

Chapter 2

Prophylactic Risk-Reducing Surgery for Breast Cancer

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Abstract Advances in the understanding of the genetics and biology of breast cancer are defining patients at increased risk for the development of breast cancer. Prophylactic risk-reducing mastectomy and bilateral salpingo-oophorectomy are very good options for reducing breast cancer risk in selected patients with elevated breast cancer risk. Technical approaches to prophylactic surgery are evolving and are leading to improved patient cosmetic outcomes and lower morbidity. Decisions regarding utilization of these procedures for patients should take into account a specific patient's risk for developing breast cancer based on genetic, family, and personal medical history; patient age; and comorbid conditions. Limitations of prophylactic surgical approaches, alternatives, and side effects of prophylactic operations should also be considered carefully with patients who are considering these surgical interventions for breast cancer risk reduction.

Keywords Breast cancer • Prophylactic surgery • Mastectomy • Risk reducing • Salpingo-oophorectomy • Genetic mutation • BRCA1 • BRCA2 • LCIS

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2.1 Introduction

Patients diagnosed with specific genetic mutations, including BRCA1 and BRCA2, are known to be at significantly elevated risk for developing breast cancer [1, 2]. Other patients without known genetic mutations including those with personal history of breast cancer, a strong family history of breast cancer, a history of high-risk atypical lesions of the breast, or a history of chest wall irradiation prior to age 30 [3] have also elevated risk for developing breast cancer. Options for managing risk in these patients include intensive radiographic surveillance with mammography and MRI [4], chemoprophylaxis [5], and risk-reducing surgical procedures [6].

Surgical prophylaxis is the most effective strategy for reducing risk for subsequent development of breast cancer in patients with elevated risk [7]. This chapter will focus on indications for considering prophylactic risk-reducing breast surgery in patients at elevated risk for breast cancer, surgical options, impact of surgery on breast cancer risk reduction, and factors associated with patient's selection of risk-reducing breast surgery. In addition, attention will be given to the impact of prophylactic surgery on quality of life in patients who have undergone prophylactic risk-reducing breast surgery.

2.2 Patients at Elevated Risk for Development of Breast Cancer

2.2.1 *BRCA Gene Mutation Carriers and Breast Cancer Risk*

Hereditary breast and ovarian cancer syndrome is caused by mutations in the BRCA1 [1] or BRCA2 gene [2]. BRCA1 and BRCA2 mutations have been estimated to be present in 1:300–1:800 members of the general population. Among patients of Ashkenazi Jewish ancestry, the frequency of BRCA1 and BRCA2 mutations has been estimated to be 1:40 [8].

Lifetime risk estimates for the development of breast cancer in BRCA1 patients have been estimated to be between 40 and 87 %, and in BRCA2 patients, the risk has been estimated to be between 40 and 84 % [7]. Risk of breast cancer substantially increases beginning at age 30 in BRCA1 and BRCA2 mutation carriers [9] (Fig. 2.1).

Newly diagnosed breast cancer patients who have a mutation in BRCA1 or BRCA2 genes are at significantly elevated risk for the development of contralateral breast cancer (RR 3.56, CI 2.5–5.08, $p < 0.001$) [10]. The 10-year risk of contralateral breast cancer development has been estimated to range between 20 and 30 % [11, 12]. Specifically, patients with BRCA1 mutation have a higher risk of contralateral breast cancer compared to patients with BRCA2 mutation (RR 1.42, CI 1.01–1.99, $p = 0.04$) [10]. Among patients with BRCA1 and BRCA2 mutations and a new diagnosis of breast cancer, older age at breast cancer diagnosis and the use of chemoprophylaxis have been associated with a lower risk of contralateral breast cancer [10, 13].

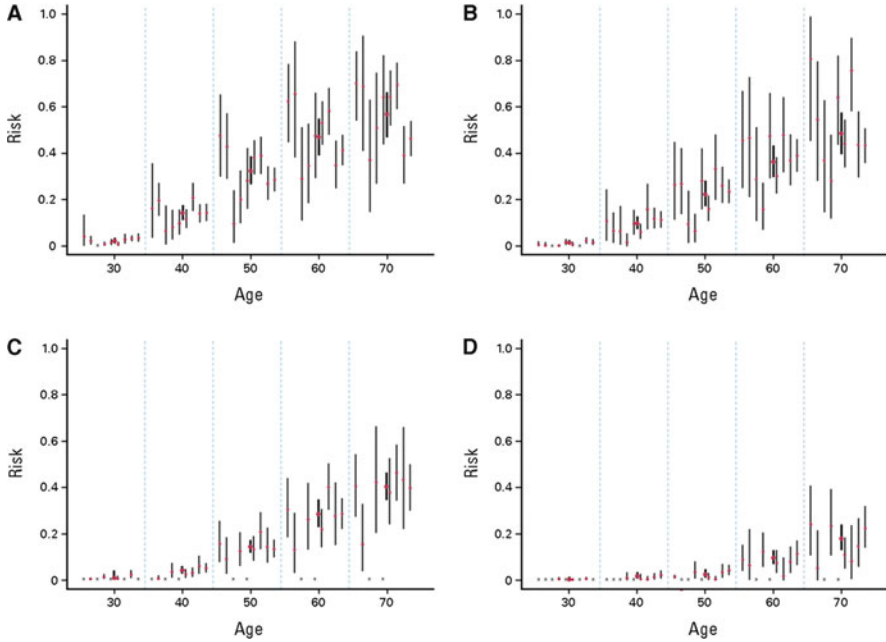


Fig. 2.1 (a) Breast cancer risk as a function of age for BRCA1 mutation carriers. (b) Breast cancer risk as a function of age for BRCA2 mutation carriers. (c) Ovarian cancer risk as a function of age for BRCA1 mutation carrier. (d) Ovarian cancer risk as a function of age for BRCA2 mutation carriers [9] (Reprinted with permission. © (2007) American Society of Clinical Oncology. All rights reserved. The authors, editors, and ASCO are not responsible for errors or omissions in the translation)

2.2.2 Other Genetic Mutations and Breast Cancer

Other genetic syndromes that have been associated with high risk for developing breast cancer include PTEN hamartoma tumor syndrome (PTEN) [14], Peutz-Jeghers syndrome (STK11) [15], Li-Fraumeni syndrome (TP53) [16], and hereditary diffuse gastric cancer (CDH1).

Other less common mutations have been associated with elevated breast cancer risk including CHEK2, ATM, BRIP1, PALB2, and RAD51C [8]. The breast cancer risk estimates associated with these less common mutations are highly variable (Table 2.1). When assessing risk for breast cancer (and appropriate screening or prophylactic strategies) in an individual patient with these less common mutations, strong consideration should be given to an individual's three-generation family history [17].

Table 2.1 Breast cancer risk among patients with high/moderate-risk genetic mutations [17, 77–81]

Genetic mutation	Breast cancer risk (%)
CHEK2	20–44
PALB2	33–58
ATM	16–60
CDH1	39–52
TP53	50–85
RAD51C	10–20
PTEN	67–85
STK11	8–45

2.2.3 Lobular Neoplasia and Breast Cancer Risk

Lobular neoplasia including atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) represents a spectrum of lesions that are associated with increased breast cancer risk [18]. ALH and LCIS are associated with a three- to fourfold and eight- to tenfold elevated risk of developing breast cancer, respectively [19, 20]. A recently reported large series of 646 patients with LCIS (median follow-up of 41.5 months) demonstrated that the risk of cancer development was 13.7 % [21]. Patients with ALH or LCIS have an elevated risk of developing breast cancer, and risk is not limited to the side of the initial diagnosis of lobular neoplasia.

2.2.4 Patients with Unilateral Breast Cancer

Among patients without a known genetic mutation or other high-risk history, a personal history of breast cancer is a well-established risk factor for synchronous and metachronous breast cancers. Patients with a newly diagnosed unilateral breast cancer have a 1–6 % chance of a synchronous contralateral breast cancer [22–24]. Patients with a personal history of breast cancer have an approximately 0.25–0.70 % risk per year of a metachronous contralateral breast cancer [25, 26].

2.3 Use of Prophylactic Mastectomy for Risk Reduction

Patients considering prophylactic mastectomy should receive multidisciplinary evaluation and risk assessment including genetic counseling where appropriate to clearly define the risks of breast cancer and discuss alternatives to prophylactic surgery. It has been observed that many women overestimate their true risk for breast cancer highlighting the importance of accurate and clear communication between physicians and patients [27, 28]. Decisions regarding prophylactic mastectomy should be made in the context of shared decision-making between the patient and provider [29].

2.3.1 Gene Mutation Carriers and Prophylactic Mastectomy

The use of prophylactic mastectomy for BRCA mutations has been observed to differ significantly by country [30]. Election of prophylactic mastectomy is related to age and is most common in women between 35 and 60 years old [31]. There is also international variation in the rate of contralateral prophylactic mastectomy in BRCA1 and BRCA2 mutation carriers following diagnosis of unilateral breast cancer with the highest rates observed in the United States (36.2 %) and lowest rates in Poland (2.7 %) and Israel (4.2 %) [32]. Predictors of prophylactic surgery among BRCA1 and BRCA2 mutation carriers include age <60, breast cancer history, and utilization of other risk-reducing operations [33].

2.3.2 Lobular Neoplasia and Bilateral Prophylactic Mastectomy

Historically, bilateral prophylactic mastectomy was the treatment of choice for LCIS [34]. Presently, bilateral prophylactic mastectomy is much less commonly used and is not the recommended approach for patients with LCIS for prophylaxis [35]. Prophylactic mastectomy may be a reasonable consideration for selected patients with LCIS and a strong family history or patients with a history of other high-risk breast lesions. A large SEER database study in 2009 demonstrated that ~18 % of patients with LCIS in the United States undergo prophylactic mastectomy [36].

2.3.3 Unilateral Breast Cancer and Contralateral Prophylactic Mastectomy

Concerns over risk of subsequent cancer development and other factors including cosmesis have led many patients in the United States to elect contralateral prophylactic mastectomy (CPM) in the setting of therapeutic unilateral mastectomy for breast cancer [37]. The rate of contralateral prophylactic mastectomy has been demonstrated to have increased dramatically in the last 10 years in the United States [38]. Factors associated with choice of CPM are young age at diagnosis, white race, higher education level, private insurance, preoperative MRI, care at an academic center, family history of breast cancer, and the decision to undergo breast reconstruction [35, 39]. Interestingly, the rate of CPM has not been observed to rise in other parts of the world [40]. International variation in physician attitudes toward prophylactic mastectomy has also been observed [41].

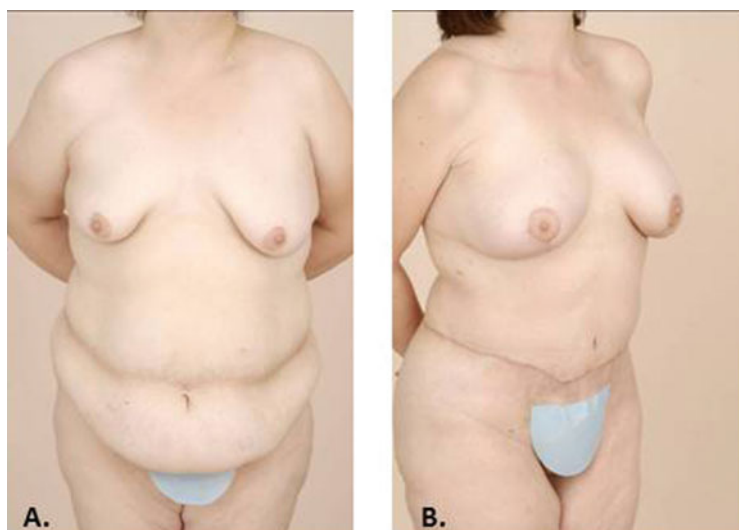


Fig. 2.2 (a) Preoperative photo of a patient with hereditary predisposition to breast cancer. (b) Postoperative photo following bilateral prophylactic mastectomy with deep inferior epigastric perforator (DIEP) flap (reconstruction)

2.4 Operative Considerations of Prophylactic Mastectomy

Traditionally, mastectomy procedures involved removal of a portion of the breast skin envelope as well as the nipple-areolar complex. Traditional approaches to mastectomy are currently performed in patients who do not desire breast reconstruction following mastectomy or in patients who prefer delayed reconstruction. In recent years, techniques have evolved to allow removal of the breast parenchyma without sacrifice of the skin envelope and/or nipple-areolar complex (i.e., nipple-sparing mastectomy or total skin-sparing mastectomy) [42]. Performance of nipple-sparing mastectomy facilitates subsequent immediate or delayed immediate breast reconstruction [43] (Fig. 2.1). Rates of breast reconstruction in BRCA1 and BRCA2 mutation carriers have been observed to vary by country [44]. Several recent series have demonstrated that nipple-sparing mastectomy is not associated with increased rate of recurrence in patients with BRCA1 and BRCA2 mutations, although oncologic follow-up in these series is relatively short [45–47].

Consideration for prophylactic mastectomy should begin at approximately age 30 in BRCA1 and BRCA2 mutation carriers as this is the time at which breast cancer risk steeply increases (Fig. 2.1).

Sentinel node biopsy is not routinely indicated in patients undergoing prophylactic mastectomy as the rates of finding histologically positive sentinel nodes associated with prophylactic mastectomy is ~1 % [22, 48, 49]. Some authors have advocated the use of preoperative breast MRI to exclude the presence of invasive

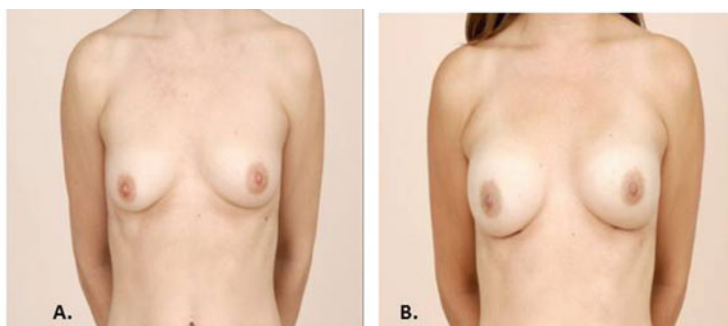


Fig. 2.3 (a) Preoperative photo of a patient with hereditary predisposition to breast cancer. (b) Postoperative photo following bilateral prophylactic mastectomy with immediate implant-based reconstruction

disease in the prophylactic mastectomy breast and hence exclude the need for sentinel node biopsy [48].

In patients undergoing prophylactic nipple-sparing mastectomy, nipple duct biopsies are helpful in evaluating the remaining nipple for the presence of any cancer or atypia [50]. However, studies have demonstrated that the incidence of a positive nipple duct biopsy in patients having prophylactic mastectomy is 1–4 % [47, 50]. BRCA1 and BRCA2 mutation patients do not have higher rates of pathologically positive nipple duct biopsies compared to non-mutation patients [47].

Overall complication rate with bilateral mastectomy with reconstruction is 10–20 % [51, 52]. Approximately half of the observed complications occur in the prophylactic mastectomy side [53]. Most common complications are hematoma, skin necrosis, cellulitis, and seroma [53]. Complications may lead to need for additional operations and loss of breast implant or even may delay delivery of necessary adjuvant therapies [54, 55]. The increased rate of complications associated with performing contralateral prophylactic mastectomy and associated potential delays in adjuvant therapy should be discussed with patients considering this option for breast cancer risk reduction [56].

2.5 Cancer Risk Reduction and Survival Associated with Prophylactic Mastectomy

Prophylactic surgery in BRCA1/2 patients reduces breast cancer risk in patients without previous breast cancer by >90 % [6, 57]. Kaas et al. have estimated that the risk of subsequent breast cancer in BRCA1 and BRCA2 mutation carriers following bilateral prophylactic mastectomy is <0.2 %/woman/year [58]. In patients without known genetic mutations determined to be at moderate to high risk for developing

breast cancer, breast cancer risk reduction has similarly been reported to be ~90 % [59, 60].

In BRCA1 and BRCA2 mutation carriers with breast cancer, prophylactic surgery reduces incidence of breast cancer and may be associated with improvement in overall survival [61, 62]. Other studies have suggested that contralateral prophylactic mastectomy in BRCA1 and BRCA2 breast cancer patients has no impact on survival though follow-up in many of these studies is short and must be interpreted with caution [63].

In patients without a known genetic mutation who have unilateral mastectomy for breast cancer, contralateral prophylactic mastectomy has not been associated with improved survival, although, as expected, reduced rates of new primary metachronous breast cancer have been observed [63, 64].

2.6 Quality of Life Following Prophylactic Mastectomy

Studies have demonstrated that most high-risk women are generally satisfied with the decision to undergo bilateral prophylactic mastectomy [65, 66]. The greatest positive impact on patients undergoing prophylactic mastectomy is related to reduction in concerns over subsequent breast cancer events [67]. Negative effects on body image, sexual function, and depression in patients undergoing prophylactic mastectomy are well documented [65, 68, 69]. Others have reported patients' concerns regarding breast reconstruction, adverse body image, and insufficient information or support as common concerns among women who were dissatisfied or very dissatisfied with prophylactic mastectomy. Physician's advice as the primary reason for choosing prophylactic mastectomy has been associated with patient dissatisfaction [70, 71]. These adverse symptoms should be considered in the management of patients choosing prophylactic mastectomy. Support systems for women before, during, and after surgery are recommended for managing potential distress related to decision for prophylactic mastectomy [70, 72].

2.7 Oophorectomy and Breast Cancer Risk Reduction

Patients with BRCA1 and BRCA2 mutations are at elevated risk for the development of ovarian cancer, and prophylactic bilateral salpingo-oophorectomy (BSO) is commonly performed as it reduces the risk of developing ovarian cancer in these patients [73]. BSO also reduces the risk of breast cancer development in patients with BRCA1 and BRCA2 mutations [74, 75]. The benefit in terms of breast cancer risk reduction is related the patient age at the time of BSO, with the greatest breast cancer risk reduction observed in patients undergoing BSO before the age of 40. In patients <40 years, BSO is associated with a 64 % and 31 % breast cancer risk reduction in BRCA1 and BRCA2 mutation patients, respectively [76]. As breast

cancer risk reduction is not complete with BSO, many patients in the United States with BRCA1 and BRCA2 mutations opt also for risk-reducing prophylactic mastectomy.

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