Chapter 1
Risk-Reducing Surgery for Breast Cancer Patients with BRCA Mutations

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Abstract Women who carry a germ line mutation in either the BRCA1 or BRCA2 gene have a higher lifetime risk of developing breast and ovarian cancers, often at young ages. Moreover, women with BRCA-associated breast cancer develop second contralateral breast cancers (CBCs) and ovarian cancers at higher rates than those with sporadic breast cancer. Although intensified screening may help identify cancers at an early, favorable stage, it cannot prevent them. Therefore, BRCA1/2 mutation carriers with breast cancer may consider prophylactic surgical strategies such as contralateral prophylactic mastectomy (CPM) and bilateral prophylactic oophorectomy (BPO). There have been increasing interests in CPM, which has been reported to reduce the risk of future CBC by at least 90 %. BPO is the prevailing preventive choice for prophylactic treatment among BRCA mutation carriers, and it reduces the risk of ovarian cancer by about 90 % and breast cancer by about 50 %. Data on the survival of BRCA-associated breast cancer patients who opt for subsequent CPM are inconsistent, but BPO seems to be associated with improved breast- and ovarian cancer-specific mortality as well as improved all-cause mortality among BRCA1/2 mutation carriers. Although prophylactic surgery does not address the cause of these cancers, which is the gene mutations, it is highly effective for cancer prevention and survival.

Keywords Risk-reducing surgery • Contralateral prophylactic mastectomy • Bilateral prophylactic oophorectomy • Contralateral breast cancer • BRCA-associated breast cancer

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1.1 Subsequent Cancer Risk and Its Prevention in Patients with BRCA-Associated Breast Cancer

Women with BRCA1 or BRCA2 mutations have a higher lifetime risk of developing breast and ovarian cancers [1]. Meta-analyses indicate that BRCA1 and BRCA2 mutation carriers have a 57–65 % and a 45–49 % lifetime probability of developing breast cancer, respectively [2, 3]. The risk of ovarian cancer is also dependent on whether the mutation has occurred in BRCA1 or BRCA2; the lifetime risks of ovarian cancer were reported to be 36–54 % for BRCA1 and 10–27 % for BRCA2 mutation carriers [1, 2, 4, 5].

It is well established that women who have had breast cancer in the past are at an increased risk for contralateral breast cancer (CBC). The Surveillance, Epidemiology, and End Results (SEER) database reported a 4.2 % incidence of CBC from 1973 to 1996. The actuarial risk of developing CBC was 0.6 % per year; thus, the actuarial risk at 5, 10, 15, and 20 years was 3 %, 6.1 %, 9.1 %, and 12 %, respectively [6]. This represents an approximately 1.5-fold to two-fold increased risk for subsequent breast cancer compared with the general population [7, 8]. Compared to patients with sporadic breast cancer, women with BRCA1- and BRCA2-associated breast cancer are reported to have 4.5-fold (95 % confidence interval [CI] = 2.8-fold to 7.1-fold) and 3.4-fold (95 % CI = 2.0-fold to 5.8-fold) increased risks of CBC, respectively [9]. The risk of CBC in patients with BRCA-associated breast cancer is 1.5–3.1 % per year, with 10-year estimates of 25–38 % reported for mutation carriers from high-risk families, compared with rates of 3–7 % for women without mutations [9–16]. Metcalfe et al. reported that the 15-year actuarial risk of CBC was 36.1 % for BRCA1 mutation carriers and 28.5 % for BRCA2 mutation carriers [17]. At 25 years, the cumulative risk for CBC in patients with BRCA1/2 mutations was reported to be 47.4 % [18] (Table 1.1).

Several factors influence the risk of CBC in BRCA mutation carriers (Table 1.2). Younger age at the first breast cancer diagnosis is reported to be associated with a higher risk of CBC in patients with BRCA1 mutations [9, 10, 12, 17, 18]. In addition, several studies have found a 1.3–1.8-fold higher risk of CBC in BRCA1 mutation carriers compared with BRCA2 mutation carriers [9, 12, 18]. Data from

Table 1.1 Rates of contralateral breast cancer in BRCA1/2 mutation carriers with breast cancer

Study [reference]	Patients (n)		CBC (%)			
	BRCA1/2	Sporadic	BRCA1/2	Sporadic	P	F/U (years)
Haffty et al. [11]	22	105	42	9	0.001	12
Pierce et al. [14]	162	445	39	7	<0.0001	15
Metcalfe et al. [17]	810	–	31.6 (BRCA1) 28.5 (BRCA2)	–	–	15
Graeser et al. [18]	1042	–	47.4	–	–	25

Abbreviations: *CBC* contralateral breast cancer, *F/U* follow-up

Table 1.2 Factors that influence the risk of metachronous contralateral breast cancer in BRCA1/2 mutation carriers with breast cancer

Factor	Risk of metachronous contralateral breast cancer
Young age at diagnosis	Elevated
Mutated gene	BRCA1 > BRCA2
Estrogen receptor status	(+) < (−)/no effect[a]
Tamoxifen	Decreased/no effect[a]
Chemotherapy	Decreased/no effect[a]
Contralateral prophylactic mastectomy	Decreased (more than 90 %)
Bilateral prophylactic oophorectomy	Decreased (about 50 %)

[a]Risk reduction demonstrated in some studies but not confirmed in all studies

the German Consortium for Hereditary Breast and Ovarian Cancer show that the risk of CBC for BRCA1 mutation carriers diagnosed with their first breast cancer before the age of 40 is 62.9 % (95 % CI = 50.4–75.4 %) after 25 years, compared with only 19.6 % (95 % CI = 5.3–33.9 %) for patients who were older than 50 years at their first breast cancer diagnosis [18]. According to this report, family members of patients with BRCA1 mutations had a 1.6-fold (95 % CI = 1.2-fold to 2.3-fold) higher risk of CBC compared to those of patients with BRCA2 mutations. More recently, Metcalfe et al. reported the results of a prospective study on 810 BRCA1/2 mutation carriers with breast cancer [17]. In this study, women younger than 50 years at the time of their first breast cancer diagnosis were significantly more likely to develop CBC at 15 years, compared with those older than 50 years (37.6 % vs. 16.8 %, $P = 0.003$). Women younger than 50 years with two or more first-degree relatives with early-onset breast cancer were at high risk of CBC, compared to women with fewer or no first-degree relatives with breast cancer (50 % vs. 36 %, $P = 0.005$). The 15-year actuarial risk of CBC was 36.1 % for women with BRCA1 mutations and 28.5 % for women with BRCA2 mutations. Estrogen receptor status of the primary cancer, chemotherapy, and the use of tamoxifen were not associated with the risk of CBC.

The principal goal in the treatment of patients with breast cancer is to minimize their likelihood of dying from their primary breast cancer. For women with BRCA1/2-associated breast cancer, however, minimizing the incidence of and the mortality due to subsequent cancers, such as metachronous CBC and ovarian cancer, is just as important as treating a primary breast cancer. While intensified screening may help identify subsequent cancers at an early, favorable stage, it cannot prevent the development of such cancers. Therefore, BRCA1/2 mutation carriers with breast cancer may consider preventive strategies such as contralateral prophylactic mastectomy (CPM), bilateral prophylactic oophorectomy (BPO), or medical treatment with tamoxifen to reduce their risk for subsequent cancer development [19]. CPM has been reported to reduce the risk of future CBC by at least 90 % [20–23], similar to the risk reduction of breast cancer with bilateral prophylactic mastectomy among unaffected BRCA1/2 mutation carriers. BPO is the most effective option for the prevention of ovarian cancer [24, 25], and the incidence of

CBC is also reduced by BPO or tamoxifen [12, 26]. In this chapter, we review the literature regarding risk-reducing surgery for BRCA1/2 mutation carriers with breast cancer.

1.2 Contralateral Prophylactic Mastectomy

CPM refers to the removal of the normal intact contralateral breast among women with unilateral breast cancer. As previously described, the cumulative risk of CBC in patients with BRCA1/2 germ line mutations has been estimated to be up to 47.4 % at 25 years [18]. Given the substantial risk of CBC and the unsatisfactory benefits of other prophylactic modalities such as tamoxifen or BPO, some patients with BRCA1/2-associated breast cancer choose to undergo CPM following treatment of the initial breast cancer or opt to be treated initially with bilateral mastectomy if rapid genotyping analysis is made available [27, 28]. Among the available risk-reducing measures, the most effective option for CBC risk reduction is CPM. CPM decreases the risk of CBC by 90–95 % in women with a family history of breast cancer and in those with BRCA1/2 mutations [20–23]. This degree of risk reduction is similar to the reduction in the risk of breast cancer with bilateral prophylactic mastectomy among unaffected BRCA mutation carriers [29–31].

Historically, CPM has been recommended for high-risk patients, including breast cancer patients with BRCA mutations, as a means to reduce the development of CBC and the associated mortality. The ultimate goal of CPM is, indubitably, to improve the survival of breast cancer patients with BRCA1/2 mutations. However, even among these high-risk patients, the efficacy of CPM in improving long-term clinical outcomes is questionable. Despite the significant risk of CBC in patients with BRCA mutations and the obvious prophylactic effect of CPM, data on the survival of primary breast cancer patients who opt for subsequent CPM have been inconsistent. Whereas some studies showed improved survival following CPM [20, 22, 32–36], others showed no survival benefit with CPM [23, 37, 38] (Table 1.3).

In the Cancer Research Network study by Herrinton et al., patients in the CPM group experienced both lower breast cancer mortality and all-cause mortality than those in the non-CPM group (hazard ratio [HR] = 0.57, 95 % CI = 0.45–0.72 and HR = 0.60, 95 % CI = 0.50–0.72, respectively) [22]. Using the SEER data of 8902 women who underwent mastectomy for primary breast cancer and CPM, Bedrosian et al. also reported improved breast cancer-specific survival with CPM (HR = 0.63, 95 % CI = 0.57–0.69) [32]. In a retrospective single-center study by Boughey et al., 10-year overall and disease-free survival rates were better in the CPM group than in the mastectomy-only group (HR = 0.68, 95 % CI = 0.54–0.86 and HR = 0.66, 95 % CI = 0.53–0.82, respectively) [33]. In another retrospective single-center study, Peralta et al. reported a 27 % absolute improvement in disease-free survival and a 15 % absolute improvement in overall survival after 15 years following CPM [20]. In a recent retrospective multicenter study, Metcalfe et al. reported that

Table 1.3 Studies assessing the effect of contralateral prophylactic mastectomy on survival

Author [reference]	Year	Design	No. of patients	Follow-up	Survival benefit of CPM
Peralta et al. [20]	2000	R	CPM: 64 Non-CPM: 182	15 years	Associated with improved DFS (15-year DFS was 55 % for the CPM group and 28 % for the non-CPM group, $P = 0.01$)
Herrinton et al. [22]	2005	R	CPM: 908 Non-CPM: 46,368	5.7 years	Associated with improved BCSS and OS (HR = 0.57, 95 % CI = 0.45–0.72 and HR = 0.60, 95 % CI = 0.50–0.72, respectively)
Bedrosian et al. [32]	2010	R	CPM: 8748 Non-CPM: 95,283	47 months	Associated with improved BCSS (HR = 0.63, 95 % CI = 0.57–0.69)
Boughey et al. [33]	2010	CC	CPM: 385 Non-CPM: 385	17.3 years	Associated with improved OS and DFS (HR = 0.68, 95 % CI = 0.54–0.86 and HR = 0.66, 95 % CI = 0.53–0.82, respectively)
Evans et al. [34]	2013	R	CPM: 105 Non-CPM: 593	10 years	Associated with improved OS (HR = 0.37, 95 % CI = 0.17–0.80)
Metcalfe et al. [35]	2014	R	CPM: 181 Non-CPM: 209	14.3 years	Associated with improved BCSS (HR = 0.52, 95 % CI = 0.29–0.93)
Heemskerk-Gerritsen et al. [36]	2014	P	CPM: 242 Non-CPM: 341	11.4 years	Associated with improved OS (HR = 0.49, 95 % CI = 0.29–0.82)
van Sprundel et al. [23]	2005	R	CPM: 79 Non-CPM: 69	7.4 years	No association with improved OS
Chung et al. [37]	2012	CC	CPM: 177 Non-CPM: 178	61 months	No association with improved OS, DFS, or DMFS
Kurian et al. [46]	2014	R	BM: 11,692 BCT: 104,420 UM: 73,622	89.1 months	No significant difference in OS between BM and BCT groups but higher mortality rates in the UM group
Fayanju et al. [38]	2014	MA	14 studies CPM: 13,142 Non-CPM: 146,174	6.1 years	No association with improved OS or BCSS

Abbreviations: *R* retrospective cohort, *CC* case-control, *P* prospective cohort, *MA* meta-analysis, *CPM* contralateral prophylactic mastectomy, *BM* bilateral mastectomy, *BCT* breast-conserving treatment (breast-conserving surgery plus radiotherapy), *UM* unilateral mastectomy, *BCSS* breast cancer-specific survival, *OS* overall survival, *DFS* disease-free survival, *DMFS* distant metastasis-free survival, *HR* hazard ratio, *CI* confidence interval

BRCA mutation carriers with stage I or II breast cancer treated with bilateral mastectomy are less likely to die from breast cancer than those treated with unilateral mastectomy; the 20-year survival rate for women who underwent CPM was 88 % (95 % CI = 83–93 %), and the rate for those who did not undergo CPM was 66 % (95 % CI = 59–73 %) [35]. In the Metcalfe study, CPM was associated with a 48 % reduction in the risk of death from breast cancer after adjustment for age, year of diagnosis, treatment, and other prognostic features (HR = 0.52, 95 % CI = 0.29–0.93). Recently, Heemskerk-Gerritsen et al. reported the results of a prospective analysis of 583 BRCA-associated primary breast cancer patients (242 who underwent CPM and 341 under surveillance) in an ongoing nationwide Dutch study (HEBON study; Hereditary Breast and Ovarian cancer study, the Netherlands) [36]. In this study, the CPM group showed lower mortality than the surveillance group (9.6 and 21.6 per 1000 person-years of observation, respectively; adjusted HR = 0.49, 95 % CI = 0.29–0.82).

The CPM-associated survival benefit seems to be more evident in patients diagnosed with primary breast cancer at a young age, those with low-grade and/or non-triple-negative tumors, those not treated with adjuvant chemotherapy, and those with early-stage (I and II) tumors [32, 36]. Using Markov modeling, Schrag et al. estimated that CPM would increase life expectancy by 0.6–2.1 years in a 30-year-old early-stage breast cancer patient with a BRCA mutation [19]. In addition, the survival advantage from CPM seems to act independently of bilateral salpingo-oophorectomy, which substantially reduces the risk of CBC and ovarian cancer as well as the risk of relapse of primary breast cancer [34].

In contrast, some studies showed no survival benefit following CPM. A retrospective cohort study conducted by van Sprundel et al. showed no difference in overall survival between the group who underwent CPM and the surveillance group in Dutch patients with BRCA-associated breast cancer [23]. In a single-center study conducted by Chung et al., CPM did not improve overall, disease-free, or distant metastasis-free survival over a median follow-up period of 61 months [37]. Recently, Fayanju et al. conducted a meta-analysis of 14 studies and reported that both the relative and absolute risks of metachronous CBC were significantly decreased among CPM recipients compared with non-recipients (HR = 0.04, 95 % CI = 0.02–0.09), but there was no improvement in overall survival or breast cancer-specific mortality with CPM [38]. A recent Cochrane analysis also concluded that "there is insufficient evidence that CPM improves survival" [39].

Despite the conflicting data regarding its survival benefit, there is increasing interest in CPM for risk reduction among breast cancer patients [40–46]. Turtle et al. reviewed the SEER database and found an increase in the use of CPM from 4.3 to 11 % for the treatment of invasive disease and from 8.4 to 16.4 % for the treatment of noninvasive disease from 1998 to 2003 [40, 41]. Other studies using different databases have confirmed this finding. Using the American College of Surgeons' National Cancer Data Base, Yao et al. reported a similar increase in CPM rates from 1998 to 2007 with no plateau at the end of the study period [44]. Based on data from the New York State Cancer Registry, McLaughlin et al. reported that the number of women undergoing CPM more than doubled from 1995 to 2005

[45]. A recent large observational cohort study based on the population-based California Cancer Registry by Kurian et al. demonstrated a significantly increased rate of bilateral mastectomy, from 2.0 % in 1998 to 12.3 % in 2013, among 189,734 patients, and showed that its associated overall survival was comparable to that associated with breast-conserving surgery plus radiation, with a median follow-up period of 89.1 months [46]. The proposed explanations for the increased rates of CPM among patients with unilateral breast cancer include the increasing use of highly sensitive breast magnetic resonance imaging (MRI), which leads to increases in anxiety-producing recall and biopsy rates that may drive patients to choose preventive surgery, and the increasing use of genetic testing, which facilitates the identification of high-risk patients who benefit from risk-reducing surgery [46].

In BRCA1/2 mutation carriers with breast cancer, the rates of CPM have been reported to be 27–48 % [27, 47]. In a multinational cohort study reporting that 27 % of BRCA mutation carriers with unilateral breast cancer elected to undergo CPM, there were large differences in the adoption of CPM by country; 38 % of North American women (women in the United States or Canada) underwent CPM, whereas only 5 % of European women chose to undergo CPM [47]. However, some studies from Europe have reported much higher CPM rates, ranging from 51 to 65 %, among breast cancer survivors [48, 49]. To date, few studies have assessed the rate of CPM among Asian patients with BRCA-associated breast cancer. The Korean Hereditary Breast Cancer (KOHBRA) study group reported that only 6.4 % of women with BRCA-associated breast cancer opted to undergo subsequent CPM for CBC prevention [50]. In 2009, the Asian BRCA (ABRCA) consortium was launched to study hereditary breast and ovarian cancer in Asian patients, and 15 countries (Korea, Japan, China, Hong Kong, Indonesia, Malaysia, Singapore, India, the Philippines, Vietnam, Thailand, Pakistan, Bangladesh, Taiwan, and Australia) are now participating in this consortium. This international collaboration is expected to elucidate the utilization patterns of risk-reducing modalities in Asian BRCA mutation carriers.

For patients with BRCA-associated breast cancer, an important factor facilitating the decision regarding CPM is the fear of developing metachronous CBC [51]. Women choose to undergo CPM to take control of their cancer and manage their fear [52]. Although periodic surveillance (mammography and breast MRI) is a more noninvasive option than prophylactic mastectomy, patients' prior experiences of undergoing intensive treatments, such as chemotherapy and radiotherapy, underlie their pleas for a more efficacious remedy. Interestingly, pathologic examination of CPM specimens, especially from women older than 40 years of age, revealed high-risk histopathologic lesions, such as atypical lobular hyperplasia, atypical ductal hyperplasia, lobular carcinoma in situ, and ductal carcinoma in situ, in 3–57 % of patients [53–55]. Younger age, high cancer-specific distress, mastectomy for primary breast cancer treatment, and prophylactic oophorectomy are suggested to influence opting for CPM among women with BRCA-associated breast cancer [27, 47].

Most patients are satisfied with their decision to undergo CPM. The greatest reported benefit contributing to patient satisfaction is a reduction in breast cancer-

related concerns [56]. Mutation carriers often report decreased anxiety about developing cancer following prophylactic mastectomy. According to Frost et al., 83 % of patients reported satisfaction with their decision to undergo CPM at a mean of 10 years after surgery [57]. Studies examining psychosocial and quality of life outcomes after prophylactic mastectomy have reported generally high levels of satisfaction, little distress, and overall quality of life comparable to that of women who chose not to undergo prophylactic mastectomy [57–59]. However, some women experience negative psychosocial outcomes following CPM, most often related to high levels of psychological distress, issues with sexual function or body image, and poor cosmetic outcome [59–61].

In an effort to improve cosmetic results and to increase the acceptance rate of prophylactic surgery, there is increasing interest in the use of nipple-sparing mastectomy (NSM), which combines skin-sparing mastectomy with preservation of the nipple-areola complex (NAC) [62]. Whereas classic subcutaneous mastectomy has been criticized because the 5–10 % of breast tissue that remains under the flaps and the NAC increases the risk of cancer at these sites [63], NSM results in thinner skin flaps and a 2- to 3-mm-thick nipple-areolar flap, with the goal of leaving less remaining breast tissue and thus reducing the risk of subsequent cancer development [62]. Currently, total (simple) mastectomy is generally recommended over classic subcutaneous mastectomy or NSM. However, technical advances in skin-sparing techniques and the availability of approaches such as muscle-containing flaps or implantable prostheses have broadened the surgical options available to women considering these procedures [64]. In a report on prophylactic NSM, in which the retroareolar ducts (nipple core) were removed, breast cancer developed in 2 of 55 patients during a median follow-up period of 24.6 months: in the upper outer quadrant in one patient and in the axillary tail in the other patient, but none at the NAC [62]. Another study on a series of 397 NSMs performed at two different institutions on 201 BRCA1/2 mutation carriers reported only four (2.0 %) cancer events: three in cancer patients and one in a patient undergoing NSM for risk reduction, but none at the NAC [65]. Prospective comparative studies with long-term follow-up are needed to precisely establish the risks of cancer after NSM.

1.3 Bilateral Prophylactic Oophorectomy

In 2002, two large case series demonstrated the efficacy of BPO for the prevention of both breast and gynecologic (ovarian, fallopian tube, and primary peritoneal) cancers in BRCA mutation carriers [24, 25], and subsequent reports have also provided strong evidence that BPO is highly protective against BRCA-associated cancers [5, 66–69]. BPO reduces the risk of ovarian cancer by about 90 % and that of breast cancer by about 50 %. In the largest of these studies, Eisen et al. performed an international case-control study on 1439 patients with BRCA-associated breast cancer and 1866 matched controls without breast cancer [67]. BPO was associated with a significant reduction in breast cancer risk among BRCA1 mutation carriers

by 56 % (odds ratio [OR] = 0.44, 95 % CI = 0.29–0.66). For BRCA2 mutation carriers, however, the difference in risk was not statistically significant. The risk reduction was greater if the oophorectomy was performed before age 40 (OR = 0.36, 95 % CI = 0.20–0.64) rather than after age 40 (OR = 0.53, 95 % CI = 0.30–0.90). The protective effect was evident for 15-years post-BPO among BRCA1/2 mutation carriers (OR = 0.39, 95 % CI = 0.26–0.57). In another retrospective analysis of 551 BRCA mutation carriers, BPO reduced the risk of ovarian cancer by 96 % (HR = 0.04, 95 % CI = 0.01–0.16) and that of breast cancer by 53 % (HR = 0.47, 95 % CI = 0.29–0.77) at a mean follow-up time of 8.8 years [25]. A prospective multicenter study also reported that the risk of both breast and ovarian cancers was significantly lower in BRCA mutation carriers who underwent BPO than in those who did not [68, 69]. Recently, Rebbeck et al. conducted a meta-analysis of 10 studies and showed that BPO is strongly associated with reductions in the risk of breast and gynecologic cancers [5]. BPO was associated with a significant reduction in the risk of breast cancer in BRCA1/2 mutation carriers (HR = 0.49; 95 % CI = 0.37–0.65), and similar risk reductions were observed in BRCA1 mutation carriers (HR = 0.47; 95 % CI = 0.35–0.64) and in BRCA2 mutation carriers (HR = 0.47; 95 % CI = 0.26–0.84). BPO was also associated with a significant reduction in the risk of BRCA1/2-associated ovarian or fallopian tube cancer (HR = 0.21; 95 % CI = 0.12–0.39).

The risk of CBC in patients with BRCA-associated breast cancer was also reported to be lower after oophorectomy when it was performed in a premenopausal carrier, presumably because of the induction of premature menopause [12, 14, 17]. By assessing 810 patients with BRCA-associated breast cancer, Metcalfe et al. reported that the strongest predictor of CBC in women with BRCA mutations is oophorectomy [17]. Patients who underwent oophorectomy had a significantly lower risk of CBC than those who did not undergo oophorectomy (relative risk [RR] = 0.48, 95 % CI = 0.27–0.82, $P = 0.002$). This effect was observed in women who were diagnosed with their initial breast cancer under the age of 50 years (RR = 0.39, 95 % CI = 0.23–0.67, $P = 0.0006$) and was significant for those with BRCA1 mutations (RR = 0.48, 95 % CI = 0.27–0.84, $P = 0.01$). In patients with BRCA2 mutations, oophorectomy was associated with a 51 % reduction in CBC risk, but this finding was not statistically significant ($P = 0.11$). Among young (<50 years) patients with two intact ovaries, the 15-year cumulative incidence of CBC was 58 %, and if a woman in this subgroup also had two or more first-degree relatives with breast cancer, the 15-year risk was elevated to 68 %. A recent meta-analysis also indicates that BPO is associated with a decreased risk of CBC in patients with BRCA1/2-associated breast cancer (RR = 0.52, 95 % CI = 0.37–0.74) [70]. Despite its apparent protective effect, the risk of CBC in patients with BRCA-associated breast cancer after oophorectomy was still higher than that seen in a control group of women with sporadic breast cancer [14]. For women with hereditary breast and ovarian cancer syndrome, the National Comprehensive Cancer Network (NCCN) guidelines recommend risk-reducing salpingo-oophorectomy (BPO), ideally performed between ages 35 and 40, and upon completion of

childbearing or on an individualized basis based on the earliest age of onset of ovarian cancer in the family [71].

Recently, Domchek et al. reported the results of a prospective multicenter cohort study of 2482 BRCA1/2 mutation carriers performed to estimate the reduction in risk and mortality with BPO [72]. In this study, women who underwent BPO experienced lower all-cause mortality (HR = 0.40, 95 % CI = 0.26–0.61), breast cancer-specific mortality (HR = 0.44, 95 % CI = 0.26–0.76), and ovarian cancer-specific mortality (HR = 0.21, 95 % CI = 0.06–0.80) than those who did not undergo BPO. Moreover, in mutation carriers with prior breast cancer, BPO was associated with significantly lower all-cause mortality (HR = 0.30, 95 % CI = 0.17–0.52) and breast cancer-specific mortality (HR = 0.35, 95 % CI = 0.19–0.67). However, studies with larger datasets and longer follow-up periods are needed to define more precisely the reduction in mortality conferred by BPO.

Currently, BPO is the prevailing choice for risk-reducing treatment among BRCA mutation carriers in the United States and Canada [73, 74]. In some ways, BPO may be superior to prophylactic mastectomy, because it reduces the risk of both breast and ovarian cancer, and there are now data to indicate that BPO also reduces both overall mortality and cancer-specific mortality. In addition, BPO is associated with lower morbidity than prophylactic mastectomy as well as a superior side effect profile [75]. Considering the later diagnosis and the higher mortality of ovarian cancer compared to breast cancer, BPO is currently recommended by most experts in the field of prevention of hereditary breast and ovarian cancer syndrome [74, 75]. In a North American survey of women who had recently received a positive BRCA test result, 60 % underwent BPO and 25 % opted for prophylactic mastectomy, whereas only 12 % chose to take tamoxifen [73]. BRCA1 mutation carriers are more likely to opt for BPO than are BRCA2 mutation carriers [76, 77]. As is the case for CPM, few studies have assessed the rate of BPO among Asian BRCA mutation carriers with breast cancer. In a single-center study conducted by the KOHBRA study group, 22.4 % of BRCA1/2 mutation carriers with breast cancer underwent BPO to prevent subsequent ovarian cancer, whereas 66.7 % opted for intensive surveillance [50].

A few studies have evaluated psychosocial outcomes and quality of life following BPO. In 2005, Madalinska et al. performed a nationwide, multicenter, cross-sectional, observational study comparing psychosocial and quality of life outcomes among high-risk women who had undergone BPO and those who had opted for screening to manage their increased ovarian cancer risk [78]. In this study, there were no differences in overall quality of life between the two groups. Patients who opted for BPO reported experiencing less worry about breast and ovarian cancers than those who opted for screening. However, women who underwent BPO reported significantly more endocrine symptoms and worse sexual functioning than those who did not undergo BPO.

1.4 In-Breast Tumor Recurrence-Reducing Surgery in Patients with BRCA-Associated Breast Cancer

Breast-conserving treatment (BCT), defined as breast-conserving surgery combined with radiotherapy, is a standard treatment for early-stage breast cancer and results in survival equivalent to that following mastectomy in women with sporadic breast cancer [79, 80]. However, in women with BRCA-associated breast cancer, outcomes of mastectomy and BCT have not yet been directly compared. Thus, the equivalence of the rates of local control, disease-free survival, and overall survival with the two treatments is not yet proven.

Several studies have shown a higher risk of ipsilateral in-breast events, including the recurrence of the initial tumor and the development of a second primary tumor, in patients with BRCA-associated breast cancer treated with BCT than in sporadic controls who received BCT [11, 14, 81–83]. In a multi-institutional study by Pierce et al., the rate of in-breast tumor recurrence at 10 years was twice as high among BRCA1/2 mutation carriers treated with BCT compared with sporadic controls who received BCT [14]. Moreover, another multi-institutional study demonstrated that BRCA mutation carriers who underwent BCT to treat their breast cancer have an elevated risk of local failure in the ipsilateral breast, most occurrences of which appeared to be second primary cancers rather than failure to control the primary tumor, compared with carriers treated with mastectomy (23.5 % vs. 5.5 %, respectively; $P < 0.0001$) [84]. Although patients with BRCA-associated breast cancer have similar survival whether treated with BCT or mastectomy [84], these findings suggest that, for patients with BRCA-associated breast cancer in whom BCT is possible, mastectomy may be an alternative treatment option from the viewpoint of preventing subsequent ipsilateral in-breast events.

If rapid presurgical BRCA testing is possible, women with breast cancer who are confirmed to carry BRCA mutations may consider more extensive surgery, such as mastectomy with or without CPM, to reduce the risk of ipsilateral in-breast events instead of choosing BCT. Recent studies have examined the impact of genetic assessment on surgical choices at the time of diagnosis of breast cancer: breast cancer patients who received positive results for BRCA mutation prior to surgery are more likely to undergo bilateral mastectomy than BCT, with rates ranging from 42 to 100 % [27, 28, 85, 86]. However, the genotyping test for BRCA1/2 mutation is time consuming, and patients may undergo BCT before receiving their BRCA1/2 test results. In addition, for the past decade, BRCA testing has usually been offered after treatment of breast cancer [87]. With respect to the prevention of future in-breast events, an ipsilateral prophylactic completion mastectomy can also be considered for patients with BRCA-associated breast cancer previously treated with BCT.

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