Oophorectomy as a preventative measure for ovarian cancer

The discovery of germline mutations, including mutations in *BRCA1/2* and the Lynch syndrome genes, which confer an increased risk of ovarian cancer, has identified a small group of women at significantly increased risk of the disease. Since screening and chemopreventive options for ovarian cancer are very limited, bilateral salpingo-oophorectomy (BSO) has become the standard of care for risk reduction in this population. BSO reduces the risk of subsequent ovarian cancer by 71–96% and also reduces the risk of breast cancer by 50%. There is a small risk of primary peritoneal cancer after surgery. Most women are candidates for the minimally invasive laparoscopic procedure. Uptake of BSO among mutation carriers is high, and is related to age, parity, family history and personal history of breast cancer. There is a growing appreciation of the short- and long-term consequences of surgical menopause and of the need for prospective studies to characterize the impact of BSO over the lifetime.

KEYWORDS: bilateral salpingo-oophorectomy ■ *BRCA1* ■ *BRCA2* ■ fallopian tubes ■ hormone replacement therapy ■ Lynch syndrome ■ surgical menopause

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Epithelial ovarian cancer is relatively uncommon, accounting for only 3% of cancers in women in the USA [1]. However, the discovery of germline mutations that confer an increased risk of ovarian cancer has identified a small group of women at significantly increased risk of the disease. Women with deleterious germline mutations in the *BRCA1/2* genes have a lifetime risk of ovarian cancer that ranges from 36 to 46% for *BRCA1* mutation carriers, and from 10 to 27% for *BRCA2* mutation carriers [2]. Women with mutations in the DNA repair genes associated with Lynch syndrome have a lifetime risk of ovarian cancer of 10–12% [3]. While the population frequencies of these mutations is moderate (one in 400 to one in 800 for *BRCA1/2* [4,5] and one in 660 to one in 2000 for Lynch syndrome mutations [6]), founder mutations have been found to occur at a higher frequency in some populations. One example of this is the identification of three *BRCA1/2* founder mutations among the Ashkenazi Jewish population, in whom the prevalence is approximately 2%, or one in 40 [7]. Several other founder mutations exist worldwide and reflect geographic distributions and population migrations [8]. The availability of clinical genetic testing for these ovarian cancer susceptibility genes makes it possible for women to estimate their personal risk for ovarian cancer and can help guide risk-management decisions for them and their at-risk relatives.

Preventive options

Screening options for ovarian cancer are limited. The bulk of experience has been with some combination of transvaginal ultrasound and the serum-based marker cancer antigen 125, neither of which has been demonstrated to decrease morbidity or mortality in either the general population or in *BRCA1/2* mutation carriers [9–11]. Given the limitations of current screening modalities, the US Preventive Services Task Force (USPSTF) and the American College of Obstetricians and Gynecologists (ACOG) discourage routine screening for ovarian cancer for the general population [12,13]. Guidelines have been proposed for women with a hereditary predisposition to ovarian cancer, but they are not evidence-based.

To date, the only pharmaceutical approach to ovarian cancer prevention is the oral contraceptive pill (OCP). OCPs were first introduced in the USA in the 1960s. Most formulations include estrogen, progesterone or a combination of the two. As well as suppressing ovulation, OCPs also reduce the pituitary secretion of gonadotropins. In addition to these potential mechanisms of protection, a 3-year study in primates demonstrated that the progestin component of an OCP has a potent effect on apoptotic and TGF-β signaling pathways in the ovarian epithelium, raising the possibility that progestin-mediated biologic effects may

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underlie the ovarian cancer protective properties of OCPs [14]. The use of OCPs appears to decrease a woman's risk for ovarian cancer by 30–60%. Risk reduction is apparent with as little as 3 months of use, increases in magnitude with increased duration of use, and persists for as long as 10 years after discontinuation of use. The risk reduction applies to nulliparous as well as parous women, to all histologic subtypes, including tumors of low malignant potential, to women with a hereditary risk for ovarian cancer, is consistent across races, and is independent of age at use or menopausal status [15–17].

While there has never been a randomized clinical trial to demonstrate the protective effect of OCPs on ovarian cancer risk, it is often recommended empirically to women with a family history of ovarian cancer or women with an inherited susceptibility for ovarian cancer to reduce their risk. However, in the case of women with deleterious mutations in *BRCA1/2*, OCP use is controversial owing to the increased risk for breast cancer that has been described in some studies [18,19]. While several other agents are being investigated as potential ovarian cancer chemopreventative agents, none have yet entered into Phase III trials.

Historically, tubal ligation has been associated with a reduced incidence of epithelial ovarian cancer. A meta-analysis of published case–control studies reported a relative risk of 0.59 when using hospital-based controls, and 0.87 with community-based controls [20]. A more recent case–control study among 232 women with deleterious mutations in *BRCA1/2* and 232 age-matched controls found a statistically significant odds ratio of 0.39 for women with a history of tubal ligation. The risk reduction was confined to women with *BRCA1* mutations [21]. Proposed biologic mechanisms include a reduction in the ovarian and/or fallopian tube blood supply leading to a decrease in local hormones and/or local tissue ischemia, or a reduction in the potential for local inflammatory processes.

Prophylactic oophorectomy

Prophylactic bilateral salpingo-oophorectomy (BSO), which is intended to remove the ovaries and fallopian tubes prior to the onset of disease, is currently the most accepted strategy for ovarian cancer prevention. A number of case–control, retrospective cohort and prospective studies have examined the efficacy of BSO in reducing the risk of ovarian cancer, and estimates of risk reduction have varied from 71 to 96% [22–26]. A recent meta-analysis of nonoverlapping studies, which included 2840 participants, provided a pooled estimate hazard ratio of 0.21 (95% CI: 0.12–0.39) [2]. At this point there is insufficient data to provide individual hazard ratios for *BRCA1* and *BRCA2* mutation carriers. In addition to the reduction in incidence in ovarian cancer after BSO, one prospective study with a mean follow-up of 3.1 years reported a reduction in overall mortality and cancer-specific mortality associated with the surgery [27]. While longer follow-up of these cohorts of women is needed to better quantify the survival benefit of BSO, a simulated Monte Carlo decision–analysis model found that the single most effective intervention for *BRCA1* carriers was BSO at 40 years of age, which yielded a survival gain of 15% [28].

Histopathologic examination of the ovaries and fallopian tubes removed at the time of BSO has demonstrated the presence of occult malignancy in 2–10% of cases [29,30]. Older age (45 years and above) has been demonstrated in some studies to predict occult malignancy [31,32]. The detection rate of occult primaries in this setting is dependent on the degree of rigor of the operative and pathologic protocols used to obtain and examine the tissues [33]. The finding of serous tubal intraepithelial carcinoma of the distal fallopian tube in a significant proportion of *BRCA* carriers [34] has particularly highlighted the need for careful sectioning and examination of the ovaries and tubes.

In addition to the risk of finding occult malignancy at the time of surgery, women undergoing BSO have a risk of developing primary peritoneal cancer (PPC) up to several years after the procedure. The frequency of PPC is estimated to be 2–5%, and appears to be more common among *BRCA1* carriers. The origin of PPC is thought to be either the deposit of an occult focus of disease from the ovaries or tubes prior to their removal, or from the development of carcinoma *de novo* from the peritoneal surface itself [32].

In addition to removing the organs at risk, BSO removes the source of ovarian hormones and has been associated with a decrease in risk of breast cancer, with hazard ratios of approximately 0.50 [2]. The magnitude of breast cancer risk reduction appears to be greater if the surgery is performed before the age of 40 years [35]. Furthermore, among women who develop

breast cancer, the age of diagnosis is significantly later among those who had undergone BSO than those who had not [36].

Uptake & timing of BSO

The decision to undergo BSO is complex owing to the many significant risks and benefits associated with the procedure, and owing to variation in sociocultural perspectives on womanhood, body image and self-identity. Rates of uptake of BSO among women with *BRCA1/2* mutations vary by country of residence, but average approximately 58% [37]. A systematic review of psychosocial factors that influence the decision to undergo BSO found that cancer-related anxiety and worry were associated with uptake of surgery [38]. Women with mutations in *BRCA1* are more likely to choose BSO than those with *BRCA2* mutations [39]. The optimal timing of BSO is a balance between undergoing the surgery prior to the development of ovarian cancer but after achieving desired family size and minimizing the sequelae of premature menopause. Although the NIH consensus conference recommended having the procedure "at age 35 or when childbearing is complete" [40], the average age of ovarian cancer is 50.8 years in *BRCA1* carriers and 57.9 years in *BRCA2* carriers [36], and most women choose to wait to have their surgery until their early- to mid-40s. In addition to age, having children, having a diagnosis of breast cancer and having a family history of ovarian cancer are important determinants of choosing BSO [37,41–43]. For women who have already achieved natural menopause, fertility is not an issue and there are fewer concerns about managing the side effects of the procedure. Although most women who elect BSO actually undergo the surgery within 2 years of receiving their *BRCA1/2* test results, some prolong the decision-making phase for several years [39,43].

Type of surgery

Most women considering BSO are candidates for a laparoscopic procedure, which accomplishes complete removal of the ovaries and fallopian tubes with minimal surgical invasion. A thorough inspection of peritoneal surfaces and examination of peritoneal washings are a standard component of this procedure [44]. When BSO is performed primarily for ovarian cancer risk reduction, the additional procedure of hysterectomy is not necessary and does not impact on the degree of ovarian cancer risk reduction. The addition of elective hysterectomy in conjunction with BSO is considered for the following situations:

- In the presence of symptomatic uterine fibroids or other benign uterine pathology;
- For women at significantly increased risk of uterine cancer, including those with Lynch syndrome, those with a strong family history of uterine cancer, or those with high BMI;
- When tamoxifen is being considered for risk reduction to eliminate the risk of tamoxifen-related uterine cancer;
- When hormone replacement therapy (HRT) is being considered to manage the symptoms of surgical menopause, to permit the use of single-agent estrogen, a regimen thought to be safer than combined estrogen and progesterone.

The choice of type of surgery is ultimately a decision reached on an individual basis by each woman in consultation with her physician.

Surgical menopause

Most of the immediate and long-term physiologic consequences of BSO are related to the removal of the reproductive hormones secreted by the ovary. Women considering BSO frequently cite concerns regarding the need for HRT, premature aging and the psychological consequences of hormone withdrawal [45]. Surgically induced menopause can result in immediate and severe vasomotor symptoms, including hot flashes, night sweats and mood swings, vaginal dryness, sexual dysfunction, sleep disturbance and cognitive changes [46]. Many of the women experiencing these symptoms are reluctant to use HRT to reduce their severity owing to concerns regarding increasing their breast cancer risk. However, a case–control study of 472 postmenopausal women with a *BRCA1* mutation did not find an association of HRT with increased breast cancer risk. In fact, in this study women who reported using HRT had a decreased breast cancer risk [47]. In addition, a prospective study of *BRCA1/2* carriers post-BSO found no difference in the reduction of breast cancer risk among HRT users compared with those who did not use HRT (median follow-up was 3.6 years) [48].

Although the evidence is scant, there is general consensus among clinicians that short-term use of HRT, up to the age of natural menopause (around 50 years) is safe in women undergoing BSO for ovarian cancer risk reduction.

The longer-term consequences of surgical menopause are less well known, particularly among women with a hereditary susceptibility to ovarian cancer, but are the subject of increased attention. A meta-analysis of 11 studies of menopausal status and cardiovascular disease found a relative risk of heart disease of 2.62 (95% CI: 2.05–3.35) among women who underwent bilateral oophorectomy compared with those who did not. The relative risk for women who underwent bilateral oophorectomy before the age of 50 years was 4.5 (95% CI: 2.56–8.01) compared with the same procedure after the age of 50 years [49]. The Danish Nurse cohort study followed almost 20,000 women aged 44 years and older for 5 years and found an adjusted risk of heart disease of 8.7 (95% CI: 2.0–38.1) among those women who had undergone bilateral oophorectomy before reaching 40 years of age compared with women undergoing the procedure after the age of 45 years. In this cohort, the use of estrogen therapy was associated with a significant protection against cardiovascular disease [50]. A large cohort of women undergoing oophorectomy for a noncancer indication was matched to a reference group of women who had not undergone oophorectomy. While overall mortality was similar in both groups, mortality rates were increased among women who had bilateral oophorectomy before the age of 45 years, particularly among those who did not receive estrogen replacement [51]. At the same time, randomized clinical trials comparing the effect of HRT to placebo among postmenopausal women have failed to find a cardioprotective effect associated with their use [52].

Current research is exploring age-related changes in vascular pathology in the context of reproductive hormones to explain these contradictory findings. Early evidence suggests a cardioprotective role for estrogen via the inhibition of smooth muscle cell proliferation and endothelial dysfunction, which is most apparent prior to the formation of plaque, making the timing of HRT after surgical menopause extremely important [53]. BSO was also found to be associated with a significant increase in metabolic syndrome, as defined by abdominal obesity, increased triglycerides, high cholesterol, elevated glucose and/or hypertension among 326 women with a hereditary risk of ovarian cancer [54], which suggests that screening for modifiable risk factors for cardiovascular disease may be worthwhile in this population.

Executive summary

Inherited susceptibility to ovarian cancer is defined by a series of germline mutations

- Deleterious mutations in *BRCA1/2* are associated with a lifetime risk of epithelial ovarian cancer ranging from 10 to 46%.
- Deleterious mutations in the mismatch repair genes of the Lynch syndrome (*MLH1*, *MSH2*, *MSH6* and *PMS2*) are associated with a lifetime risk of epithelial ovarian cancer of 10–12%.
- Ovarian cancer among women with a hereditary susceptibility occurs 10–20 years earlier than it does in the general population.

Benefits of bilateral prophylactic oophorectomy

- Prophylactic bilateral salpingo-oophorectomy (BSO) reduces the risk of epithelial ovarian cancer by 71–96%.
- BSO also reduces the risk of breast cancer by 50%.
- Removal of the fallopian tubes, a site for early intraepithelial neoplasia and/or fallopian tube cancer, is a routine part of the risk-reducing surgery.
- Rates of uptake of BSO vary across geographic region, but average 57%.
- Older age (up to 60 years), higher parity, having had breast cancer and having a family history of ovarian cancer are all associated with increased uptake of BSO.
- Models have demonstrated that the greatest survival benefit occurs when women undergo BSO at the age of 40 years.

Long- & short-term adverse effects of BSO

- Surgically induced menopause can result in severe vasomotor symptoms, mood swings, vaginal dryness, sexual dysfunction, sleep disturbance and cognitive changes.
- Long-term side effects include increased rates of metabolic syndrome, cardiovascular disease and osteoporosis.
- Short-term use of hormone replacement therapy after BSO appears to be safe and may actually have a favorable impact on cardiovascular disease.

Future perspective

- The identification of genetic and environmental modifiers of mutation risk of ovarian cancer will be an important step. These modifiers may include other genetic polymorphisms that either lessen or increase the impact of the gene mutation, as well as reproductive factors, exogenous and endogenous hormone exposures and other lifestyle factors.
- Genotype–phenotype correlations will allow more personalized estimates of ovarian cancer risk and perhaps more precise estimates of expected age at onset.
- The identification of novel screening approaches may result in the ability to detect ovarian cancer at an early, curative stage and may obviate the need for risk-reducing surgeries.

Both early age at natural menopause and oophorectomy before the age of 45 years are well-known risk factors for osteoporosis later in life [55]. Estrogen and the selective estrogen receptor modulators, tamoxifen and raloxifene, as well as the family of *bis*-phosphonate drugs, have all been demonstrated to reduce the risk of osteoporosis in postmenopausal women.

Although there is considerable anecdotal data suggesting a relationship between both natural and surgical menopause and cognitive decline, clinical trials evaluating the effect of oophorectomy and estrogen on cognitive function are contradictory. For all of these potential long-term effects of BSO, there is, to date, very little data specific to women with *BRCA1/2* mutations or mutations of the Lynch syndrome. However, there is some preliminary data on quality-of-life measures following BSO in these populations. Overall, studies comparing women post-BSO to either similar at-risk women who have chosen surveillance or women from the general population have found no differences in depression, fatigue or quality of life associated with the surgery. Women who have undergone BSO typically report a reduction in cancer-related distress and a decrease in their cancer-risk perception [56,57], supporting the notion that BSO is a psychologically acceptable strategy for risk reduction in this high-risk population.

Future studies that examine the factors that impact women's decisions regarding risk-reducing measures in a prospective fashion will further elucidate the process of coping with risk throughout the lifecycle. A more comprehensive approach to the medical, psychosocial and social needs of women throughout the decision-making process will contribute to the development of decision support tools and improve satisfaction with the decision-making process.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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