BRCA2* pathogenic variants, risk-reducing salpingo-oophorectomy should be performed between age 35–40 and 40–45 years, respectively, ideally after child-bearing is complete.[17] In general, risk-reducing salpingo-oophorectomy is discouraged before these target age recommendations, because of the substantial negative effects of premature surgical menopause (including effects on cardiovascular, bone, and cognitive health, in addition to menopausal symptoms), which may outweigh the risk of development of ovarian cancer. For women who present later than the target age range, risk-reducing salpingo-oophorectomy is still encouraged, because ovarian cancer risk continues to increase with age.

Risk-reducing salpingo-oophorectomy is typically a 1-hour, minimally invasive laparoscopic surgery performed on an outpatient basis, with a short recovery time (1–2 wk). Surgical technique for risk-reducing salpingo-oophorectomy has been standardized, and includes careful inspection of the pelvis and abdomen, pelvic washings, removal of the entire ovary and fallopian tube, and specimen extraction within an endoscopic bag.[4,17] It is critical that specimens are processed according to the Sectioning and Extensively Examining the Fimbria (SEE-FIM) protocol, which maximizes fimbrial surface area examination and has been shown to substantially increase the detection rate of occult malignant disease at the time of prophylactic surgery.[22]

Several large prospective cohort studies have found a 3.5%–5% rate of precursor lesions and occult ovarian cancer in women with *BRCA1/2* pathogenic variants undergoing risk-reducing salpingo-oophorectomy,[23,24] particularly if surgery is performed above the target age recommendation. Patients may require additional surgery or chemotherapy if occult cancer is detected.

Salpingectomy (with or without delayed oophorectomy)

Despite the substantial protection offered, not all women choose to proceed with salpingo-oophorectomy (or to have the procedure within the target age). This is a result either of late recognition of carrier status, or a choice to delay or defer surgery, most commonly for fertility preservation or the substantial short- and long-term morbidity of iatrogenic premature menopause.[25] Risk-reducing salpingo-oophorectomy performed within the target age (where most women are premenopausal) induces iatrogenic premature menopause. Early menopause has substantial health implications, especially in women who cannot receive hormone replacement therapy because of a personal history of breast cancer. The risks of iatrogenic menopause, combined with current evidence suggesting the distal fallopian tube (fimbriae) as the source of high-grade serous carcinoma, have resulted in the

emergence of other surgical strategies for risk reduction, in which the ovaries are retained.

Risk-reducing salpingectomy alone, or with delayed oophorectomy (where the completion oophorectomy is performed closer to the time of natural menopause) is appealing for premenopausal women who have completed child-bearing and who desire protection against ovarian cancer, but who want to avoid the negative health outcomes associated with premature menopause. Two multicentre, nonrandomized trials are currently under way to assess salpingectomy with delayed oopherectomy as an alternative to risk-reducing salpingo-oophorectomy in high-risk premenopausal women (the Early Salpingectomy with Delayed Oophorectomy in *BRCA1/2* Mutation Carriers study [clinicaltrials.gov, no. NCT02321228][26] and the Women Choosing Surgical Prevention trial [clinicaltrials.gov, no. NCT02760849]). In addition, the effect of radical fimbriectomy alone on ovarian cancer in young women with *BRCA1/2* mutations is also under investigation (clinicaltrials.gov, no. NCT01608074).

At present, however, the degree of risk reduction achieved through risk-reducing salpingectomy (alone, or with delayed oopherectomy) in women at high risk is unknown, and women with *BRCA1/2* pathogenic variants should be aware that salpingo-oophorectomy within the target age is still the gold standard for risk reduction. Women below the target age for risk-reducing surgery who have completed child-bearing may be offered interval salpingectomy (with completion oophorectomy performed once the patient reaches the target age). Women who are at or above the target age who decline salpingo-oophorectomy should also be offered salpingectomy (with or without delayed oopherectomy), but should be counselled regarding the limitations of this strategy with respect to achieving optimal risk reduction. Additionally, the SOGC recommends that women at average risk (without *BRCA1/2* pathogenic variants) who have completed child-bearing should consider opportunistic salpingectomy (with complete removal of the fimbriated end of the fallopian tube), either for family planning (instead of tubal ligation) or at the time of benign gynecologic surgery,[27] for ovarian cancer risk reduction.

Hysterectomy

Performing hysterectomy at the time of risk-reducing salpingo-oophorectomy in women with *BRCA1/2* pathogenic variants remains controversial, and observed increased rates of endometrial cancer in this population may be confounded by tamoxifen use. In general, *BRCA1/2* pathogenic variants are not associated with an overall elevated risk of endometrial cancer. However, a large prospective cohort study of 1083 women with *BRCA1/2* pathogenic variants undergoing risk-reducing salpingo-oophorectomy found that women with *BRCA1* did have an increased risk of serous or serous-like endometrial cancer (4 cases observed, 0.18 cases expected, in 3781.0 woman-years).[28] Although concurrent prophylactic hysterectomy is not routinely recommended[2] for women with *BRCA1/2* pathogenic variants at the time of salpingo-oophorectomy for the sole purpose of risk reduction, care should be individualized. Hysterectomy adds surgical time, can incur more perioperative complications and postoperative morbidity, and requires a longer recovery period. However, hysterectomy can simplify hormone replacement therapy in premenopausal women by eliminating the need for progesterone and preventing bleeding or spotting. Hysterectomy will also simplify tamoxifen use, as it eliminates endometrial cancer risk and tamoxifen-associated endometrial pathology. In general, women with additional uterine or cervical pathology (e.g., prolapse, large symptomatic fibroids, cervical dysplasia) or women who feel strongly about removing the uterus may be offered concurrent hysterectomy as part of their risk-reducing procedure.[2]

Chemoprophylaxis

Combined hormonal contraceptives have been shown to substantially reduce the risk of ovarian cancer by 40% to 50% in both the general population of women[29] and in women with a *BRCA1/2* pathogenic variant.[30] A 2013 meta-analysis with 14 included studies showed a 42% risk reduction for ovarian cancer associated with use of combined hormonal contraceptives in women with *BRCA1/2* pathogenic variants, with no statistically significant increase in breast cancer risk.[30] As such, *BRCA1/2*–affected women should be aware of the potential risk reduction associated with combined hormonal contraceptives, in addition to their use as effective contraception.[2]

Several large, population-based, case-controlled studies have also suggested a beneficial role of daily low-dose acetylsalicylic acid (ASA) use for the prevention of ovarian cancer in *BRCA1/2*–affected women.[31,32] An ongoing prospective Canadian trial aims to address the role of ASA in this population of women (clinicaltrials.gov, no. NCT03480776).

What should be considered with respect to contraception and fertility?

Contraception

Hormonal contraception and the risk of breast cancer

Given the substantially elevated lifetime risk of breast cancer in this population *(*72% in *BRCA1* and 69% in *BRCA2*[9]), there is understandable concern regarding the use of hormonal contraception in terms of breast cancer risk in women with *BRCA1/2* pathogenic variants. In a large, prospective study of almost 1.8 million unselected (at average risk) women followed for a mean of 10.9 years, current or recent use of any type of hormonal contraception had a relative risk of breast cancer of 1.20 (95% CI 1.14–1.26) or 1 additional case of breast cancer diagnosed for every 7693 women using hormonal contraception for 1 year.[33]

When analyzed by type of hormonal contraception, women using combined hormonal contraceptives had a relative risk of 1.19 (95% CI 1.13–1.26; 1 additional breast cancer diagnosis for every 7693 women using combined hormonal contraceptives for 1 year). In those women using progestin-only contraception, the relative risk (RR) was increased only with oral levonorgestrel (RR 1.93, 95% CI 1.18–3.16; 1 additional breast cancer diagnosis for every 2127 women using oral levonorgestrel for 1 year), and the levonorgestrel intrauterine system (RR 1.21, 95% CI 1.11–1.33; 1 additional breast cancer diagnosis for every 6667 women using the levonorgestrel intrauterine system for 1 year).

In women at high risk, although the literature is controversial, a recent large meta-analysis found no significant effect of combined hormonal contraceptive use on breast cancer risk (OR 1.21, 95% CI 0.93–1.58).[30] The data on breast cancer risk associated with progestin-only contraception in this population are very limited. If the small increased risk in breast cancer with progestin-only use in the general population is extrapolated to women at high risk, where the lifetime risk of breast cancer is already so high, it is unlikely that the small increase is clinically significant.

Combined (estrogen plus progestin) hormonal contraception

The use of combined hormonal contraceptives for reduction of ovarian cancer risk is described above, with clear benefit in women with *BRCA1/2* pathogenic variants. In the absence of medical contraindications to estrogen, combined hormonal contraceptives comprise an excellent option for women seeking reliable contraception, with the added benefit of ovarian cancer chemoprophylaxis.[2]

Progestin-only contraception

Although there are no specific studies looking at progestins alone in this patient population, progestins as part of combined hormonal contraceptives appear to be safe. As such, when indicated, progestins (including norethindrone, depo medroxyprogesterone acetate, and the levonorgestrel intrauterine system) can be used when combined hormonal contraceptives are not tolerated or are contraindicated. It is important to note, however, that the degree of reduction of ovarian cancer risk with progestins is unclear.

Copper intrauterine device

The copper-containing intrauterine device (IUD) has not been studied specifically in this group of women, but given it is a hormone-free product, it is unlikely to affect breast or ovarian cancer risk. For women who prefer to avoid hormone-containing products, or in whom hormones are contraindicated (women with a personal history of breast cancer), the copper IUD is an ideal choice. As with progestin-only options, the benefit beyond reliable contraception (with respect to ovarian cancer risk reduction) is unknown.

Permanent contraception

The role of bilateral salpingectomy for reducing risk of ovarian cancer in this population is discussed above. If permanent contraception is desired, an interval salpingectomy should be considered (instead of tubal ligation) for the anticipated decreased risk of ovarian cancer.

Fertility

Decisions about fertility and family planning in women with *BRCA1/2* pathogenic variants are complex, given the inheritance pattern and substantial health implications for offspring. In addition, risk-reduction surgery before completion of child-bearing and the effect of chemotherapy on fertility are important considerations. As such, early discussion of fertility options with referral to a fertility specialist is encouraged.

Pre-implantation genetic diagnosis

Given that germline *BRCA1/2* pathogenic variants are inherited in an autosomal dominant fashion, women should understand the 50% chance of passing their *BRCA1/2* mutation to their offspring. In addition, paternal risk of harbouring a *BRCA1/2* pathogenic variant must also be considered. For women who find this risk unacceptable, in vitro fertilization with pre-implantation genetic diagnosis permits detection of the *BRCA* mutation in embryos, with the goal of implanting only embryos without a deleterious variant. Adoption, or donor-egg or sperm pregnancy are alternative options for women who wish to have children without the risk of passing on the *BRCA1/2* pathogenic variant.

Infertility

Balancing fertility with prophylactic surgery can also be challenging, as all forms of risk-reducing surgery prevent spontaneous conception. Women who choose to proceed with risk-reducing salpingo-oophorectomy before completing child-bearing may wish to undergo in vitro fertilization with either egg or embryo-cryopreservation, which have similar live birth rates and perinatal outcomes.[34] In women who choose risk-reducing salpingectomy, in vitro fertilization is required, but the patient's own eggs can be retrieved. Several studies have suggested that *BRCA1*-affected women may have a lower ovarian reserve than unaffected individuals,[35] which may be explained by the role of *BRCA* proteins in DNA repair. Accelerated ovarian aging can contribute to overall lower fertility rates, in addition to earlier onset of natural menopause, but this lower ovarian reserve has not been associated with reduced fecundity.[36] Furthermore, young women with *BRCA1/2* pathogenic variants who develop breast cancer and require chemotherapy will likely have a reduction in fertility potential, depending on the woman's age at the time of treatment and the chemotherapy regimen used. Together, these factors may encourage *BRCA1/2*–affected women not to delay child-bearing, or to meet with a fertility specialist for counselling.

How can menopausal symptoms be safely managed?

Given the current age recommendations for risk-reducing surgery, many women will enter iatrogenic premature menopause after risk-reducing salpingo-oophorectomy. Women with a personal history of breast cancer may also have premature menopause secondary to chemotherapy or medications that suppress ovarian function.

Risks of premature menopause

Several population-based cohort studies have shown increased risks of several negative health outcomes after surgical premature menopause (oophorectomy before the onset of natural menopause).[37] Women who undergo surgical premature menopause are at increased risk of all-cause mortality,[38] premature cognitive decline or dementia,[39] cardiovascular disease[40] and bone loss.[41] Many of these outcomes were shown in the Mayo Clinic Cohort Study of Oophorectomy and Aging; a population-based cohort study of women who underwent bilateral or unilateral oophorectomy before the onset of natural menopause (for

noncancer indications) matched by age with a referent population that did not undergo oophorectomy. Similar findings have been noted in other large cohort studies.[42,43]

Women with *BRCA1/2* pathogenic variants who undergo risk-reducing salpingo-oophorectomy can expect to have substantial menopausal symptoms (including vasomotor symptoms, genitourinary syndrome of menopause, sexual dysfunction, sleep disturbances and mood changes), even if they were postmenopausal at the time of surgery,[44,45] and symptoms have been shown to be more severe than those experienced by women who undergo natural menopause.[46]

Hormone replacement therapy

In women who undergo risk-reducing salpingo-oophorectomy before menopause, hormone replacement therapy should be started, in the absence of absolute clinical contraindications, in order to mitigate the negative health outcomes of iatrogenic premature menopause. Although hormone replacement therapy has been shown to ameliorate vasomotor symptoms, and reduce cardiovascular disease, bone loss and mortality,[43] this therapy may not prevent all the symptoms or sequelae of premature menopause.[44]

Women without a personal history of breast cancer

Concern regarding the use of hormone replacement therapy in women with *BRCA1/2* pathogenic variants is understandably centred on risk of breast cancer. A large meta-analysis of 1100 women with *BRCA1/*2 pathogenic variants who underwent risk-reducing salpingo-oophorectomy found no increased risk of breast cancer with use of hormone replacement therapy (HR 0.98, 95% CI 0.63–1.52).[47] For women without a personal history of breast cancer, hormone replacement therapy is safely recommended up until the natural age of menopause.

A recent systematic review assessed the risks and benefits of this therapy in women with *BRCA1/2* pathogenic variants after risk-reducing salpingo-oophorectomy. Hormone replacement therapy was associated with improved quality of life, sexual function and menopause symptoms.[48] In addition, hormone replacement therapy after risk-reducing salpingo-oophorectomy is likely associated with improved bone health, and women who decline hormone replacement therapy or who have additional risk factors for bone disease should have their bone health monitored. Although specific data in *BRCA1/*2 mutation carriers are limited, in the general population hormone replacement therapy has been shown to mitigate cardiovascular disease and cognitive decline associated with premature iatrogenic menopause.

Hormone replacement therapy regimens include estrogen and progestins (for endometrial protection), conjugated equine estrogens with tissue selective estrogen complex, or estrogen alone (in women without a uterus), and a variety of formulations are available. For women above the average age of menopause, hormone replacement therapy is generally not provided after iatrogenic menopause from risk-reducing salpingo-oophorectomy.

Women with a personal history of breast cancer

For women with a personal history of breast cancer, hormone replacement therapy has been shown to increase the risk of recurrence of breast cancer[49] and is therefore not recommended.[50] For this group of women, nonhormonal options (including selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors, gabapentin, clonidine and oxybutynin) can be used to ameliorate adverse effects, and referral to a menopause specialist is suggested. As per the North American Menopause Society 2017 position statement, low-dose vaginal estrogen can be considered in this population for the treatment of genitourinary syndrome of menopause if nonhormonal options have failed, after consultation with the patient's oncologist. Caution should be used in women who are on aromatase inhibitors.[50]

In all women, lifestyle interventions to optimize bone and cardiovascular health, including diet, exercise, calcium and

Box 3: Unanswered questions

What is the degree of risk reduction obtained with salpingectomy (alone, or as part of a salpingectomy with delayed oophorectomy)? The degree of risk reduction obtained may be compromised by the presence of microscopic residual fimbrial tissue that persists on the ovarian surface in up to 16% of women after salpingectomy.[51] The degree of risk reduction for salpingectomy alone is currently unknown and cannot, at present, be recommended as surgical prophylaxis in women at high risk who are above the target age for definitive risk-reducing surgery.

Box 4: Applying the results of this review in clinical practice

A 31-year-old woman who has completed child-bearing after 2 spontaneous, uncomplicated pregnancies presents for discussion about reducing her risk of ovarian cancer. Her mother died of ovarian cancer at the age of 45 years, and 2 maternal aunts received a diagnosis of breast cancer at 38 and 42, respectively. There is a known familial pathogenic *BRCA1* mutation, and the patient has tested positive for this familial variant. She has no personal history of cancer. Important points to consider when counselling this patient include:

- A discussion regarding her cancer risk. Breast screening should take place, and she should be referred to a multidisciplinary breast team for counselling and consideration of risk-reducing mastectomy. Her lifetime risk of ovarian cancer should also be reviewed.
- She should understand that screening has not been shown to improve ovarian cancer survival.
- Given that she has completed child-bearing but is below the target age for risk-reducing salpingo-oophorectomy, the patient could wait until age 35–40 years for the procedure, or consider an interval salpingectomy, with completion oophorectomy to be performed at age 35–40 years.
- After completion oophorectomy, she will enter iatrogenic premature menopause and should be counselled regarding the risks and benefits of hormone replacement therapy, which is recommended to be continued until the average age of menopause. If she chooses not to undergo concurrent hysterectomy at the time of her oophorectomy, she will require both estrogen and progestin for endometrial protection. She should undergo screening for bone health and cardiovascular disease.

This clinical scenario is fictional.

vitamin D supplementation and smoking cessation, should be reviewed with the patient by their primary care physician.

Box 3 outlines some important areas of uncertainty about the management of ovarian cancer risk in women with *BRCA1/2* genetic variants. An example of the principles of management discussed in this review is available in Box 4, with resources for patients in Box 5.

Box 5: Resources for patients

- Facing Our Risk of Cancer Empowered: www.facingourrisk.org
- Menopause and U: www.menopauseandu.ca/
- Prevent Ovarian Cancer Program: www.preventovariancancer.ca/

Conclusion

Women with germline *BRCA1/2* pathogenic variants have unique and broad medical needs requiring care from multiple specialists with expertise that includes minimally invasive surgical gynecology, gynecologic oncology, genetics, menopause, fertility, social work, counselling and nursing. Therefore, multidisciplinary management of these women is essential and referral to a multidisciplinary clinic for women with *BRCA1/2* pathogenic variants should be considered, where available.[52,53]

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