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RISK AND PREVENTION (TB BEVERS SECTION EDITOR)

Current Approach to Breast Cancer Risk Reduction for Women with Hereditary Predispositions to Breast Cancer

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Abstract Risk reduction strategies for women at an increased risk for breast cancer include prophylactic mastectomy, prophylactic salpingo-oophorectomy, and chemoprevention. These techniques have been well studied in certain high-risk populations such as women with significant family histories of breast cancer and women with BRCA1 and BRCA2 mutations. Rapid evolution in genetic testing technology has enabled increased access and ability to analyze genes associated with an increased risk for breast cancer. These genes include but are not limited to BRCA1 and BRCA2. This technological progress has expanded the definition and number of women classified as having a genetic predisposition to breast cancer; however, literature specifically evaluating efficacy of breast cancer risk reduction strategies in this expanded population does not yet exist. In order to appreciate the effectiveness of risk-reducing strategies for women with a hereditary predisposition to breast cancer, we provide an overview of current literature and recommendations for risk-reducing mastectomy, risk-reducing salpingo-oophorectomy, and chemoprevention in the high-risk breast cancer population.

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Introduction

Hereditary predisposition to breast cancer encompasses well-known genes such as BRCA1 and BRCA2 as well as less common genes including ATM, CDH1, CHEK2, PALB2, PTEN, STK11, and TP53. These genes, along with other genes with less well-described risks, are suspected to account for a minority of breast cancer diagnoses. Women with hereditary predispositions to breast cancer are known to be at an increased risk for developing breast cancer throughout their lifetime. Additionally, hereditary predispositions to breast cancer can be associated with an increased risk for developing breast cancers at younger ages than the general population.

Strategies to reduce breast cancer risk include prophylactic mastectomy (bilateral or contralateral), prophylactic bilateral salpingo-oophorectomy, and chemoprevention. The efficacy of these strategies in reducing risk has been studied in women with a strong family history of breast cancer and in women with BRCA1 and BRCA2 mutations. Due to improvements in genetic testing technology, multiple hereditary cancer genes can now be analyzed simultaneously and are routinely tested for in a clinical setting. At this time, there are no studies proving survival benefit of these strategies in the less common genes associated with hereditary predispositions to breast cancer. However, genetic information obtained from this testing currently informs medical management decisions. Therefore, guidelines now incorporate recommendations for breast cancer prevention using literature available on these less common hereditary breast cancer predisposition genes.

These risk reduction strategies, although effective in reducing breast cancer risk, can have an impact on a women's psychosocial well-being. It is important to consider the physical and emotional impact of these strategies when discussing them with patients. Early detection through breast cancer screening and surveillance is also recommended to women with hereditary predispositions to breast cancer; however, this review will focus on risk-reducing strategies only and does not include a discussion of screening recommendations.

In order to describe the current approach to breast cancer risk reduction for women with hereditary predispositions to breast cancer, this review explores current literature regarding the efficacy of prophylactic bilateral salpingo-oophorectomy, chemoprevention, and prophylactic mastectomy. We also review the psychosocial impact of these strategies on women and topics for future research.

Genes Associated with Hereditary Predisposition to Breast Cancer

Disease-causing (pathogenic) mutations in the BRCA1 and BRCA2 genes are the most common cause of hereditary breast cancer. Based on recent studies, the risk of developing breast cancer by age 70 is estimated to be 49–60 % [1, 2]. However, there is significant variability in reported cancer risks associated with inherited BRCA1 and BRCA2 mutations. Studies using different methodologies suggest risks of breast cancer may vary between 65–85 and 45–84 % in BRCA1 and BRCA2 mutation carriers, respectively [3–8]. Moreover, BRCA1/BRCA2 mutation carriers have an estimated 10.8–40 % cumulative 10-year risk, 45.7 % 20-year risk, and 47.5 % 25-year risk of developing contralateral breast cancer [9–11]. There is an increased lifetime risk of other cancers including ovarian cancer, pancreatic cancer, prostate cancer, and possibly melanoma [1, 3, 5, 12–16]. Men carrying BRCA1/BRCA2 mutations also have an increased risk of breast cancer compared to the general population (1.2 % with a BRCA1 mutation and approximately 6–8 % with a BRCA2 mutation) [17, 18].

Additional rare hereditary cancer syndromes also confer high risk of developing breast cancer that are comparable to BRCA-related breast cancer risks. Other highly penetrant breast cancer predisposition genes include TP53, CDH1, PTEN, and STK11. Each of these conditions is associated with an increased risk to the development of other cancers. Our discussion will focus on lifetime breast cancer risks associated with these syndromes. Li-Fraumeni syndrome (LFS), associated with germline mutations in the TP53 gene, is known to be associated with increased lifetime risk of four core cancers, including adrenocortical carcinoma, soft tissue and bone sarcomas, brain cancer, and early-onset breast cancer. Lifetime risk of cancer with LFS approaches 93–100 % for females and 68–73 % for males [19, 20]. Hereditary diffuse gastric cancer syndrome (HDGC), associated with deleterious mutations in the CDH1 gene, causes high risk of lobular breast cancer and diffuse gastric cancer. Lifetime risk of breast cancer in CDH1 mutation carriers is estimated to be between 39 and 52 % [21–23]. PTEN hamartoma tumor syndrome or Cowden syndrome has a variable clinical presentation, but individuals with this genetic condition are at high risk of developing female breast cancer as well as other cancers. Cumulative lifetime breast cancer risk has been reported to be approximately 67–77 % in PTEN mutation carriers [24, 25]. Finally, STK11 is generally considered a hereditary colorectal cancer syndrome, but individuals with Peutz-Jeghers syndrome also have a high risk of developing female breast cancer. There is an estimated lifetime breast cancer risk of 31–50 % associated with STK11 mutations [26, 27]. These well-described hereditary cancer syndromes are recommended the same breast cancer screening and preventive therapies as BRCA1/BRCA2 mutation carriers given their well-described association with increased breast cancer risk.

Historically, PALB2 has been categorized as a moderately penetrant cancer predisposition gene [28–31]. A recent study published by Antoniou et al. [32] concluded that PALB2 has a higher risk of breast cancer than previously reported. Estimates of cumulative risk of breast cancer in PALB2 mutation carriers may approach that of highly penetrant genes, approximately 14–35 %. The cancer risks are estimated to be higher (58 %) in individuals with a significant family history of breast cancer [32]. For the purpose of this review, PALB2 will be included as a highly penetrant cancer predisposition gene. ATM and CHEK2 are moderately penetrant cancer genes for which current research has suggested a two- to fourfold increased risk for breast cancer compared to general population risk [33–38]. Professional societies and organizations such as National Comprehensive Cancer Network, Society of Surgical Oncology, and the American Society of Clinical Oncology have released surgical and medical recommendations for individuals who carry pathogenic mutations in highly penetrant and moderately penetrant genes, creating clinical guidelines for providers to utilize in interpreting and managing outcomes related to genetic testing results (Table 1). Other genes have been associated with an increased risk for development of breast cancer, but current literature is limited and insufficient to impact clinical management. Therefore, the following review will address current approaches to breast cancer risk reduction strategies in regards to highly penetrant cancer genes (BRCA1, BRCA2, TP53, CDH1, PTEN, STK11, and PALB2) and moderately penetrant cancer genes (ATM and CHEK2).

Table 1 Position statements and recommendations

	RRM [39]			RRSO [39, 40]			Chemoprevention [39, 41][a]		
	NCCN	SSO	ASCO	NCCN	SSO	ASCO	NCCN	SSO	ASCO
BRCA1/2	X	X	–	X	X	X	X	X	X
TP53	X	–*	–	–	–	–	–*	–*	–*
CDH1	X	–*	–	–	–	–	–*	–*	–*
STK11	X	–*	–	–	–	–	–*	–*	–*
PALB2	X	–*	–	–	–	–	–*	–*	–*
PTEN	X	–*	–	–	–	–	–*	–*	–*
ATM	No	–*	–	–	–	–	–*	–*	–*
CHEK2	No	–*	–	–	–	–	–*	–*	–*

X explicit recommendation, – no recommendations, * encompassed in general recommendations

[a] For all but BRCA1/2, chemoprevention can be recommended to any woman who is 35 years of age or older and have at least a 1.7 % predicted 5-year risk of developing breast cancer based on Gail model calculation

Risk-Reducing Strategies

In general, hereditary breast cancer accounts for approximately 5–10 % of breast cancer [42]. HBOC accounts for the vast majority of hereditary breast cancer. Due to the low prevalence of mutation carriers in other hereditary breast cancer predisposition genes (non-BRCA genes), robust data in this population are limited. The majority of data available focus on women who have known BRCA1/BRCA2 mutations or are at high risk of developing breast cancer based on personal and family history characteristics calculated by validated breast cancer risk calculation models. Moreover, due to the fact that conducting randomized clinical trials on the efficacy of prophylactic surgeries is considered unethical, the effects of risk-reducing mastectomy (RRM) and risk-reducing salpingo-oophorectomy (RRSO) on the reduction of breast and ovarian cancers are concluded based on observational cohort and case-control studies. The aforementioned inherent limitations to the studies that can be conducted in this population limit our understanding of the true breast cancer risk reduction associated with the strategies discussed below.

Risk-Reducing Mastectomy

Prophylactic bilateral and contralateral mastectomies are surgical risk reduction strategies performed on women with known hereditary predispositions to breast cancer. The efficacy of prophylactic mastectomy in women with a high risk for breast cancer due to family history or a pathogenic BRCA1 or BRCA2 mutation is well studied. However, similar studies have not been conducted for other types of hereditary breast cancer syndromes. Current NCCN guidelines recommend discussing the option of prophylactic mastectomy in women who have a known mutation in any of the high penetrance genes (BRCA1, BRCA2, CDH1, PALB2, PTEN, and TP53).

Bilateral

Bilateral prophylactic mastectomy has been estimated to have a 90–95 % breast cancer risk reduction for women at an increased risk for developing breast cancer [7, 43–47]. A study published by Hartmann et al. on the efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer indicated a reduction in the incidence of breast cancer of at least 90 % [7]. This study was later updated when clinical BRCA1 and BRCA2 analysis became available; of note, the analysis performed in this study was not comprehensive; thus, some mutation carriers were likely missed. The updated study indicated a similar (89.5–100 %) risk reduction in BRCA1- and BRCA2-positive women who underwent bilateral prophylactic mastectomy [43]. Several additional studies have indicated similar breast cancer risk reduction in women with a BRCA1 or BRCA2 mutation after undergoing bilateral prophylactic mastectomy [44–47]. A study by Evans et al. concluded that risk-reducing mastectomy is highly effective after studying the outcome of risk-reducing mastectomy in 550 women with a 25–80 % lifetime risk of breast cancer, either based on calculations using personal and family history or based on known hereditary risk. After greater than 334 women years of follow-up, none of the women had developed breast cancer at the time of the study, further validating the 90–95 % risk reduction conferred in high-risk women who pursue prophylactic bilateral mastectomy [46]. These publications provide considerable evidence for the efficacy of bilateral prophylactic mastectomy; however, it should be noted

that limitations exist in all of these studies. In addition to the limitations discussed in the opening paragraph of this section, a common limitation is length of follow-up time, given that some of these studies are based on 10 years or less of follow-up time; thus, the women in these studies may develop breast cancer later on outside of the study window. Other limitations such as ascertainment bias were addressed using various research techniques by the researchers.

Contralateral

Several studies have attempted to determine the efficacy of contralateral prophylactic mastectomy in women who have unilateral breast cancer and are at an increased risk for breast cancer based on family history or a known hereditary cancer syndrome. Considering strong evidence indicating bilateral prophylactic mastectomy is associated with a significant reduction of risk in women at an increased risk of developing breast cancer, it is reasonable to assume that contralateral prophylactic mastectomy in this population would also show a reduction in risk for development of contralateral breast cancer. Overall, research has shown contralateral prophylactic mastectomy decreases the risk for women in the high-risk population to develop contralateral breast cancer [48–50, 51•, 52, 53•, 54•]. Some studies have also concluded that contralateral prophylactic mastectomy improves survival in the high-risk population [49, 50, 53•]. However, after controlling for confounding factors and assessing several studies on this topic, contralateral prophylactic mastectomy has not been shown to improve survival among women at an increased risk for breast cancer [54•]. It is important to note that studies on this topic include several limitations; thus, the data produced may not reflect the actual risk reduction conferred through contralateral prophylactic mastectomy in the high-risk population.

There are a limited number of publications looking at the efficacy of contralateral prophylactic mastectomy in women at a high risk for breast cancer based on family history or genetic predisposition. A recent review by Fayanju et al. conducted a meta-analysis looking at the efficacy of contralateral prophylactic mastectomy based on two studies in which all patients had a BRCA1 or BRCA2 mutation and two studies in which all patients had a family history of breast cancer [49, 50, 51•, 52, 54•]. Contralateral prophylactic mastectomy was not associated with improved overall survival in the stratified meta-analysis [54•]. Additionally, the meta-analysis indicated that women with an increased risk for breast cancer who underwent contralateral prophylactic mastectomy did not experience a significant decrease in breast cancer-related mortality as compared to women at an increased risk for breast cancer who did not undergo a contralateral prophylactic mastectomy [54•]. However, the meta-analysis did indicate that relative and absolute risks of contralateral breast cancer were significantly decreased in women with an increased risk for breast cancer who underwent prophylactic contralateral mastectomy as opposed to those who did not [54•]. These findings suggest that contralateral prophylactic mastectomy may be considered in women with unilateral breast cancer who are considered to be at an increased risk to develop breast cancer. However, it is important to note that all of the studies used in this meta-analysis have significant limitations and confounding factors. One significant limitation is that some of the publications included in the analysis did not require a standard time at contralateral prophylactic mastectomy, such as only including women who had contralateral surgery at the time of primary surgery. Thus, data from these studies are inconsistent with relation to the time range from diagnosis to contralateral prophylactic mastectomy which could result in a bias such that healthier women are undergoing contralateral mastectomy, therefore, leading the data to suggest lower risks and higher survival rates. Selection bias may also be a limitation in these studies as women who undergo contralateral prophylactic mastectomy may have less aggressive tumors at baseline. However, this theory is contradicted by other data that indicate larger tumor size is associated with choosing contralateral mastectomy [55–57]. Additional limitations exist, including survival bias, and are individual to each study included in this meta-analysis. In summary, the meta-analysis looking at the efficacy of contralateral prophylactic mastectomy in women at an increased risk for breast cancer based on genetic predisposition or family history indicated that contralateral prophylactic mastectomy in this population would significantly decrease the risk of contralateral breast cancer but will not necessarily prolong the women's lives.

Type of Surgery

Data exists regarding differences in efficacy of prophylactic mastectomy based on surgery type including total (simple) mastectomy, total skin-sparing mastectomy, and subcutaneous mastectomy. All surgery types when performed prophylactically have been associated with a significant reduction in breast cancer risk for woman at an increased risk for breast cancer [7, 58•]. However, data indicates that bilateral total, total skin-sparing mastectomy, or technically appropriate nipple-sparing mastectomy should be the preferred surgical procedure as subcutaneous mastectomy leaves behind more glandular tissue than the other approaches resulting in a risk for future cancers compared to the other approaches [44, 58•]. Nipple sparring mastectomy has been shown to be as effective in reducing breast cancer risk in BRCA1 and BRCA2 mutation carriers as total and total skin-sparring mastectomy when performed using precise technique as detailed by Manning et al. [58•]. There are no current practice guidelines recommending a specific type of prophylactic mastectomy at this time. Surgical practice may differ depending on center,

surgeon, and patient characteristics as with any medical practice.

Risk-Reducing Salpingo-oophorectomy

Current NCCN guidelines recommend RRSO starting at the age of 35–40 and 40–45 for women who have a known BRCA1 and BRCA2 mutation, respectively. RRSO is a well-established surgical intervention recommended for women with known BRCA1/BRCA2 mutations due to their high risk of developing ovarian cancer. Studies have shown that RRSO reduces risk of ovarian cancer in BRCA mutation carriers by approximately 80 % [59–62]. Additionally, it has been suggested that RRSO in BRCA mutation carriers may be associated with approximately 50 % decreased risk of breast cancer [45, 63, 64]. The benefit of breast cancer risk reduction may be most pronounced in premenopausal women who undergo RRSO under the age of 50 [63, 65–67]. For women undergoing RRSO prior to the age of 50 and opting for short-term hormone replacement therapy, research suggests that there is no decrease in protective effects of RRSO in reducing breast cancer risks [68]. Moreover, studies suggest that there is an overall increase in life expectancy and decrease in all-cause mortality and breast cancer- and ovarian cancer-specific mortality following RRSO in women with BRCA1/BRCA2 mutations, thus further supporting the recommendation of this surgery in this high-risk population [62, 66, 69•].

Several authors have discussed limitations regarding the study designs and statistical analyses of these studies beyond the fact that randomized clinical trials were not conducted [70•, 71]. For example, some studies included research participants in their analyses who have had previous diagnoses of breast cancer, which may introduce a selection bias favoring either the surgery or surveillance group. Other limitations include immortal time bias relating to when follow-up is initiated for participants who elect RRSO and those who choose surveillance, small sample size, and short duration of follow-up. Therefore, these studies may have inflated the significance of breast cancer risk reduction in BRCA mutation carriers who undergo RRSO.

In an unmatched prospective study of 98 women who have a BRCA1 mutation, Kramer et al. estimated a 62 % breast cancer risk reduction in those women who underwent RRSO compared to the control group who did not [63]. However, a selection bias may have been introduced in their study design as their research participants were recruited through high-risk familial ovarian cancer families for which those families may have inherently lower risk of development of breast cancer. A large matched case-control study of BRCA1 and BRCA2 mutation carriers reported similar breast cancer risk reduction estimates of 56 and 46 % in BRCA1 and BRCA2 mutation carriers, respectively [64]. Mavaddat et al. followed 1887 women with known BRCA1 or BRCA2 mutations prospectively and estimated a RRSO-associated breast cancer risk reduction of 48 % in BRCA1 mutation carriers and 21 % in BRCA2 mutation carriers, though their data did not reach statistical significance [2].

A recent study published by Heemskerk-Gerritsen et al. replicated the study designs and statistical analyses of four previous research studies in their Dutch cohort of BRCA1 and BRCA2 mutation carriers and reached a similar breast cancer risk reduction of 38–64 % following RRSO [71]. However, when they used their own proposed study design and statistical analysis that eliminated ascertainment bias and immortal time bias, the researchers did not find a statistically significant reduction of breast cancer risk in women with a BRCA1/BRCA2 mutation following RRSO. Therefore, they concluded that previous estimates of breast cancer risk reduction following RRSO may be inflated due to various study design and analytical biases. In response to the published data of this research, Chai et al. [70•] re-analyzed data supplied by Kauff et al. [61] and Domchek et al. [45]. The authors accounted for immortal time bias and reached similar conclusions as previous studies, with a breast cancer risk reduction of approximately 41–50 % following RRSO, thereby supporting previous evidence that RRSO confers protective effects on development of breast cancer in BRCA1/BRCA2 mutation carriers.

Several studies report a more significant breast cancer risk reduction in BRCA1 mutation carriers following RRSO [63, 66, 67]. It has been postulated that the breast cancer risk reduction associated with RRSO may be attributable to estrogen deprivation in breast tumor development [59, 72–75]. However, women with BRCA1 mutations are more likely to develop estrogen, progesterone, and Her2-neu receptor-negative (triple negative) breast cancers [76, 77]. The specific breast cancer pathology studied in these publications was not specified; therefore, it is not possible to determine what percentage are triple negative- versus ER-positive breast cancer. Other studies did report a higher breast cancer risk reduction in BRCA2 mutation carriers compared to BRCA1 mutation carriers [59, 61]. Thus, conclusions from these studies may contradict current understanding of the role of RRSO in prevention of breast cancer.

Available research provides inconsistent evidence supporting RRSO as an effective breast cancer risk reduction strategy in women who have a known BRCA1/BRCA2 mutations. Current recommendation for BRCA1/BRCA2 mutation carriers to undergo RRSO upon completion of childbearing is based on the well-established ovarian cancer risk reduction and decrease in ovarian cancer-related mortality in this high-risk population. As breast cancer risk reduction associated with RRSO has not been established in other breast cancer hereditary predisposition genes or in women at high risk of developing breast cancer, current guidelines do not recommend consideration of RRSO

in other high and moderately penetrant genes for the purpose of breast cancer risk reduction.

Chemoprevention

Selective estrogen-receptor modulators (SERM) tamoxifen and raloxifene are U.S. Food and Drug Administration (FDA)-approved medications that can be prescribed to women for the prevention of breast cancer. Tamoxifen has been reported to reduce the risk of breast cancer by 50 % in premenopausal women, and studies have reported the efficacy of tamoxifen and raloxifene in the prevention of breast cancer in postmenopausal women who are at high risk of developing breast cancer [78, 79]. Moreover, tamoxifen use following a breast cancer diagnosis is known to be an effective treatment in preventing ER+ breast tumor recurrences and new primary tumors [80].

However, data on the use of tamoxifen in women with known BRCA1/BRCA2 mutations are limited. Women with BRCA1 or BRCA2 mutations are at increased risk of primary and contralateral breast cancer. Studies have evaluated the use of tamoxifen in BRCA mutation carriers and their effects of breast cancer risk reduction for primary and second primary breast cancer. As a subset study of the National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial, King et al. [81•] concluded that tamoxifen use in BRCA2 mutation carriers reduces the risk of breast cancer by 62 %. Tamoxifen use in BRCA1 mutation carriers was not associated with any breast cancer risk reduction. However, due to the small sample size of the study, their results did not reach statistical significance [81•]. Duffy and Nixon [80] evaluated previous randomized studies and the effect of tamoxifen in prevention of primary and recurrent/second primary breast cancer based on ER tumor status. The authors concluded that tamoxifen use for the prevention of primary and secondary ER+ breast cancer is significant in both BRCA1 and BRCA2 mutation carriers; however, the effect may be more pronounced in BRCA2 mutation carriers. Their data regarding tamoxifen use and prevention of ER− breast cancer in BRCA1/BRCA2 mutation carriers did not reach statistical significance, and conclusions could not be drawn for this criterion [82•]. Other cohort and case-control studies have reported a 50–62 % and a 67–68 % reduction in CBC in BRCA1 and BRCA2 mutation carriers, respectively [83, 84, 85]. Limitations to these studies include confounding factors where women who took tamoxifen were more likely to have been treated with chemotherapy and have undergone BSO; both of which are factors that may also reduce risk of CBC, small sample size, and absence of information on the ER status of tumors [83, 85].

The majority of BRCA1 mutation carriers develop ER− breast cancer. Several studies report protective effects of tamoxifen in the prevention of primary and CBC risks in BRCA2 mutation carriers. However, the protective effects in BRCA1 mutation carriers appear to be less clear. If the majority of BRCA1 mutation carriers develop ER− breast cancer, the assumption is that tamoxifen use would not confer the same protective effects as it would in women who carry a BRCA2 mutation. However, several studies still suggest primary breast cancer and CBC risk reduction with tamoxifen use in BRCA1 mutation carriers [83, 84, 85]. One explanation is that tamoxifen may still be an effective agent in the prevention of ER+ breast cancer for BRCA1 mutation carriers.

There is a lack of research on the efficacy of tamoxifen in the prevention of breast cancer in other hereditary breast cancer predisposition genes. However, as early studies of tamoxifen have been demonstrated to be effective in prevention of primary and CBC development in women who are at high risk of developing breast cancer based on personal and family history, the use of tamoxifen as a chemoprevention agent has been extrapolated to include women who carry mutations in other genes that predispose them to a high or moderate risk of developing breast cancer. Current NCCN guidelines recommend the option of tamoxifen as a chemoprevention agent in women who have a known mutation in the BRCA1 and BRCA2 genes and any woman who is 35 years of age or older and have at least a 1.7 % predicted 5-year risk of developing breast cancer based on Gail model calculation, including individuals with a mutation in other high and moderately penetrant genes (ATM, CDH1, CHEK2, PALB2, PTEN, and TP53) if they have a predicted 5-year breast cancer risk of at least 1.7 %. There are currently no data available on the effectiveness of raloxifene in the prevention of breast cancer in postmenopausal women with a hereditary breast cancer predisposition.

Genes other than BRCA1 and BRCA2 associated with a well-described high risk for breast cancer are often included in risk reduction recommendations made for BRCA1 and BRCA2 mutation carriers. The research described above is based on individuals with BRCA1 or BRCA2 mutations or a significant family history of breast cancer, and the efficacy of these strategies has not been evaluated for other hereditary cancer predisposition genes. However, it is reasonable to utilize data indicating the efficacy of prophylactic mastectomy and chemoprevention in women at an increased risk for breast cancer due to family history or BRCA1 or BRCA2 mutations to legitimize the recommendations for consideration of utilizing these strategies for women at an increased risk for breast cancer due to other types of hereditary predisposition.

Psychosocial Impact of Risk-Reducing Strategies

The risk-reducing strategies discussed above, although efficacious in decreasing an individual's risk for breast cancer, are

significant procedures and treatments with potentially profound psychosocial implications.

Several studies have assessed the psychosocial impact of and satisfaction with prophylactic mastectomy [86–89]. In general, studies have found that prophylactic mastectomy is associated with decreased anxiety related to developing breast cancer [86–88, 90]. Several studies note some negative experiences with prophylactic mastectomy which include but are not limited to breast pain, discomfort, lost or much reduced sexual sensation, problems with body image, and reduced enjoyment during sex [86, 87, 89]. As expected, studies have also found that the psychosocial impact of prophylactic mastectomy decreases over time; thus, it is important to assess women's perspective on the procedure at various points in time.

The impact of prophylactic salpingo-oophorectomy on quality of life is well studied. Many studies have concluded that although women experience symptoms associated with surgically induced menopause including increased vasomotor symptoms and decreased sexual function, most women are satisfied with the procedure and have decreased anxiety related to ovarian and breast cancer risk [91–97]. Decreased quality of life has been observed in the months directly following the procedure but has been found to return to baseline within a year [91].

Psychosocial issues pertaining to chemoprevention are varied. Research indicate mixed findings ranging from no impact to vasomotor and sexual function issues similar to those experienced by women who have undergone prophylactic risk-reducing salpingo-oophorectomy [98–100]. Upon assessing the impact of chemoprevention on quality of life, research suggests that treatment-related side effects do not impact psychosocial well-being [98].

Medical and surgical breast cancer risk reduction strategies, although generally found to have favorable psychosocial outcomes including reducing cancer-related anxiety, have potentially serious physical and emotional side effects. It is important that the impacts of these interventions are comprehensively discussed in order to promote autonomous and informed decision making.

Conclusions

Future Directions

Mutations in the BRCA1 and BRCA2 genes are the most common hereditary cause of breast cancer. Though limited, most of the research on breast cancer prevention strategies in women who have a hereditary predisposition of breast cancer is focused on individuals with BRCA1/BRCA2 mutations. Therefore, there is limited data on the efficacy of the previously described prevention strategies in women who have mutations in other genes that predispose them to an increased risk of breast cancer. Moreover, there is limited data on long-term outcomes of women electing prophylactic mastectomy (bilateral or contralateral), bilateral salpingo-oophorectomy, or chemoprevention in this population who have a hereditary predisposition to development of breast cancer, including BRCA1 and BRCA2 mutation carriers. Medical and psychosocial impacts of these breast cancer prevention strategies should be thoroughly explored in prospective studies to better appreciate the risks associated with these strategies. With additional research, patients may be better counseled on the risks, benefits, and limitations of these strategies, which will lead to a more informed decision-making process and better patient outcomes in this high-risk population.

Compliance with Ethical Standards

Conflict of Interest Grace Tran, Monica Helm, and Jennifer Litton 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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