Challenging and Complex Decisions in the Management of the BRCA Mutation Carrier

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Abstract

Women afflicted by the hereditary breast and ovarian cancer syndrome face complex decisions regarding medical interventions aimed at reducing their risk of ovarian and breast cancer, interventions which in turn may interfere with their fertility and cause early menopause. This review addresses selected topics of importance and controversy in the management of the BRCA mutation carrier, such as psychological well-being and quality of life, breast and ovarian cancer screening, risk-reducing interventions for breast cancer and ovarian cancer, the issue of hysterectomy at the time of the risk-reducing salpingo-oophorectomy, health consequences of early surgical menopause, and safety of hormonal therapy after oophorectomy. The information presented is based on an extensive review of the literature on the selected topics and on the expertise of our multidisciplinary team.

Introduction

Most hereditary breast and ovarian cancer (HBOC) is due to germline mutations within the BRCA1 or BRCA2 genes. BRCA mutation carriers face important and challenging decisions regarding cancer prevention, screening and early detection, risk-reduction surgical and pharmacological options, and menopausal hormonal management. Medical management of the BRCA mutation carrier requires a multidisciplinary and individualized approach.1 Breast specialists, menopause experts, geneticists, and breast, plastic, and gynecologic surgeons have important roles in counseling women about available risk-reducing medical and surgical therapies, the health consequences of such treatments, and the management of the side-effects caused by these therapies.

The objectives of this article are to provide a review of the literature on selected topics pertaining to the management of the BRCA mutation carrier and to provide the clinician caring for these patients with recommendations based on our expertise as a multidisciplinary team working within a dedicated high-risk breast practice.

Cancer Risks Associated with the BRCA Mutation

Since the BRCA genes were cloned in the mid-1990s, more than 1600 deleterious mutations have been identified in the BRCA1 gene, and more than 1800 in BRCA2.2 In the general population, the prevalence of BRCA1/2 mutations is 1 per 400 to 1 per 800.3,4 There is an increased prevalence in ethnic groups such as those of Ashkenazi Jewish descent and Icelanders, with a prevalence of 1 per 40 and 1 per 167 respectively.5 While individuals with BRCA1/2 mutations are at highest risk for breast and ovarian cancer, other cancers consistently associated with BRCA1 mutations include prostate and male breast cancer; BRCA2 mutations are associated with prostate cancer, male breast cancer, and pancreatic cancer.2 The likelihood that a BRCA mutation carrier will develop a cancer depends on other genetic modifiers and environmental determinants.6 Although HBOC accounts for only 5% of breast cancers and 10%–15% of ovarian cancers,7 women with BRCA mutations have a markedly increased risk of early-onset breast and ovarian cancer. A meta-analysis revealed that by age 70, the mean cumulative risk for breast cancer is 57% in BRCA1 mutation carriers and 49% in BRCA2 mutation carriers; similarly, ovarian cancer risk is 40% in BRCA1mutation carriers and 18% in BRCA2 mutation carriers.8 A cohort study of Ashkenazi Jewish women, BRCA1 or BRCA2 mutation carriers, reported a lifetime (to the age of 80) breast cancer risk as high as 82% for both BRCA1 and BRCA2 mutation carriers and ovarian cancer risk of 54% and 23% for BRCA1 and BRCA2 mutation carriers, respectively.9 Another study found a cumulative risk for breast cancer to the age of 70 to be 65% and 45% for BRCA1 and BRCA2 mutation carriers, respectively.10 These risks are substantial when compared to the risks of breast cancer (13%) and ovarian cancer (1.5%) in...
the general population. As part of the ovarian cancer spectrum, the risk of fallopian tube and primary peritoneal carcinoma is also increased in BRCA mutation carriers. In fact, emerging data over the last several years has indicated the fallopian tube as an important site of carcinogenesis in BRCA mutation carriers, and this has prompted the study of salpingectomy for risk reduction.

Psychosocial Well-Being in BRCA Mutation Carriers

BRCA mutation testing should be offered after professional genetic counseling with a genetic counselor or medical geneticist. These specialists are trained to provide nondirective counseling, thereby following the principles of autonomy, beneficence, and nonmaleficence. The patient is provided with comprehensive information about genetic testing, risks to self and family members, management options and is supported in his or her decisions regarding testing and management. Genetic counselors are individuals with a graduate degree and training in medical genetics and counseling. Counselors facilitate testing in several ways: (1) determine which tests are appropriate for a given patient, (2) identify the most informative family member for testing, (3) facilitate test ordering and consenting processes, (4) understand and interpret test results, (5) discuss screening and prevention options, (6) counsel regarding medical management decisions, (7) help manage emotional aspects of a hereditary cancer diagnosis including the impact of increased cancer risks and communicating with at-risk family members, and (8) provide information about community resources and support groups. Therefore, genetic testing is best offered after a thorough consultation in medical genetics.

Anxiety levels appear to be higher in BRCA mutation carriers who opt for ovarian cancer surveillance versus risk-reducing salpingo-oophorectomy (RRSO). However, premenopausal women undergoing RRSO may experience hot flashes and night sweats (40%), dyspareunia (17%), and decreased libido (22%). In some studies, risk-reducing mastectomy (RRM) has been associated with chronic pain, difficulties with body image, sexual dysfunction, decreased quality of life (QOL), and regret over the decision to undergo the surgery. Other studies have found no regrets and also no decreased QOL among women who decided to undergo RRM. A high level of general satisfaction after prophylactic surgery was reported in some studies and women who underwent surgery reported they would do the same again.

Reproductive concerns in BRCA mutation carriers may include guilt associated with transmission of HBOC to future generations, consideration of in vitro fertilization, preimplantation genetic diagnosis (PGD) to avoid transmission to future generations, and fertility preservation for those who choose RRSO prior to completing childbearing. Early consultation with a Reproductive Endocrinology and Infertility specialist with expertise in PGD and embryo/oocyte cryopreservation may be helpful. Women with psychological concerns may benefit from referral to a mental health provider with expertise in this area and from participating in a support group such as FORCE (Facing Our Risk of Cancer Empowered).

Screening for Breast and Ovarian Cancer

The National Comprehensive Cancer Network (NCCN) has published guidelines for surveillance and risk-reducing surgical and medical options for women with HBOC. Breast cancer screening methods are proven to detect cancer at earlier stages. A recent study illustrated that an annual magnetic resonance imaging (MRI) decreases the risk of advanced-stage breast cancer in women with BRCA1/2 mutations. Current breast cancer screening recommendations for the BRCA mutation carrier include monthly breast self-exam beginning at 18 years of age, semiannual clinical breast exam beginning at age 25, and annual mammography and breast MRI beginning at ages 25–35. Screening should be modified based on the earliest age of onset of breast cancer in a first-degree relative in a given family. The American Cancer Society guidelines recommend screening with breast MRI beginning at age 30 in BRCA mutation carriers.

Early detection methods for ovarian cancer are, unfortunately, less effective than for breast cancer screening. The NCCN recommends that BRCA mutation carriers be followed with pelvic examinations, transvaginal ultrasounds, and serum CA-125 levels every 6 months beginning at age 30 or 5–10 years earlier than the youngest diagnosed relative with ovarian cancer, whichever comes first. It is important to recognize, however, that these surveillance methods have not been shown to reduce ovarian cancer mortality.

The phase 1 results of the United Kingdom Familial Ovarian Cancer Screening Study (UKFOCSS) recently showed that annual CA-125 and transvaginal ultrasound increased the likelihood of detecting ovarian cancer at an earlier stage in women with high-risk mutations. However, 60% of stage 1 cases were in women with Lynch syndrome, and nearly all of the screen-negative, occult ovarian cancers were among women with BRCA mutations and of advanced stage. Nevertheless, this study provides support for current surveillance strategies.

CA-125 is useful in evaluating a suspicious pelvic mass, but its sensitivity and specificity in screening for ovarian cancer is limited. Demographic (e.g., age, race), clinical factors (e.g., smoking, prior hysterectomy, menstruation), and benign gynecologic conditions (e.g., fibroids, endometriosis, and pregnancy) can increase CA-125 values. The frequency of these underlying factors makes it difficult to define a static cutoff value for CA-125; thus, an algorithm was developed using longitudinal changes in CA-125 coupled with age-specific risk. Longitudinal CA-125 changes and the risk of ovarian cancer algorithm (ROCA) were initially investigated in average-risk women revealing a sensitivity of 40%–50% to detect early-stage disease. These early studies guided development of studies in women at high risk for ovarian cancer, and the results of phase 2 of UKFOCSS, Gynecologic Oncology Group (GOG) protocol 199 along with the ROCA trial headed by the National Cancer Institute’s Cancer Genetics Network are eagerly awaited. Newly available serum markers, HE4 and the OVA1 test, are used to distinguish between benign and malignant ovarian masses and are not intended for screening.

Prevention of Breast and Ovarian Cancer

Preventive strategies against breast and ovarian cancer are the mainstay of cancer risk management in BRCA mutation carriers. Surgical and pharmacological options are available.

Risk-reducing surgical options

Bilateral RRM decreases breast cancer risk by 90% in BRCA mutation carriers. There is no clear recommendation...
regarding the age at which RRM should be considered, but it appears that the largest gains in life expectancy are derived from RRM in the fourth decade of life. In clinical practice, individualized recommendations should be made, based on the age at which family members developed breast cancer. Surgery should be pursued only after thorough multidisciplinary consultation with a breast health provider, and breast and plastic surgery specialists. A psychology referral should be offered to women who struggle emotionally with their decision.

While the optimal timing of RRSO in the BRCA mutation carrier remains undefined, the NCCN recommends RRSO between ages 35 and 40 years and upon completion of childbearing, regardless of the type of BRCA mutation. This recommendation may be modified based on the age of the youngest affected relative with an ovarian cancer diagnosis and whether they have previously undergone RRSO. Importantly, after RRSO, the risk of developing ovarian cancer in the remaining ovary is low, and the risk of developing breast cancer in the remaining breast is not significantly increased. RRSO should be pursued only after thorough multidisciplinary consultation with a breast health provider, and breast and plastic surgery specialists. A psychology referral should be offered to women who struggle emotionally with their decision.

Thus, a strategy of RRSO around the age of 40 years appears most beneficial for survival, with RRM by age 40 offering a slight additional survival benefit. Delaying RRSO until the age of 50 might be reasonable for BRCA2 mutation carriers; however, as shown in other studies, this strategy might not provide breast cancer risk reduction.

Bilateral salpingectomy has been proposed as a bridge to oophorectomy, due to evidence that ovarian cancer in BRCA mutation carriers may originate in the distal, fimbriated portion of the fallopian tube. Radical fimbriectomy has been suggested as a risk-reducing strategy for BRCA1 mutation carriers, thus sparing the ovaries until future oophorectomy, offering delay of surgical menopause and allowing for preservation of some reproductive options. Currently, salpingectomy and fimbriectomy are not included in the NCCN guidelines as strategies for risk reduction in BRCA mutation carriers. Additional evidence is needed regarding the effectiveness of these procedures for ovarian cancer risk reduction.

Risk-reducing pharmacologic options

Selective estrogen-receptor modulators (tamoxifen and raloxifene) and aromatase inhibitors (AIs) (e.g., exemestane) significantly decrease the risk of breast cancer in women at high risk, although limited data exist on their efficacy in BRCA mutation carriers. In a subset analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention (P-1) trial investigating prior use of tamoxifen in 19 BRCA mutation carriers who developed breast cancer in this trial, tamoxifen use was associated with a 62% breast cancer risk reduction in BRCA2, but not in BRCA1 mutation carriers. In contrast, a case-control study of BRCA1/2 mutation carriers with breast cancer demonstrated a strong protective effect of tamoxifen against contralateral breast cancer in both BRCA1 (OR, 0.5) and BRCA2 (OR, 0.4) mutation carriers, irrespective of estrogen-receptor status of the initial breast cancer. Studies are underway evaluating AIs for chemoprevention in BRCA mutation carriers. Raloxifene has not been studied in this population.

In women at increased risk for breast cancer, tamoxifen chemoprevention is sometimes met with resistance given concerns about side effects (vasomotor symptoms, leg cramps, vaginal discharge, and irritation) and a small increase in the risk of stroke, thromboembolic events, cataracts, and endometrial cancer.

Until prospective studies become available, the use of tamoxifen for chemoprevention in BRCA mutation carriers should be approached with caution. It is not known if tamoxifen adds to the magnitude of breast cancer risk reduction by RRSO in BRCA mutation carriers. Data from adjuvant trials in this population suggest that tamoxifen does not further decrease the risk of contralateral breast cancer in women who have undergone oophorectomy. For BRCA mutation carriers who decline RRSO, alternative ovarian cancer risk-reduction strategies should be discussed. Chemoprevention with low-dose oral contraceptives (OCs) is presumed to work via ovulation suppression and decreases ovarian cancer risk in BRCA mutation carriers by as much as 44%–60%. There is a strong correlation between the duration of OC use and the degree of ovarian cancer protection, quantified as a 5%–13% risk reduction per year of OC use. Importantly,
studies showing ovarian cancer protection do not differentiate between continuous and discontinuous OC use as duration of OC use is primarily obtained via subject self-reporting.69

The relationship between OC use and the risk of breast cancer in BRCA mutation carriers remains controversial, with studies showing conflicting results.66,71,72 Results vary based on the length of OC use (increased risk with use beyond 5 years),73 formulation of OC (newer lower dose OC are associated with less risk than older formulations),74 age at which OC commenced, and time since cessation of OC.71,73,75,76 A recent meta-analysis highlighted a significant ovarian cancer risk reduction and no increased breast cancer risk with OC use by BRCA mutation carriers.75 As we await prospective studies on the long-term risks and benefits of OC use in BRCA mutation carriers, an individualized discussion for short-term use is recommended.71-73,75,76

**Risks and Benefits of Undergoing Hysterectomy at the Time of RRSO**

BRCA mutation carriers who elect to undergo RRSO also face the complex decision of whether or not to undergo removal of the uterus along with the ovaries and tubes. Performing a hysterectomy at the time of RRSO slightly increases surgical risks and short-term morbidity but might provide long-term benefits. While having a BRCA mutation does not appear to increase the risk of uterine cancer,40 some women may elect to undergo hysterectomy to eliminate the small risk of tamoxifen-induced uterine cancer or to avoid the need for a progestin if estrogen therapy (ET) is planned. A crucial decision for a premenopausal BRCA mutation carrier contemplating RRSO is whether or not to initiate ET after surgery, to reduce the consequences of premature estrogen deficiency as well as for menopausal symptom relief. Progestin-containing hormone therapy (HT) has been associated with a higher risk of breast cancer than estrogen-alone therapy.77,78 and hysterectomy at the time of RRSO eliminates the need for progestin use to protect the endometrium.

Studies analyzing surgical risks of gynecologic surgery performed solely for cancer risk reduction are lacking. However, rates of urinary tract injury in benign bilateral salpingo-oophorectomy (BSO) and hysterectomy are well-reported, and risks of BSO alone are reported to be lower than when BSO is combined with a hysterectomy.79-81 Overall, the incidence of ureteral injury during laparoscopic gynecologic surgery is low, ranging from 0.025%-2%,79,82 however, the risk is two- to four-fold higher in laparoscopically-assisted hysterectomy than in laparoscopic BSO.79,80 Adding abdominal hysterectomy to BSO increases the risk of bladder injury by 0.3%; pelvic abscess, 0.3%; cuff cellulitis, 3%; transfusion, 4%; urinary fistula rate, 0.4%; wound infection, 4%; rehospitalization, 3%; and reoperation, 1.5%.83 Although the surgical risks of minimally-invasive hysterectomies tend to be lower than the risks of laparotomy, the rate of vaginal cuff dehiscence after laparoscopic or robotic hysterectomy ranges between 1.4%-5%.84 This risk is nonexistent if the uterus remains in situ.

Hysterectomy at the time of RRSO eliminates the small risk of uterine cancer in women who are considering tamoxifen for breast cancer chemoprevention.85 While the Breast Cancer Linkage Consortium reported an increased risk of uterine cancer in BRCA1/2 mutation carriers,86 other investigations, including a study examining the frequency of BRCA mutations in Ashkenazi Jewish women with uterine cancer, did not find an excess of BRCA1/2 mutation carriers.57 One prospective study suggested that tamoxifen use accounted for the increased incidence of uterine cancer in BRCA1/2 mutation carriers,87,88 and GOG 199 recently found no increase in uterine cancer among BRCA mutation carriers.89 While the interstitial portion of the fallopian tube traverses the uterine cornua and is retained when the uterus remains in situ, tubal carcinogenesis appears to occur in the distal tubal fimbria80 and has not been reported in the interstitial segment.90 An individualized discussion on the benefits and risks of considering a hysterectomy at the time of the RRSO is prudent.

**Health Consequences of Early/Premature Surgical Menopause**

RRSO before the onset of natural menopause may result in troublesome menopausal symptoms, sexual dysfunction, and potential long-term health consequences. Bilateral oophorectomy (BO) in premenopausal women induces the abrupt onset of menopause, with a precipitous decline in estrogen, progesterone, and testosterone levels, along with a rise in gonadotropins.91 The hormonal milieu of surgically-induced menopause continues to differ from that of natural menopause years later, when testosterone levels remain lower in women who underwent oophorectomy compared with natural menopause.92 The intact postmenopausal ovary continues to be a hormonally active organ throughout life, secreting androgens.92 The consequences—either favorable or unfavorable—of relative androgen deficiency in women who undergo oophorectomy have not been well studied. The consequences of lower estrogen levels are inferred by evaluating differences in outcomes following use or nonuse of ET after surgery.

Vasomotor symptoms are generally reported to be worse and require treatment more often after surgical menopause than after natural menopause.93 RRSO has a negative impact on menopause-specific QOL.93 ET ameliorates some, but not all, symptoms contributing to this QOL impairment. Notably, dyspareunia, low sexual desire, and decreased sexual satisfaction are more frequent after RRSO and may not be relieved by ET.16,93,94

Extensive evidence, including that from large, well-characterized cohorts of women including the Nurses' Health Study (NHS) and the Olmsted County Study of Oophorectomy and Aging (OCSOA), as well as the National Health and Nutrition Examination Survey, links early menopause and BO to an increased risk of mortality,95,96 cardiovascular disease,96,97 stroke,98 cognitive decline,99 depressive or anxiety symptoms,100 osteoporosis,101 and worse physical function.98,102 The risks are greater with an earlier age of oophorectomy, and are partly ameliorated by taking ET until at least age 45. Interestingly, the Women's Health Initiative (WHI) study found that women who underwent BO at the time of hysterectomy had no increase in mortality, coronary heart disease, stroke, or hip fracture compared with those who underwent hysterectomy alone.103 This cohort was comprised mostly of women older than age 40 at the time of oophorectomy, and had a mean follow-up of only 7.6 years, insufficient...
to detect late complications of oophorectomy. The mean follow-up from time of RRSO in the largest cohort of BRCA mutation carriers reported by Domchek et al. was only 3.1 years, also not long enough to detect differences in the development of age-related cardiovascular and neurodegenerative diseases.

Thus, consideration regarding the balance of long-term benefits and risks of RRSO at this point is by necessity limited to data from the well-characterized large cohorts including NHS and OCsSA, through which longitudinal outcomes after oophorectomy were ascertained over a mean follow-up interval of nearly 25 years or longer.

**Is HT Safe in BRCA Mutation Carriers after RRSO?**

Breast cancer risk reduction after RRSO is thought to be secondary to decreased levels of circulating sex hormones following oophorectomy. As such, concerns exist that treatment with HT will negate the beneficial effects of the RRSO. Data from the WHI and Million Women’s Study demonstrate an increased risk of breast cancer with combination estrogen plus progestin compared with estrogen-alone therapy. The use of estrogen-alone therapy was slightly decreased after 2002, but was associated with an increased risk of breast cancer in the Million Women’s Study. These findings have led to a significant decrease in the use of HT (including estrogen-alone and estrogen plus progestin therapy) after 2002 and a subsequent decrease in the incidence of breast cancer. This trend was also demonstrated in a survey of 73 unaffected BRCA mutation carriers who underwent RRSO between 1972 and 2005. In this group, the use of HT decreased after 2002 from 53% to 36%, and fewer women with an intact uterus took HT after 2002 (25% vs. 63%). There was no increase in hysterectomy rates in this study after 2002, suggesting that BRCA mutation carriers’ interest in using any type of HT decreased after 2002.

To elucidate the effect of HT on the breast cancer risk reduction offered by RRSO in BRCA mutation carriers, Rebbeck et al. identified a prospective cohort of 462 BRCA1/2 mutation carriers, 115 of whom had undergone RRSO. Women with RRSO were more likely to use HT (60% vs. 7%) and their risk of breast cancer was 60% lower compared to women without RRSO (HR 0.40). The use of HT of any type did not alter the benefit in breast cancer risk reduction derived from RRSO (HR 0.37). Within the RRSO group, women who took HT had a nonsignificant increase in the risk of breast cancer compared to women who did not take HT. The risk was higher (HR 2.56) with the use of combined estrogen plus progestin versus estrogen-alone, although not statistically significant. With a short follow-up of 3.6 years, the investigators concluded that short-term HT use after RRSO was safe, but there was insufficient power to analyze the effects of duration and type of HT use.

Similarly, a case-control study of BRCA1 mutation carriers in which 236 index cases of postmenopausal breast cancer were matched with 236 controls without breast cancer, revealed that a higher proportion of controls than cases had used HT (29% vs. 20%, p = 0.03), suggesting that HT was safe in this population. Additionally, the use of HT was inversely related to the development of breast cancer for both the estrogen-alone and the combined HT users, regardless of the type of menopause (surgical or natural), duration of HT use, current versus past use, age at menopause, or age at diagnosis.

Further information on the impact of HT on breast cancer risk after RRSO in BRCA mutation carriers comes from a Markov decision analysis, based on epidemiological data of expected outcomes of RRSO with or without HT, inclusive of breast and ovarian cancer, coronary heart disease, osteoporosis, and venous thrombosis. In this model, the women were 30–40 years old and it was assumed that they had an intact uterus; consequently, HT entailed a combination of estrogen and progestin. Irrespective of the use of HT, RRSO lengthened life expectancy in women with BRCA1/2 mutation by 3.3–4.6 years, depending on age at RRSO. If HT users discontinued HT by age 50, changes in life expectancy were small (+0.17 to −0.34 years) whereas continuation of HT for life led to decrements in life expectancy (−0.79 to −1.09 years). The addition of RRM further increased life expectancy by 2.15–2.98 years. In women who underwent both RRSO and RRM, HT use compared with non-use was associated with increased life expectancy. As shown above in the section Risk-reducing surgical options, the ideal timing of RRSO that provides breast cancer risk-reduction and the most survival benefit is around the age of 40 years, when most women are premenopausal. The risks of maintaining the tubes and ovaries after this age appear to greatly surpass the risks of ET. Delaying RRSO until around menopausal age (age of 50) is associated with less survival benefit, especially for BRCA1 mutation carriers, and does not decrease the risk of breast cancer.

Based on these studies, it seems reasonable that ET use after RRSO in BRCA mutation carriers may be safely considered for a few years; some propose on the order of 3–4 years. Guidelines on HT use for women with a history of premature menopause in general advise continuation of HT until around the median age of natural menopause in order to prevent the consequences of premature estrogen deprivation. Progestin-containing HT formulations continue to pose concerns, however, of increasing the risk of breast cancer. BRCA mutation carriers who undergo RRM might be safer candidates for combined estrogen and progestin HT, although this has not been demonstrated.

**Conclusion and Key Points**

HBOC is a complex genetic disease with significant health risks, and management options entail consideration of surgical, medical, and psychosocial needs. Appropriate care requires a compassionate, multidisciplinary approach, with individualized counseling and shared decision-making. There is good evidence that RRSO is effective in ovarian and breast cancer risk reduction if completed premenopausally. RRM is associated with longer life expectancy and a significant breast cancer risk reduction.

Women who decide against prophylactic surgery should undergo surveillance per evidence-based guidelines, and should be educated about the risks and benefits of risk-reducing interventions versus surveillance.

Chemoprevention with tamoxifen may be considered if RRM or RRSO is not desired, although the evidence for its benefit in BRCA mutation carriers is weak, based on retrospective studies. Ovarian cancer chemoprevention with OC
use should be considered for women who decline RRSO, but should not be used in addition to tamoxifen.

Consideration may be given to performing a hysterectomy at the time of RRSO if therapy with tamoxifen is contemplated or HT without progestin use is desired.

Premenopausal women who elect to undergo RRSO should be counseled regarding the risks and benefits of preserving the uterus, consequences of early surgical menopause, risks and benefits of HT, and possible psychosocial difficulties.

The decision to pursue short-term use of ET needs to be individualized and, if implemented, it is generally recommended to discontinue its use by the average age of natural menopause (around age 51 years).

Table 1 provides a summary of the interventions discussed in this manuscript.

**Table 1. Summary of Interventions for Breast and Ovarian Cancer Surveillance and Risk-Reducing Surgery in BRCA Carriers**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Surveillance for breast cancer (monthly breast self-exam, semiannual clinical breast exam, annual mammogram, annual breast MRI)</td>
<td>Relatively noninvasive</td>
<td>Breast MRI has low specificity and may lead to more diagnostic testing</td>
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<tr>
<td>Surveillance for ovarian cancer (semiannual pelvic exam, serum CA-125 and pelvic ultrasound)</td>
<td>Noninvasive</td>
<td>No evidence for efficacy of early-stage ovarian cancer detection</td>
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<tr>
<td>RRM</td>
<td>Breast cancer risk reduction by 90%</td>
<td>No effect on ovarian cancer mortality</td>
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<tr>
<td>RRSO</td>
<td>Ovarian cancer risk reduction by 72%</td>
<td>Serum CA-125 has low specificity</td>
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<td></td>
<td>Breast cancer risk reduction by 50% if completed before onset of menopause</td>
<td>May be associated with emotional distress</td>
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<tr>
<td></td>
<td>Decreases overall mortality by 60%, breast cancer mortality by 56% and ovarian cancer mortality by 79%</td>
<td>Body-image issues</td>
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<td></td>
<td>Laparoscopic procedure</td>
<td>Surgical risks: seromas, wound infection, skin flap necrosis, pain, lymphedema, shoulder dysfunction</td>
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<tr>
<td>RRSO + hysterectomy</td>
<td>As for benefits of RRSO (above)</td>
<td>Increases risk of symptoms and health consequences of premature menopause (if performed before age 35): vasomotor symptoms, sexual dysfunction, cardiovascular disease, stroke, cognitive decline, depression, anxiety, osteoporosis, mortality</td>
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<tr>
<td></td>
<td>Allows for estrogen-only HT (alleviating need for progestogen) use</td>
<td>Surgical risks: urinary tract injury, wound infection, pelvic abscess</td>
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<td></td>
<td>Eliminates small risk of uterine cancer if tamoxifen is used</td>
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<tr>
<td>Salpingectomy/fimbriectomy</td>
<td>May decrease risk of ovarian cancer</td>
<td>No clear evidence of ovarian cancer risk reduction</td>
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<td></td>
<td>May be considered as a bridge to RRSO in premenopausal women</td>
<td>Unknown effect on breast cancer risk</td>
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<tr>
<td>Tamoxifen</td>
<td>Limited evidence from small studies for breast cancer risk reduction in BRCA carriers</td>
<td>Slightly increases risk of uterine cancer</td>
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<td></td>
<td></td>
<td>Increases risks of stroke, cataracts, thromboembolic events</td>
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<tr>
<td></td>
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<td>Side effects (vasomotor symptoms, vaginal dryness and discharge, fatigue, arthralgias)</td>
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<tr>
<td>OC</td>
<td>Ovarian cancer risk reduction by 50%</td>
<td>Concern for possible increased risk of breast cancer with prolonged use (&gt;5 years)</td>
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<td></td>
<td></td>
<td>Increased risk of venous thromboembolic events</td>
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<td>Side effects (nausea, bloating, breast tenderness, breakthrough bleeding)</td>
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<tr>
<td>HT after RRSO in premenopausal women</td>
<td>Alleviates symptoms and reduces health consequences of early menopause (cardiovascular disease, osteoporosis, Parkinsonism, dementia)</td>
<td>Side effects and risks (venous thromboembolism, stroke, breast cancer with E+P HT, cholelithiasis)</td>
</tr>
</tbody>
</table>

E, estrogen; HT, hormonal therapy; MRI, magnetic resonance imaging; OC, oral contraceptives; P, progestogen; RRM, risk-reducing mastectomy; RRSO, risk-reducing salpingo-oophorectomy.
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