Original Article

Bilateral Risk-Reducing Oophorectomy in *BRCA1* and *BRCA2* Mutation Carriers

Susan M. Domchek, MD,[*] Jill E. Stopfer, MS, CGC,[*] and Timothy R. Rebbeck, PhD,[*†]
Philadelphia, Pennsylvania

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BRCA1, *BRCA2*, oophorectomy, hormone replacement therapy, estrogen, hysterectomy, breast cancer, ovarian cancer

Abstract
Bilateral risk-reducing oophorectomy (BRRO) is widely used for cancer risk reduction in women with *BRCA1* and *BRCA2* (*BRCA1/2*) mutations. BRRO significantly reduces breast cancer risk by approximately 50% and ovarian cancer risk by 85% to 95%, but it may be accompanied by menopausal symptoms, impaired quality of life, and accelerated bone loss. Therefore, decisions regarding the timing of BRRO, the risks and benefits of a simultaneous hysterectomy, and the use of hormone replacement therapy (HRT) must be made in concert with the patient and individualized to their circumstances. However, recent data demonstrate that HRT after BRRO in unaffected premenopausal women does not negate the breast cancer risk reduction that BRRO provides. This article reviews the studies regarding BRRO in *BRCA1/2* mutation carriers, with particular focus on the use of HRT. (*JNCCN* 2006;4:177–182)

Bilateral risk-reducing oophorectomy (BRRO) involves removing the ovaries before clinically apparent cancer occurs. The motivation for this approach is to remove at-risk ovarian tissue to reduce the risk for ovarian cancer. Another benefit of this surgery is an apparent reduction of breast cancer risk, presumably caused by reduction of ovarian hormones. The benefits of BRRO in reducing cancer risk in *BRCA1* and *BRCA2* (*BRCA1/2*) mutation carriers are clear, but there are considerations in clinical decision-making associated with this procedure.

From the [*]Abramson Cancer Center, The University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, and [†]Center for Clinical Epidemiology and Biostatistics, The University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

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Correspondence to: Susan M. Domchek, MD, Abramson Cancer Center, University of Pennsylvania, 14 Penn Tower, Philadelphia, PA 19104. E-mail: susan.domchek@uphs.upenn.edu

Risk Reduction

Ovarian Cancer Risk Reduction

Several studies have estimated the ovarian cancer risk reduction that may be achieved in women with *BRCA1/2* mutations.[1–3] Rebbeck et al.[1] used a sample of 551 women with disease-associated germline *BRCA1/2* mutations collected from 11 centers in North America and Europe to estimate the relationship of BRRO to ovarian cancer risk reduction. The researchers saw significant differences between subjects and controls in the occurrence of ovarian cancer and the number of censored observations. Eight subjects who underwent BRRO (3.1%) were diagnosed with ovarian cancer or primary peritoneal cancer (e.g., papillary serous carcinoma of the peritoneum [PSCP]) at or after BRRO, compared with 58 controls (19.9%). During follow-up, 185 subjects who underwent BRRO (71.4%) developed neither breast nor ovarian cancer, compared with 153 controls (52.4%). Subjects were followed up for an average of 8.2 years after BRRO and controls for an average of 8.8 years after the matched surgical subject's BRRO. Although all subjects who underwent BRRO did so to prevent the occurrence of ovarian cancer, 6 of 8 subjects diagnosed with ovarian cancer were diagnosed at the time of BRRO. All 6 were diagnosed with stage I tumors, suggesting that the use of BRRO may have afforded an earlier ovarian cancer detection than usual and that subsequent mortality from ovarian cancer may have been reduced in these women. After women were excluded whose ovarian cancer was identified at the time of BRRO, only 2 women (both with *BRCA1*

mutations) who underwent BRRO subsequently developed PSCP. Review of pathology records from these surgeries revealed no evidence of ovarian cancer at BRRO. Compared with women who did not undergo BRRO (controls), the occurrence of post-BRRO ovarian cancer corresponded to a hazard ratio (HR) of 0.04 (95% confidence interval [CI], 0.01–0.16). This result represents a substantial and significant reduction in ovarian cancer after BRRO.

Kauff et al.[2] identified 170 women with *BRCA1/2* mutations who had not previously undergone BRRO, who then chose to undergo either surveillance or BRRO. During a mean follow-up of 24.2 months, PCSP was diagnosed in 1 of 98 women who chose to undergo BRRO compared with 5 ovarian or peritoneal cancers in the 72 women who chose surveillance. This risk reduction corresponded to an HR of 0.15 (95% CI, 0.02–1.31). Although this risk-reduction estimate is not statistically significant, it is consistent with the findings of Rebbeck et al.[1]

No randomized clinical trials have been undertaken to assess the efficacy of BRRO on ovarian cancer risk reduction in *BRCA1/2* mutation carriers. Because BRRO is known to reduce the risk for ovarian cancer in *BRCA1/2* carriers, such a trial would most likely be unacceptable to patients, and randomizing *BRCA1/2* mutation carriers to a trial arm that did not include BRRO would be unethical at this time because no effective screening exists.

Breast Cancer Risk Reduction

Decreased exposure to ovarian steroid hormones is believed to affect a woman's risk for developing breast cancer. To address this hypothesis, Rebbeck et al.[1,4] evaluated a set of *BRCA1/2* mutation carriers and compared women who had undergone BRRO with a matched set of women who did not undergo this surgery. Surgical subjects were followed up for an average of 9.6 years after BRRO (range, < 1–36 years) and controls were followed up for an average of 8.1 years (range, < 1–43 years) after BRRO in the matched surgical subject. BRRO significantly reduced the risk for developing breast cancer in the whole sample (HR, 0.53; 95% CI, 0.33–0.84). When 6 subjects who underwent BRRO after 50 years of age and their matched controls were removed from the sample, the effect remained the same (HR, 0.57; 95% CI, 0.36–0.92). Rebbeck et al.[1] confirmed these results using a larger set of women identified in the same manner as in the earlier study. This analysis showed breast cancer risk reduction of approximately 50% after BRRO (HR, 0.47; 95% CI, 0.29–0.77).

Limitations in Risk Reduction

Despite the magnitude of risk reduction after BRRO, this procedure clearly does not completely eliminate breast and ovarian cancer risk. Occurrence of PSCP after oophorectomy has been widely reported outside the *BRCA1/2* carrier population.[5–11] PSCP refers to the diffuse involvement of tumor on peritoneal surfaces, with a neoplasm looking identical to papillary serous carcinoma of the ovary without evidence of a primary ovarian tumor. PSCP can occur after oophorectomy or with the ovaries in situ,[12] and is clinically undistinguishable from stage III ovarian cancer.[13,14] Therefore, women considering BRRO should be made aware that risk reduction is incomplete, although very effective.

An estimated PSCP frequency of 2% to 4% after BRRO has been reported in women with *BRCA1/2* mutations, and it may occur more frequently in *BRCA1* compared with *BRCA2* carriers.[1,2,9,15] PSCP may occur either because of an occult ovarian focus or from carcinoma arising de novo in peritoneal mesothelium. Occult ovarian and fallopian tube carcinomas have been found at BRRO in 2% to 10% of *BRCA1/2* mutation carriers.[16–21] Cancers of the fallopian tube, although rare in the general population, represent a part of the hereditary breast/ovarian cancer syndrome associated with *BRCA1/2* mutations,[22] with an estimated relative risk (RR) of greater than 100 and a lifetime risk of 3% (95% CI, 1.3–4.7).[23] These observations support the recommendation that clinicians should conduct a thorough pathologic examination of the ovaries and fallopian tubes removed by BRRO to confirm the absence of tumor at surgery.

Powell et al.[18] reported a more rigorous pathologic assessment, including cytology of peritoneal washings, serial sectioning of ovaries and fallopian tubes, and peritoneal and omental biopsies. In 67 procedures, 7 occult malignancies were found in the ovaries and fallopian tubes and all 7 occurred in cases in which the surgical and pathology protocol was followed. Whether this level of assessment, including peritoneal washings,[24] is necessary will require additional follow up. Finally, although removal of the fallopian tube during BRRO is standard procedure, a portion of the fallopian tube is left in the uterine wall. This raises the possibility of hysterectomy, which is discussed later.

Considerations in the Use of BRRO

Timing of Surgery

The optimal timing of BRRO in women with *BRCA1/2* mutations is not yet known. BRRO in premenopausal women induces the sudden onset of menopause, which can result in severe hot flashes, vaginal dryness, sexual dysfunction, sleep disturbances, and cognitive changes that may affect quality of life.[25] Premature menopause is also a significant risk factor for osteoporosis.[26] These factors must be weighed against the risk for cancer. Ovarian cancers have been reported in *BRCA1* mutation carriers in their 30s,[27] although the median age at diagnosis of *BRCA1/2*-associated ovarian tumors is approximately 50 years.[1,27–29] In the series by Rebbeck et al.,[1] the overall mean age at diagnosis of ovarian cancer was 50.8 years in *BRCA1* mutation carriers and 57.9 in *BRCA2* mutation carriers.

These data suggest that BRRO could be delayed at least into a woman's 30s to minimize the negative consequences of premature loss of ovarian function. In a decision analysis, Schrag et al.[30] reported that delaying BRRO for 10 years in a 30-year-old carrier with a 40% risk for ovarian cancer decreased the expected gain in life expectancy from 1.7 to 1.2 years. However, standard timing for consideration of BRRO is commonly after completion of childbearing or age 35 years.[31]

Post-BRRO Hormone Replacement Therapy

As described previously, the induction of surgical menopause by BRRO in young women has important implications for a woman's quality of life and possibly long-term health. Thus, some premenopausal women who undergo BRRO elect to use at least short-term hormone replacement therapy (HRT) to alleviate symptoms. Other women may delay BRRO because of concerns about HRT and breast cancer risk, and therefore remain at high risk for ovarian cancer. Because multiple studies suggest that HRT, particularly combined estrogen-progesterone use, increases the risk for breast cancer in postmenopausal women,[32] legitimate concern exists that HRT may offset the breast cancer risk reduction conferred by BRRO.

Although several studies suggest that HRT use has deleterious effects, these studies were conducted in postmenopausal women and may not be directly applicable to premenopausal women with *BRCA1/2* mutations undergoing BRRO. For example, the median age of the participants in the Women's Health Initiative (WHI) was over 60, well past the average age of menopause in the United States, and participants were included who had previously taken HRT.[32,33] Most importantly, participants in the WHI were not selected for premature menopause, and most underwent natural (i.e., non-surgical) menopause. Despite these limitations, the results of the WHI study are widely known to patients and physicians and have led to a dramatic reduction in the use of HRT in postmenopausal women in the United States.[34] However, physicians must interpret the results of the WHI with caution when counseling women with *BRCA1/2* mutations who are undergoing premature surgically-induced menopause for risk reduction purposes.

To address this concern, the authors recently reported that HRT of any type after BRRO did not significantly alter the reduction in breast cancer risk associated with BRRO in *BRCA1/2* mutation carriers. This study prospectively examined 462 unaffected women with *BRCA1/2* mutations and evaluated breast cancer risk after BRRO with or without HRT.[35] BRRO was associated with a significantly lower risk for breast cancer (HR, 0.40; 95% CI, 0.18–0.92), which was not altered by the use of HRT (risk for breast cancer HR, 0.37; 95% CI, 0.14–0.96). These results suggest that short-term HRT use does not negate the protective effect of BRRO on subsequent breast cancer risk in *BRCA1/2* mutation carriers. Although questions remain, such as the optimal type, duration, and timing of HRT, reasonable decisions can now be made about clinical management of women with *BRCA1/2* mutations who have undergone BRRO.

Many women who undergo premenopausal BRRO take HRT only until they would have experienced natural menopause, generally age 50. Because risk reduction for breast cancer increases the earlier a woman has BRRO,[1] many women consider this surgery after childbearing decisions are completed, often in their mid- to late 30s. Although the authors' recent study[35] supports the decision to use short-term HRT to manage immediate postoperative menopausal symptoms, it does not address the fact that long-term use of HRT may have very different implications for breast cancer risk than long-term hormone exposure in postmenopausal women. Furthermore, these results are consistent with the results of a recent decision analysis using hormone-associated risk data from the recently published WHI that suggest that short-term

use of HRT after premenopausal BRRO is associated with little change in life expectancy, whereas the impact of long-term use after age 50 is more substantial.[36]

Surgical Procedure

Risks of morbidity and mortality from BRRO exist that may vary depending on the type of procedure (e.g., laparotomy vs. laparoscopy[37]). Many reports describe the complications related to elective gynecologic surgery, and these data suggest a low incidence of serious complications. For example, in a U.S. hospital-based review, the case-fatality rate for elective tubal sterilization was estimated at 1 to 2 per 100,000 procedures.[38] The RRs of one surgical type or another are unlikely to be related to mutation status. The surgical complications attributable specifically to BRRO in *BRCA1/2* mutation carriers have not been well described. However, surgical characteristics and outcomes have been reported in small series of women who underwent BRRO because of a family history of ovarian cancer.[39,40] The studies reported no unusual adverse surgical sequelae and no indication that the surgery was different in these women than in the general population of women who underwent this procedure.

Several options are available to women with *BRCA1/2* mutations who have no history of breast cancer and are considering surgical risk reduction. These include 1) bilateral salpingo-oophorectomy (BSO) alone with combined estrogen/progesterone replacement; 2) BSO alone with short-term estrogen-only replacement, considering the potential for increased risk for uterine cancer; 3) total abdominal hysterectomy (TAH) with BSO, followed by use of unopposed estrogen; or 4) BSO with or without TAH and without HRT.

Numerous considerations must be made when deciding among the possible interventions. Women with *BRCA1/2* mutations may wish to weigh the risks and benefits of TAH at BRRO based on the following: 1) impact on HRT decisions; 2) risk for uterine and cervical cancer; 3) impact on decisions regarding tamoxifen; and 4) risk for fallopian tube carcinoma.

First, TAH allows women unaffected by breast cancer to use unopposed estrogen replacement therapy rather than combined estrogen plus progesterone replacement therapy. This decision has implications for the use of TAH at BRRO, because use of unopposed estrogen in the absence of hysterectomy is associated with an increased risk for endometrial cancer (RR, 2.3; 95% CI, 2.1–2.5).[41] Recent data from the WHI demonstrated a significantly increased risk for breast cancer among postmenopausal women who took estrogen and progesterone (HR, 1.26; 95% CI, 1.00–1.59),[32] but not among women who took estrogen alone (HR, 0.77; 95% CI, 0.59–1.01).[33] This difference is also supported by the results of the Million Women Study, which found a twofold increase in breast cancer risk for users of estrogen and progesterone (RR, 2.00; 95% CI, 1.89–2.12) compared with users of estrogen alone (RR, 1.30; 95% CI, 1.21–1.40).[42] The effect of unopposed estrogen versus combined estrogen and progesterone has not been well characterized in *BRCA1/2* mutation carriers. However, based on the risk associated with estrogen and progesterone use shown in the Million Women Study and the difference in the effect of estrogen alone compared with estrogen and progesterone in the WHI, the addition of progesterone remains a concern. Therefore, undergoing a TAH at BRRO allows the use of estrogen alone for HRT, which minimizes potential breast cancer risk and eliminates the endometrial cancer risk associated with unopposed estrogen exposure.

Second, several reports suggest *BRCA1/2* mutation carriers have an increased risk for uterine and possibly cervical cancer (uterine cancer RR, 2.65; 95% CI, 1.69–4.16; cervical cancer RR, 3.72; 95% CI, 2.26–6.10).[43,44] Although early detection of these cancers is often possible, women already planning to undergo BRRO may consider whether they wish to eliminate uterine and cervical cancer risks by undergoing TAH at the time of their BRRO.

Third, tamoxifen has been shown to decrease the risk for contralateral breast cancer in *BRCA1/2* mutation carriers (odds ratio, 0.50; 95% CI, 0.28–0.89).[45] Therefore, tamoxifen use for preventing breast cancer is a consideration for *BRCA1/2* mutation carriers who have completed HRT or are not candidates for HRT. The reported increased uterine cancer risk associated with tamoxifen[46] is an additional consideration for women contemplating TAH.

Fourth, carriers of *BRCA1/2* mutation have an excess risk for fallopian tube carcinoma compared with the general population, with an estimated RR of over 100.[23] Because a remnant of the fallopian tube is left in the uterine wall at BSO without TAH, there is a theoretical benefit to considering TAH. However, the absolute lifetime risk for developing fallopian tube

cancer in mutation carriers is small (estimated at 3%), and very little information exists about the occurrence of fallopian tube cancer among women who have undergone BRRO without TAH.

Women contemplating a TAH in addition to BRRO should consider the added risk and recovery time. BRRO is an acceptable option partially because surgical risks and recovery time are outweighed by the benefit of a marked breast and ovarian cancer risk reduction. However, the risk–benefit ratio for TAH in addition to BRRO is more complex, both because of the small absolute advantages of TAH and the potential for higher morbidity associated with this procedure. All of these elements must be factored into the patient's decision about the surgical approach to cancer risk reduction. Premenopausal women who are unaffected with cancer and will face decisions on HRT and future tamoxifen use are likely to benefit most from having a TAH at the time of BRRO. The potential benefits of TAH are likely extremely small in women who are already postmenopausal or who have had breast cancer and will not be considering issues of HRT.

Summary

Based on the current literature, women with *BRCA1/2* mutations should be discouraged from deferring BRRO out of fear of symptoms related to surgical menopause and should be reassured that use of short-term HRT, if needed to manage menopausal symptoms, does not negate the breast cancer risk reduction conferred by BRRO. BRRO, even with short-term HRT, results in dramatic reductions in both breast and ovarian cancer risk.

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