

# Surgical Management of Hereditary Breast Cancer

Magdalena Plasilova · Anees B. Chagpar

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**Abstract** Hereditary breast cancer (HBC) has been linked to mutations in a number of genes, most notably BRCA1 and BRCA2. With the widespread availability of large panel testing and whole genome sequencing, an increasing number of individuals may discover their susceptibility for breast cancer as a result of genetic mutations. Surgical interventions may significantly reduce the risk for subsequent development of breast cancer. Patients should be counselled, however, about alternatives for risk reduction as well as the risks and benefits of surgery in order to make an informed decision regarding whether such an intervention is right for them.

**Keywords** Hereditary breast cancer · BRCA1 · BRCA2 · PALB2 · p53 · Li Fraumeni · Cowden syndrome · Prophylactic mastectomy · Prophylactic bilateral salpingoophorectomy

## Introduction

While the majority of breast cancer cases are sporadic, roughly 5–10 % are associated with germline mutations, primarily in the tumor suppressor genes BRCA1, located on chromosome 17q, and BRCA2, located on chromosome 13q [1–4].

However, with the discovery of lower penetrance genes, the contribution of a number of other genes to hereditary breast cancer risk has become better elucidated. Figure 1 demonstrates the relative prevalence of a series of genetic mutations in a study of 3000 patients referred for BRCA1/2 testing [5].

Women carrying the BRCA1 mutation have up to an 87 % risk of developing breast cancer before the age of 70 and an approximately 40–50 % risk of developing a second primary breast cancer [6]. Other syndromes have been linked to an increased risk for breast cancer as well, including the Li Fraumeni syndrome that is associated with breast cancer and soft tissue sarcomas and involves a p53 gene mutation [7]. Similarly, Cowden syndrome, associated with PTEN mutations, is characterized by an increased risk of breast cancer, thyroid cancer, and multiple hamartomas [8]. Mutations in the ataxia-telangiectasia gene are also associated with a three to fourfold increased risk of breast cancer [9]. Furthermore, mutations of the more recently characterized PALB2 gene are associated with an absolute breast cancer risk of 33–58 % in women by age of 70, with even higher rates for those with two or more first-degree relatives with breast cancer at 50 years of age [10]. Table 1 illustrates the lifetime breast cancer risk conferred by various genetic mutations reported in the literature [11].

Given our burgeoning knowledge of genetic factors that increase breast cancer risk, and the ubiquity of technology to facilitate this assessment, access to genetic evaluation has never been greater. Increasingly, patients are aware of genetic mutations, but may be less savvy regarding their propensity to carry such a mutation nor the array of genes that may be involved. As such, genetic counselling may clarify an individual patient's risk as well as crystallize the need (or lack thereof) for genetic testing for particular mutations [12]. Current guidelines for referral to genetic counselling are shown in Table 2 [13].

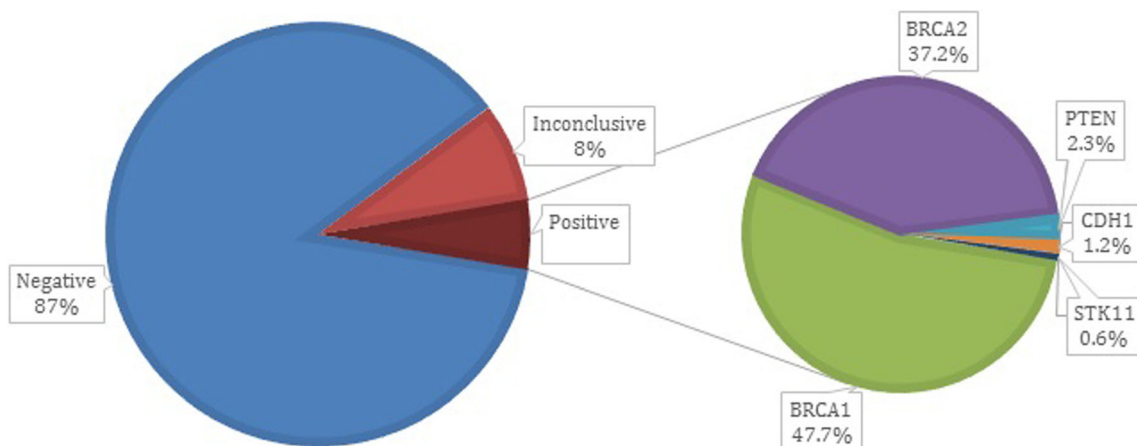
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M. Plasilova · A. B. Chagpar (✉)  
Department of Surgery, Yale University School of Medicine, 20 York Street, First Floor, Suite A, New Haven, CT 06510, USA  
e-mail: anees.chagpar@yale.edu

M. Plasilova  
e-mail: magdalena.plasilova@yale.edu



**Fig. 1** Distribution of results for patients referred for genetic testing for hereditary breast cancer, including prevalence of specific germline mutations based on a study of 3000 patients [5]

**Indications for Surgical Management**

For individuals who are diagnosed with a deleterious mutation for hereditary breast cancer, options for managing their risk should be discussed. Screening with annual MRI and mammography for those over the age of 30 is recommended to detect malignancy early; however, this does not lower an individual’s risk of developing breast cancer. Chemoprevention may be considered, but only reduces breast cancer risk by ~50 %. Given the increased risk associated with genetic mutations (Table 1), individuals may wish to consider prophylactic mastectomy which can reduce the risk for developing breast cancer by 95 %. Furthermore, prophylactic bilateral salpingo-oophorectomy may not only reduce the risk of developing breast cancer by 50 % but also ovarian cancer by 90 %; therefore, this is often a consideration for patients with BRCA mutations.

While the decision with regards to risk reducing options is a personal choice for patients at hereditary risk for breast cancer, the advantages and disadvantages of each option should be discussed along with the potential risks and benefits of surgical options. Mutation carriers who develop breast cancer are candidates for standard surgical approaches for breast cancer management, although may opt for bilateral

mastectomies in order to manage the index cancer, and further to reduce the risk of contralateral breast cancer.

**Prophylactic Mastectomy**

Whether or not patients with hereditary risk harbor a known breast cancer, many may consider bilateral prophylactic mastectomy to reduce their risk. This procedure reduces the risk of development of future breast cancers by ~95 %; however, the

**Table 1** Lifetime risk associated with genetic mutations

Gene	Chromosomal location	Lifetime risk of developing breast cancer
BRCA1	17q21	65–81
BRCA2	13q12.3	45–85
CDH1	16q22.1	39–52
PTEN	10q23.3	50–85
STK11	19p13.3	35–50
TP53	17p13.1	50–80

**Table 2** Indications for genetic counselling

An affected individual with one or more of the following:	An unaffected individual with a family history of one or more of the following:
<ul style="list-style-type: none"> <li>•Known breast cancer susceptibility gene mutation in family</li> <li>•Male breast cancer</li> <li>•≥1 family member on the same side of family with breast cancer and one or more of the following: pancreatic cancer, prostate cancer (Gleason score ≥7), sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, leukemia/lymphoma, thyroid cancer, dermatologic manifestations of Cowden’s and/or macrocephaly, hyperpigmented macules suggestive of STK11, hamartomatous polyps of GI tract, diffuse gastric cancer</li> <li>•Breast cancer ≤50 years of age</li> <li>•Triple negative breast cancer</li> <li>•Two breast cancer primaries</li> <li>•≥1 relative (1st, 2nd, or 3rd degree) with breast cancer ≤50 years of age</li> <li>•≥1 relative (1st, 2nd, or 3rd degree) with ovarian cancer at any age</li> <li>•≥2 relatives (1st, 2nd, or 3rd degree) with breast cancer and/or pancreatic cancer at any age</li> <li>•From a population at increased risk (e.g., Ashkenazi Jewish)</li> <li>•Ovarian cancer</li> </ul>	<ul style="list-style-type: none"> <li>•≥2 breast primaries in a single relative (1st, 2nd, or 3rd degree)</li> <li>•≥2 relatives (1st, 2nd, or 3rd degree) on the same side of the family with breast cancer</li> <li>•≥1 relative with ovarian, fallopian tube or primary peritoneal cancer on the same side of the family</li> <li>•1st or 2nd degree relative with breast cancer ≤45 years of age</li> </ul>

impact on survival is less clear. While some studies have found no impact of prophylactic mastectomy on survival in BRCA carriers [14], others using a population-based sample have found an improvement in survival associated with this procedure [15].

Women with BRCA-associated breast carcinoma who undergo breast conservation therapy (BCT) have a twofold risk ipsilateral breast tumor recurrence compared with sporadic breast cancer patients [16, 17]. While the BRCA mutation does not confer increased toxicity from radiation therapy [18], women harboring a BRCA mutation who undergo breast-conserving surgery with adjuvant radiation therapy have a 23 % chance of developing a subsequent ipsilateral breast cancer at 15 years, compared to 5 % in those choosing mastectomy [19, 20].

For those who opt for prophylactic mastectomy, whether bilateral or contralateral, there are a number of techniques available. These include a conventional mastectomy without reconstruction or a skin-sparing, areolar-sparing or nipple-sparing procedure, each of which is accompanied by immediate reconstruction. These procedures are, in general, equivalent in terms of oncologic risk for risk-reducing mastectomy. However, for patients who have an index breast cancer, sparing the nipple is controversial, particularly for those with larger tumors that are close to the nipple and those with extensive DCIS.

With the advent of a number of reconstructive techniques, patients can often choose between tissue expander/implant-based reconstruction and that using autologous tissue. Autologous options may include latissimus dorsi flaps, transverse rectus abdominus myocutaneous flap, deep inferior epigastric perforator flaps, and less common flaps such as gluteal artery perforator flaps. It is known that reconstruction does not increase the risk of developing subsequent breast cancers nor does it impede finding or managing chest wall recurrences if they do occur [21].

Lymph node evaluation with sentinel lymph node biopsy (SLNB), while standard of care in patients undergoing mastectomy for DCIS or invasive cancer, is more controversial in the prophylactic setting. While the risk of finding lymph node metastases is small in the absence of known cancer, some argue that the risk of the ramifications of not performing this minimally invasive procedure at the time of mastectomy thereby requiring an axillary node dissection if an invasive cancer is found on final pathology far outweigh the risk of the sentinel node biopsy itself [22].

#### Risks vs. Benefits

When considering the option of prophylactic mastectomy, patients must weigh the benefit of risk reduction with potential risks of surgery. Beyond the risks of anesthesia, bleeding, and infection which are common to most surgical procedures, prophylactic mastectomy is associated with additional risks. Patients should be aware that while the risk of developing future breast cancers is significantly reduced, it is not

eliminated. For patients who opt for a skin-sparing, areola-sparing, or nipple-sparing mastectomy, there is a risk of skin necrosis, particularly in patients that are smokers or diabetics. If the nipple is spared, patients should be aware that it will be insensate and will not respond to cold or sexual stimulus as a native nipple would. Furthermore, there are risks associated with reconstruction. These include, but are not limited to, implant-related complications, capsular contracture, autologous donor site morbidity, fat necrosis, hernia formation, deep vein thrombosis, asymmetry, prolonged recovery, muscle weakness, and others [23–25]. Some have found that patients who underwent contralateral prophylactic mastectomy were 1.5–2 times more likely to report complications than those who opted for unilateral procedures [26, 27].

In addition to considering the physical sequelae of prophylactic mastectomy, some studies have found that body image declined after bilateral prophylactic mastectomy with immediate reconstruction, as did sexual satisfaction [28, 29]. Similarly, 31 % of women undergoing contralateral prophylactic mastectomy reported poorer body image, 24 % reported reduced femininity, and 23 % reported diminished sexuality [30]. While studies have found that the majority of patients undergoing prophylactic mastectomy will report at least one body image issue at 2 years, this does not seem to correlate with differences in health-related quality of life, anxiety, depression, or sexuality before vs. after the surgery. In addition, while 42 % of patients who underwent contralateral prophylactic mastectomy (CPM) felt that their sense of sexuality was worse than what they expected, 80 % reported that they were “extremely confident in their decision to have CPM,” and 90 % would have made the same decision again [31]. This is in sharp contrast to patients who opted for unilateral mastectomy who reported that they would have made a different decision if they had to do it again ( $p=0.0007$  compared to patients who opted for bilateral prophylactic mastectomy and  $p=0.0005$  compared to those who opted for contralateral prophylactic mastectomy) [32].

#### Prophylactic Bilateral Salpingo-Oophorectomy

In high-risk patients carrying the BRCA mutation, there are other prophylactic procedures that may need to be considered including prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) or bilateral salpingo-oophorectomy (BSO) alone [33, 34]. Even without mastectomy, bilateral salpingo-oophorectomy lowers the risk of developing breast cancer by 56 % (for BRCA1 mutation carriers) and 46 % (for BRCA2 mutation carriers), in addition to reducing the risk of ovarian cancer by 90 %. The availability of a laparoscopic salpingo-oophorectomy provides patients a less invasive option for this procedure.

In women who carry a BRCA mutation, the benefit of prophylactic BSO for breast cancer reduction is greatest when performed before the age of 40 [35]. However, particularly in young women, the decision to proceed with this procedure needs to be viewed in the context of the patient's desire to have more children. Fertility preservation options should therefore be considered prior to performing this procedure. Particularly in the prophylactic context, the procedure may be delayed until after childbearing is complete.

For patients opting for both prophylactic mastectomy and TAH-BSO, the order in which these procedures is performed does not significantly affect the surgical complication rates. In addition, combining prophylactic mastectomy, reconstruction, and salpingo-oophorectomy in the same operative setting has been shown to be a safe option as well [36].

## Conclusions

While accounting for a minority of breast cancers, the prevalence of patients with known mutations in breast cancer susceptibility genes will become increasingly common with public awareness and the availability of large panel testing and whole genome sequencing. The decision of how best to manage the concomitant increased risk associated with these mutations is a personalized decision that patients will make with their physicians. This will require a multidisciplinary approach, with a discussion of various options from screening to chemoprevention to surgical approaches such as prophylactic mastectomy and/or salpingo-oophorectomy. For all surgical approaches, patients must be made aware of the risks and benefits of the procedures, which may be particularly relevant in the prophylactic setting, where risk reduction must be weighed against the physical and psychological sequelae of the procedures.

## Compliance with Ethics Guidelines

**Conflict of Interest** Magdalena Plasilova and Anees B. Chagpar declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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