


# Risk-Reducing Options for Women with a Hereditary Breast Cancer Predisposition

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## ABSTRACT

Genetic testing is now widely utilized to identify women with a hereditary predisposition for breast cancer. Women who carry mutations that increase breast cancer risk may consider three options to reduce risk: screening, chemoprevention, and prophylactic surgery. Yet, no randomized trials have specifically assessed the efficacy of these options in mutation carriers. In many developed countries, mammography is regarded as the optimal means of screening for breast cancer in the general population. However, breast MRI is a more sensitive screening tool, and for mutation carriers, any breast cancer screening strategy should incorporate screening with MRI. In randomized trials of women at high risk for developing breast cancer, chemoprevention reduces that risk, but it has not been shown to reduce mortality. Finally, observational studies suggest that, in mutation carriers, prophylactic surgery may reduce the risk of developing breast cancer by 90-95%. There are several prophylactic mastectomy procedures to choose from, and these are generally done in conjunction with breast reconstruction. In this article, we discuss management of women who carry mutations that have been associated with an increased breast cancer risk. Mutation carriers should be informed of the potential risks and benefits of the three available options to reduce breast cancer risk.

**Keywords:** Hereditary predisposition, breast cancer, risk-reducing options

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## Introduction

In recent years, there has been growing interest in identifying women with a hereditary predisposition for breast cancer. Interest in genetic testing for breast cancer predisposition surged following the actress Angelina Jolie's op-ed in the New York Times in May, 2013, revealing that she carried the BRCA 1 mutation and had undergone bilateral prophylactic mastectomy to reduce her breast cancer risk (1). Today, genetic counselling and testing for breast cancer predisposition is available in cancer centers throughout the world, and the number of women who seek genetic testing continues to increase. In this article, we review options for the management of women identified as having a hereditary predisposition for breast cancer.

The three major risk factors for the development of breast cancer are gender, age, and family history/genetic predisposition (2-4). Gender is clearly the greatest risk factor. Approximately 12.7% of all women in the United States will be diagnosed with breast cancer, while only 0.1% of all men develop this disease (4). Thus, breast cancer is approximately 100-fold more common in women than men. The second greatest risk factor for breast cancer is ageing. Breast cancer risk increases dramatically with ageing (4). The risk of a 30-year old woman developing breast cancer during the next 10 years of her life is 0.44% (1 in 227), but that 10-year risk is 3.82% (or 1 in 26) for a woman aged 70. Finally, the family history and hereditary predisposition are important risk factors (5). In this article, we will briefly review the mutations that confer a high risk of breast cancer (high-penetrance mutations), and discuss strategies to manage these patients.

The vast majority of breast cancers are non-hereditary (sporadic), and environmental and life-style factors are the most important determinants of the risk. Only 10% of all women with breast cancer have a hereditary pre-disposition for the disease (6). Yet, environmental and life-style factors may modify risk in women with a hereditary pre-disposition for breast cancer as well. For instance, a population-based study suggested that breast cancer risk among BRCA 1 or BRCA 2 mutation carriers was much greater for women born after 1958 when compared to those born before that year (7). Changes in life-style are likely responsible for these differences between birth cohorts, and one might speculate that the rising incidence of obesity is partly responsible.

### Mutations

Of the 10% of breast cancer cases attributable to germline mutations, BRCA 1 and BRCA 2 gene mutations are the most common, and comprise about half (5%) of the total number of cases (8). Among BRCA 1 mutation carriers, the average cumulative risk of breast cancer by 80 years of age is about 67% and the average cumulative risk of ovarian cancer is about 45% (9). For BRCA 2 mutation carriers, the cumulative risks of breast and ovarian cancer are 66% and 12%, respectively (9). However, there is considerable variation in risk of breast and ovarian cancer among BRCA 1 and BRCA 2 mutation carriers, and risk appears to partly depend upon the location of the mutation within the gene (10). It should also be noted that, after their initial diagnosis of breast cancer, BRCA 1 and BRCA 2 mutation carriers have an elevated risk of developing contralateral breast cancer, and this may have therapeutic implications (11). Thus, mutation carriers who present with unilateral breast cancer may wish to consider bilateral mastectomy with breast reconstruction, rather than breast conserving surgery or unilateral mastectomy (12).

Although the BRCA 1 and BRCA 2 mutations are widely discussed in both the lay and medical media, there are several other gene mutations that dramatically increase breast cancer risk (high-penetrance mutations). These include mutations in the STK11 (Peutz-jeghers syndrome), pTen (Cowden's Syndrome), p53 (Li-Fraumeni Syndrome), CDH1 (Diffuse Hereditary Gastric Cancer Syndrome), and PALB2 (partner and localizer of BRCA 2) genes (13, 14). These mutations are also often associated with an increased risk of other malignancies and disease manifestations. Thus, the STK11 mutation is associated with gastrointestinal polyposis and breast cancer, the pTen mutation with thyroid cancer and breast cancer, the p53 mutation with numerous other cancers such as sarcomas, brain tumors, GI tumors, as well as breast cancer, the CDH1 mutation is associated with gastric cancer and lobular breast cancer (15). Women who wish to consider genetic testing, should be referred to genetic counsellors, and a detailed family history obtained to determine if genetic testing is warranted.

Once a gene mutation is identified in an asymptomatic woman, she may consider three options to reduce breast cancer risk: screening, chemoprevention, and risk-reducing surgery. Sometimes, a woman may choose an appropriate combination of these options. For instance, a BRCA 1 mutation carrier may choose to undergo breast cancer screening until she has had children and completes breast-feeding. After that, she may opt for risk-reducing surgery (bilateral mastectomy with reconstruction and bilateral salpingo-oophorectomy).

### Screening

Although no randomized trials have specifically addressed the efficacy of breast cancer screening in mutation carriers, there are trials that have examined efficacy in the general population. Specifically, in the general population, nine trials have examined the efficacy of mammography screening, two have examined the efficacy of screening breast self-examination (BSE), and two trials in India examined the efficacy of screening clinical breast examination (CBE) (16). The two screening BSE trials were undertaken in St. Petersburg, Russia and Shanghai, China, and neither showed any benefit to screening BSE (17, 18). Mortality results have not yet been reported for the two screening CBE trials in India (19, 20).

In the mammography screening trials, meta-analyses indicate that screening reduced breast cancer-specific mortality by about 25%, but this benefit appears to be largely limited to women aged 50-69 years

of age at entry into these trials (21). Most mutation carriers are young, and the efficacy of mammography screening in younger women has not been conclusively demonstrated. Younger women are more likely to have ER (Estrogen receptor)-negative cancers when compared to older women, and screening is perhaps more likely to benefit patients with ER-positive cancers when compared to ER-negative cancers, as the ER-positive cancers are more indolent and therefore spend a greater length of time in the pre-clinical phase (22, 23). Indeed, two mammography screening trials (the Canadian National Breast Screening Study I and the United Kingdom Age Trial) were specifically designed to assess the efficacy of mammography screening in women below age 50, and these trials showed no benefit (24, 25). Moreover, improvements in breast cancer therapy are likely reducing the benefit of population-based mammography screening (i.e., as breast cancer treatments improve, the efficacy of mammography screening will likely decline) (26). This is evident with the trends over time in the mammography screening trials. The oldest trial, the Health Insurance Plan (HIP) of New York was initiated in 1963, and demonstrated that mammography screening could reduce breast cancer mortality by about 30% (27). However, adjuvant systemic therapy was not generally available to patients during the era of the HIP trial. In the three more recent mammography screening trials, (Canadian National Breast Screening Study I and II, and the United Kingdom Age trial), adjuvant systemic therapy was widely available to patients, and these trials failed to show any benefit from mammography screening (24, 25).

There are theoretical concerns with respect to mammography screening in mutation carriers. Mammography screening is associated with ionizing radiation, and mutation carriers may lack the ability to effectively repair DNA damage that results from ionizing radiation (28). Thus, mammography screening may potentially increase breast cancer risk in mutation carriers (29). However, it should be emphasized that there are no randomized prospective studies that have assessed the potential effects of mammography screening in mutation carriers. Nonetheless, for mutation carriers, a better alternative to mammography screening is perhaps screening with magnetic resonance imaging (MRI). Screening breast MRI is much more sensitive than screening mammography (it detects twice as many cancers), and it is not associated with ionizing radiation (30, 31). Moreover, in a prospective cohort study among women with an elevated familial risk of breast cancer, the addition of screening mammography to screening breast MRI did not increase breast cancer detection rates when compared to screening MRI alone (30). Thus, screening breast MRI alone is perhaps the optimal breast cancer screening strategy for mutation carriers.

However, for BRCA mutation carriers, the European Society of Medical Oncology (ESMO) recommends screening clinical breast examination (CBE) every 6-12 months starting at age 25, or 10 years before the youngest breast cancer diagnosis in the family, whichever is earlier (32). Annual screening MRI is recommended starting at age 25, with the addition of annual mammography starting at age 30. The ESMO breast cancer screening recommendations vary slightly for women with other moderate or high-penetrance mutations. For example, for p53 mutation carriers (Li-Fraumeni Syndrome), ESMO recommends screening CBE every 6-12 months starting at age 20-25, with annual breast MRI at age 20-75 (with mammography considered if MRI is not available) (32).

### Chemoprevention

Chemoprevention is also a potential means of reducing breast cancer risk in mutation carriers (33, 34). Again, there are no randomized tri-

als that have specifically addressed the efficacy of breast cancer chemoprevention in mutation carriers, but there are trials that have addressed its efficacy in women at increased risk for breast cancer, and mutation carriers were undoubtedly included in those trials. These trials indicate that tamoxifen (a selective estrogen receptor modulator-SERM), raloxifene (also a SERM), exemestane (an aromatase inhibitor) and anastrozole (an aromatase inhibitor), can all effectively reduce the risk of breast cancer if administered daily for five years (35). Of these drugs, only tamoxifen can be utilized in both pre- and postmenopausal women. The other agents (raloxifene, exemestane, and anastrozole) are utilized only in postmenopausal women.

In clinical trials, these agents have been shown to reduce the risk of developing breast cancer, but a mortality benefit has not been conclusively demonstrated (33). Moreover, there remains some concern that these agents are only effective in the primary prevention of estrogen receptor (ER)-positive breast cancer, and have no benefit in preventing ER-negative cancers. Thus, in the case of the BRCA mutation carriers, these agents might be beneficial for patients with BRCA 2 mutations but not for those who carry the BRCA 1 mutation (36). Approximately 77% of the breast cancers in BRCA 2 mutation cohorts are ER-positive (similar to breast cancer patients in the general US population), while 75% of the breast cancers in the BRCA 1 mutation carriers are ER-negative and 69% are triple negative (ER-negative, Progesterone receptor-negative, and human epidermal growth factor receptor negative) (9).

#### **Risk-Reducing Surgery**

For women who harbor a gene mutation that puts them at increased risk for breast cancer, risk-reducing surgery has been associated with the greatest potential benefit. However, there are no randomized trials that have examined the efficacy of risk-reducing surgery in mutation carriers. Observational studies suggest that for BRCA 1 and BRCA 2 mutation carriers, bilateral prophylactic mastectomy may reduce breast cancer risk by about 90% (9). Moreover, among BRCA 1 and BRCA 2 mutation carriers, bilateral prophylactic salpingo-oophorectomy may reduce ovarian cancer risk by about 80% (9). Additionally, there is some evidence to suggest that prophylactic bilateral salpingo-oophorectomy undertaken during the pre-menopausal years may reduce breast cancer risk by about 50% (presumably as a result of estrogen deprivation) for BRCA 1 and BRCA 2 mutation carriers, but that benefit may potentially be largely confined to BRCA 2 mutation carriers (37, 38). Thus, combining both bilateral prophylactic mastectomy (which by itself may reduce the risk of developing breast cancer by 90%) and bilateral prophylactic salpingo-oophorectomy may potentially reduce the risk of developing breast cancer by 95%. It should be emphasized that prophylactic salpingo-oophorectomy (rather than oophorectomy alone) should be recommended for BRCA 1 and BRCA 2 mutation carriers because these patients are also at increased risk for developing fallopian tube cancers (38).

Although the ESMO guidelines recommend that BRCA 1 and BRCA 2 mutation carriers undergo bilateral prophylactic salpingo-oophorectomy at age 35-40, the optimal age for undertaking bilateral prophylactic mastectomy is not specified (32). Breast cancer incidence increases rapidly in early adulthood until 30-40 years of age for BRCA 1 mutation carriers, and until 40-50 years of age for BRCA 2 mutation carriers, and thereafter both have a similar, constant incidence until age 80 (39). Most BRCA mutation carriers choose to undergo bilateral prophylactic mastectomy prior to bilateral prophylactic salpingo-oophorectomy. For mutation carriers who undergo bilateral prophylac-

tic mastectomy, the risk of finding an occult breast cancer is less than 5%, so a sentinel node biopsy is not generally warranted (32).

However, systematic biases pose a threat to the validity of any observational studies, and studies that have examined the effect of risk-reducing surgery, in particular, are prone to four biases: performance bias, attrition bias, detection bias, and selection bias (40). Performance bias may result if the performance of a specific risk-reducing operation is not confirmed in an objective way (i.e., from medical or surgical records), and the investigators instead rely on self-reports. Attrition bias may result if follow-up of patients who undergo risk-reducing surgery is different from that of the control group. For instance, patients who undergo risk-reducing surgery might be discharged from further follow-up while those without the surgery might continue to be followed, and the development of malignancies in the risk-reducing surgery group might therefore be reported less frequently. Detection bias may result if outcomes are not assessed in the same manner in both groups of the study. For instance, women who undergo risk-reducing mastectomy no longer require screening mammography, while those who choose not to have this operation continue to be screened. As a result, detection rates of occult cancers would be higher in women who do not undergo risk-reducing surgery. Finally, the baseline characteristics of women who undergo risk-reducing surgery may differ from those who do not, and this is referred to as selection bias. For instance, women who undergo risk-reducing surgery might come from a higher socioeconomic status with better access to healthcare, and this may potentially influence outcomes as well.

Moreover, any observational study suggesting a possible beneficial effect of bilateral salpingo-oophorectomy in reducing breast cancer risk are subject to selection bias (41). There are potentially important unmeasured differences between women in the oophorectomy and comparison groups, with the oophorectomy groups perhaps comprised of women with a lower baseline risk for breast cancer. Thus, a selection bias may at least partly account for the lower risk of breast cancer associated with BRCA mutation carriers who choose to undergo bilateral prophylactic salpingo-oophorectomy.

Mutation carriers who choose to undergo bilateral prophylactic mastectomy may consider three surgical options: total mastectomy, skin-sparing mastectomy, and nipple-sparing mastectomy (42). These procedures are generally done in conjunction with breast reconstruction. Total mastectomy refers to resection of the nipple-areolar complex, some skin overlying the breast, and the breast tissue. Of the three surgical options, this operation is the least technically challenging for the surgeon, but the cosmetic results are not optimal, and it is therefore not the preferred method of prophylactic mastectomy. Nipple-sparing mastectomy refers to resection of the breast only, with preservation of the nipple-areolar complex and the skin overlying the breast. The resection of the breast is generally done through an inframammary incision, although a semilunar incision along the nipple-areolar complex with extension of that incision medially and laterally, can also be utilized. The nipple-sparing mastectomy is perhaps the optimal procedure for preserving cosmesis and quality of life, but some breast ductal tissue may remain underneath the nipple following this operation, and this may slightly increase the risk of breast cancer. Finally, skin-sparing mastectomy refers to removal of the nipple-areolar complex and the breast, with preservation of the skin envelop overlying the breast. Cosmesis and quality of life is inferior when compared to nipple-sparing mastectomy, but less breast ductal tissue is likely to be left behind.

Surgeons should discuss these three surgical options with any patient who is contemplating prophylactic mastectomy. Illustrations are often helpful to aid the patient in better understanding these options. Moreover, the surgeon should inform the patient that bilateral prophylactic mastectomy does not completely eliminate the risk of breast cancer. At best, it will reduce risk by 90-95%.

## Conclusion

Any patient found to have a hereditary predisposition for breast cancer should be informed of all three options to reduce their risk: screening (preferably to include screening with MRI), chemoprevention, and risk-reducing surgery. Benefits and harms of each option should be discussed, and limitations of studies that have assessed the efficacy of these strategies mentioned as well. Patients should be actively involved in deciding which of these options might best suit them. Further studies are needed to better elucidate long-term outcomes following risk-reducing surgery. We also need to better understand what effect these risk-reducing strategies have on quality of life and how to optimize those outcomes.

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