REVIEWS

Breast conserving surgery and radiation as a choice for patients with BRCA mutations

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Abstract

Patients who are diagnosed with early stage breast cancer and who test positive for the BRCA1 and/or BRCA2 genetic mutations have been considered better candidates for bilateral mastectomy (ipsilateral therapeutic and contralateral prophylactic) as an accepted standard of care as compared to breast conserving surgery. Recently the increasing evidence that mastectomy may not be required has prompted us to review the literature and develop evidence-based recommendations in order to allow patients the option of mastectomy avoidance as long as they are well-informed and agreeable to close surveillance.

Key words

BRCA, Genetics, Breast conservation, Mastectomy, Breast cancer, Radiation

1 Introduction

Multiple studies have demonstrated equivalent overall and disease-free survival for breast-conserving surgery and radiation in patients with early-stage breast cancer treated by lumpectomy and post-operative radiotherapy compared to mastectomy in women who desire breast preservation; two with more than 20 years of follow-up [1, 2]. However, most women facing early stage breast cancer who express BRCA1 and BRCA2 mutations are recommended to undergo bilateral mastectomy with therapeutic (ipsilateral) and prophylactic (contralateral) intent due to higher rates of recurrence. We challenge this view by summarizing the world literature and developing evidence-based conclusions that support breast conservation therapy followed by close observation, in lieu of mastectomy. We hypothesize that breast-conservation surgery and radiation remains a safe and effective treatment in germline carriers when combined with other risk reduction strategies and close surveillance. The purpose of this selective review paper is to provide an up-to-date overview of the current evidence.

2 The nature of the problem

BRCA1 and BRCA2 genes confer a 50% to 85% lifetime risk of breast cancer and a 15% to 40% lifetime risk of ovarian cancer [3, 4]. Furthermore, some authors have shown a higher rate of ipsilateral and contralateral breast tumor recurrence

among those carriers [5, 6]. Concerns regarding the success of breast-conserving therapy in BRCA mutation carriers have emerged, causing many women to opt for prophylactic mastectomy since this procedure has shown to reduce risk of breast cancer in those carriers by 90% [7-9]. However, mastectomy can be a psychologically devastating choice that affects self-image for the patients' entire life [10].

More recently, some authors have raised the hypothesis that patients with a BRCA mutation could have breast cancers that are more radiosensitive, with a high rate of local control [11-14]. These reports arise from the observation that these genes appear to be involved in DNA damage repair, and that the rate of cell death after exposure to ionizing radiation increases in the presence of mutations of these genes [14].

3 Molecular and genetic determinants

Significant advances have been made in understanding genetic events that contribute to breast cancer development and also in its response to ionizing radiation treatment. Somatic or inherited, mutations in tumor suppressor genes may play an important role in the early process of malignant transformation and are common in breast cancer [15]. Some reports showed that mutations in the BRCA1, and BRCA2 tumor suppressor genes, PTEN or p53, have been associated with breast cancer formation, although approximately only 7% to 10% of newly diagnosed breast cancer patients carry a mutation [15].

Over the last decade, researchers have made significant discoveries in how BRCA1 and BRCA2 are involved in the process of DNA damage repair and in the preservation of genomic integrity [11, 15].

It is known that ionizing radiation induces DNA damage and subsequent cell death. The double-strand break is the most difficult damage to repair and the effectiveness of this repair constitutes a major determinant of radiation sensitivity [16].

Because BRCA1/BRCA2 appear to be involved in DNA double-strand fracture repair, it is possible that tumor cells in mutation carriers may be more radiosensitive compared to wild type patients, showing high rates of cell death with subsequent increased local control and higher rates of cure [14].

4 Clinical and pathologic characteristics

According to the Centers for Disease Control and Prevention (CDC), breast cancer is the most common cancer among women in the United States. In 2007 a total of 202,964 diagnosed cases and 40,598 deaths were recorded. Approximately 7% to 10% of newly diagnosed breast cancer patients carry genetic mutations [15]. Of these cases, the genes BRCA1 and BRCA2 account for 65% of the mutations in the familial breast cancer cases [17].

In their meta-analysis, of 22 studies, Antoniou et al. [18] showed the average risks of breast and ovarian cancer are higher in BRCA1 than in BRCA2 mutation carriers. Women carrying a BRCA1 mutation face a 65% risk of breast cancer and a 39% risk of ovarian cancer by age 70, with the corresponding estimates for BRCA2 being 45% and 11%. Another study among Ashkenazi Jewish women with inherited mutations of the tumor suppressor genes BRCA1 and BRCA2 have also reported that the risk of breast cancer for this population appears to be increasing with time [19]. The lifetime risk in mutation carriers born before 1940 was 24% and among those born after 1940 it was 67%; suggesting that non-genetic factors may significantly influence penetrance of mutations.

Some reports demonstrated that BRCA mutated genes appear to be involved not only in an increased risk of female breast and ovarian cancer but also in a higher risk of colon, gastric, fallopian tube, pancreatic and uterine cancer for BRCA1 [20, 21] and male breast, prostate, pancreatic, gallbladder, gastric and melanoma in association with BRCA2 [22].

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Breast cancer in BRCA1/2 mutation-carriers is characterized by younger age at diagnosis and a higher incidence of metachronous contralateral cancer, with the yearly rate of 3.1% significantly more expressive than 0.7% in non-carriers [6, 23, 24].

The relationship among BRCA mutations, early age at diagnosis and the prevalence of breast and ovarian cancer has been widely reported [6, 18, 23, 24]. Recently, some authors also demonstrated a remarkable association between triple-negative breast cancer (TNBC) and BRCA mutations [25-27]. TNBC has been classified as a subgroup of breast cancer negative for estrogen and progesterone receptors and receptor 2 of human epidermal growth factor (her 2 neu). The TNBC phenotype accounts for approximately 15% of all breast cancer cases and is associated with a relatively poor prognosis. Meyer et al. [26] found among patients diagnosed with TNBC a 20% germline mutation rate in BRCA1/2 genes. Comen et al [27] also reported an association between TNBC and BRCA mutations, which was not limited to young women. The results of these studies suggest that women with TNBC, despite age at diagnosis and a family history of breast and ovarian cancer, should be offered complete genetic testing.

5 Psychological effects following mastectomy

The primary goal when treating breast cancer is increased overall and disease-free survival. However, physicians need to be aware of the impact of surgery on the breast cancer patients' quality of life. Mastectomy is an irreversible surgical disfiguration with physical and psychological consequences that must be taken into account when making decisions.

BRCA1 and BRCA2 testing is frequently offered for some newly diagnosed high-risk breast cancer patients at the time of diagnosis. This practice provides information on their mutation status and can assist in medical decision-making. Conversely, this practice has led women to make decisions under duress and to quickly initiate treatment for fear of the malignancy. Decisions to undergo more extensive surgery such as unilateral mastectomy (UM) to treat their current cancer and prophylactic mastectomy (PM) of their unaffected breast, are sometimes made after genetics counseling but without adequate psychological counseling and the sharing of information [24, 28]. Physicians need to be aware of the impact of surgery on the breast cancer patients' quality of life.

Some reports have shown higher distress levels among mutation carriers opting for PM than those opting for surveillance. This is likely influenced by factors such as cultural variations [29-31], incidence and mortality patterns in relatives [24, 31, 32], marital status and earlier pregnancy [24], having young children, and the doctors' approach in giving information about other preventive strategies [28, 31, 33].

Frost, et al in their study with 609 women with a family history of breast cancer and who elected to undergo bilateral prophylactic mastectomy, showed that regret was more often reported when the physician recommendation was the main reason for women to consider this procedure [34]. Metcalfe also demonstrated high levels of psychological distress among some patients after PM because they continue to overestimate their breast cancer risk [35].

Several studies showed adverse effects on body image, feminine identity and sexual relationships in women undergoing prophylactic mastectomy [34-39]. Furthermore, Weitzel et al. strongly suggest that the health care professional involved in these patients' treatment be aware of the consequences of the genetic information delivery upon their patients' choices [24]. It is worth noting that part of the role of the health care professional is to provide available data in order for the patients to weigh the options on their own.

6 Evidence supporting breast conservation and close observation

As a result of the widespread availability of genetic testing for hereditary breast cancer, individuals who have not developed cancer but come from a family with a strong history of breast cancer may wish to characterize their risk of

developing malignant lesions in order to consider treatment alternatives. Some authors have written guidelines to provide prophylactic options for high-risk women and include: surveillance (consisting of self-examination of the breast, regular physical examinations by a physician and screening with different imaging techniques); chemoprevention therapy (e.g. tamoxifen); and risk-reducing surgery [40, 41].

In their study of 236 Canadian women with BRCA1 or BRCA2 mutations who underwent surveillance with annual screening examination, Warner et al. demonstrated that the combination of magnetic resonance imaging (MRI), ultrasound and mammography had a sensitivity of 95% compared with 45% for mammography and clinical breast examination. They concluded that the addition of MRI and ultrasound to annual screening with mammography and clinical breast examination every 6 months improved the sensitivity of surveillance for detecting early breast cancers [42]. Similarly, in a study of 529 women with increased familial risk who were suspected or proven to carry a BRCA mutation, Kuhl et al. have also demonstrated that MRI conveyed significantly higher sensitivity (91%) than mammography (33%) and ultrasound (40%) or the combination of both (49%) [43].They suggested that MRI be incorporated into the surveillance recommendations for women at high familial risk, allowing an earlier diagnosis of breast cancer. These two recent studies suggest that surveillance with MRI might benefit women at high risk. Two additional studies report that breast MRI is more accurate than mammography in detecting breast cancer in women at high risk, being almost twice as sensitive [44, 45]. Annual MRI has been included into the current practice guidelines for BRCA carriers [46].

Another challenge is how to manage non-carriers in a family with a BRCA mutation. Previous studies have shown that in high-risk families, women who test negative for the family-specific mutation have an increased risk of breast cancer and should be considered for continuing surveillance [47, 48]. More recently, Tilanus-Linthorst showed that increased surveillance, or any other preventive recommendation after a negative test for the family mutation, was unsuitable for these women [49]. In addition, more recent data from a study of 3,047 population-based families recruited from three countries showed that non-carriers from a family with a BRCA mutation do not have any increase in breast or ovarian cancer risk compared with the general population [50]. These results suggest that the practice of guiding non-carriers in affected families toward prophylactic options is inappropriate, and that these patients should follow screening guidelines for the general population.

7 Chemoprevention

Studies in the general population have supported the use of tamoxifen to protect against contralateral breast cancer [51, 52]. In a large case-control study, Narod et al. found that tamoxifen reduces the risk of contralateral breast cancer by 50% in BRCA1 and BRCA2 mutation carriers [53]. Moreover, in a matched case-control study, Gronwald et al. studied 285 women with bilateral breast cancer and 751 control women with unilateral breast cancer. Cases and controls were carriers of BRCA1 or BRCA2 mutations. They found a 50% risk-reduction for contralateral breast cancer in carriers of BRCA1 and BRCA2 mutations when treated with tamoxifen for the initial breast cancer, and suggest that tamoxifen may be effective in BRCA mutation carriers regardless of the mutation status [54].

Prophylactic bilateral salpingo-oophorectomy (PBSO) is often recommended to BRCA-carriers to reduce the risk of ovarian cancer, as the ovarian epithelium is removed, which, consequently reduces the risk of breast cancer by reducing the exposure of the breast to ovarian hormones. Early studies have shown that prophylactic oophorectomy in premenopausal women has a protective effect against breast cancer in these high-risk patients [55, 56]. Upon analyzing 1,439 patients with breast cancer and 1,866 matched controls from a registry of BRCA1 and BRCA2 carriers, Eisen et al. found 56% of reduction in breast cancer risk for BRCA1 and 46% for BRCA2 carriers after history of oophorectomy. In addition, they found that the protective effect was greater for women who underwent the procedure before age 40 [57]. Other studies suggest a protective effect of PBSO against ovarian and breast cancer in women who carry BRCA mutation and advocate the practice of performing this surgery in mutation carriers after childbearing is completed [58]. The primary concern about

PBSO that causes the younger patients to reject the surgery is the premature menopause that might be associated with increased risk of cardiovascular disease and osteoporosis [59, 60].

A more radical strategy for breast cancer risk reduction is the removal of the mammary tissue. Prophylactic Mastectomy (PM) has been shown to reduce the risk of developing breast cancer by as much as 90% in some studies [7-9, 61]. Although PM has been performed for decades, there is little information on the long-term effectiveness of the procedure and most retrospective studies did not show benefits in overall survival [61-63]. More recent studies have shown that PM is associated with a small improvement in survival but mainly in young women, with earlier stage and negative estrogen receptor status. Using data from the Surveillance, Epidemiology, and End Results data base, Bredosian et al. identified 107,106 women with breast cancer treated with mastectomy between 1998 and 2003. Of these patients, 8,902 women also underwent contralateral prophylactic mastectomy (CPM). In a univariate analysis, CPM was associated with improved disease-specific survival and it was mostly observed among women younger than 50 years of age with early-stage ER-negative tumors [64].

Decision-making management of women with BRCA mutations is very complex and the fear of presenting with more advanced disease despite close observation might have led many of these women to choose more aggressive therapy such as PM. However, since the impact of this surgery on survival is currently under debate, we believe that the options of less mutilating effective treatment and close surveillance strategy should be thoroughly discussed with these patients.

Rennert et al., in their larger population-based study of Israeli women who were diagnosed with breast cancer, reported that the presence of a BRCA mutation did not significantly impact overall survival among the Ashkenazi Jewish women followed for a minimum of 10 years [65]. Similarly, a second study compared breast cancer survival and recurrence rates between BRCA1/2 mutation carriers and non-carriers among 715 patients identified with 739 breast cancer cases. The investigators concluded that there was no difference in either overall or breast cancer-specific survival between women of both groups [66]. One of the limitations of this study was the short average follow-up period of only 50 months. In addition, Brekelmans et al. selected 103 BRCA2-, 223 BRCA1- and 311 non-BRCA1/2 patients with breast cancer from the Rotterdam Family Cancer Clinic and compared them with a group of 759 patients with sporadic breast cancer. Among the four groups, the authors did not find a significant difference in breast cancer specific survival, for node-negative or node-positive tumors [23].

Table 1. Breast-Conserving Surgery and Radiotherapy in BRCA Carriers

Sources		**Genetic Cohort**			**Sporadic Cohort**	
	# of Patients		Years of follow-up	# of Patients		Years of follow-up
Robson et al 1999 (6)	28	14.9% 22%	5 10	277	4.5 % 6.9%	5 10
Pierce et al 2000 (67)	71	4.2%	5	213	3.7%	5
Haffty et al 2002 (5)	22	22% 41%	5 10	105	15% 19%	5 10
Pierce et al 2006 (69)	160	12% 24%	10 15	445	9% 17%	10 15
Kirova et al 2010 (70)	29	36%	Median 13.4	58	33%	13.4

Although the National Comprehensive Cancer Network (NCCN Guidelines Version 1.2012) considers breast-conserving therapy a relative contraindication for known or suspected BRCA mutation carriers [46], keeping the debate alive, the opinions regarding the appropriateness of this therapy have been on the rise. Some authors report similar outcomes to those observed in sporadic breast cancer patients while others suggest higher rates of in-breast tumor recurrence among BRCA mutation carriers [5, 6, 14, 67, 68] (Table 1). Turner et al. presented one of the first reports showing the rates of in-breast

recurrence in BRCA1/2 mutations [68]. They identified 52 breast cancer patients treated with lumpectomy and radiation therapy that developed an ipsilateral breast tumor recurrence (IBTR) and studied the rate of BRCA mutations in these patients. Fifty-two patients had local relapse and 8 (15%) of these 52 patients showed a deleterious BRCA1/2 mutation. When analyzed by age, 6 (40%) of 15 patients with IBTR under age 40 carried the mutation compared to only 1 (6.6%) of 15 matched control patients without an IBTR. The results of this study provide evidence that BRCA patients experience a higher rate of in-breast recurrence when treated with lumpectomy and radiotherapy. However, the relatively long time to recurrence as well as the analyses of the pathology and location of the relapses, suggest that these recurrent cancers might represent second primary tumors.

In another report designed as a retrospective cohort study and with data from 11 institutions in the United States, Pierce et al. [69] (Table 1) compared the outcomes of breast-conserving surgery and radiotherapy in 160 breast cancer patients carrying a BRCA1/2 mutation with 445 matched sporadic controls. The primary goal of this study was to evaluate the rates of ipsilateral breast tumor recurrence (IBTR) and contralateral breast cancers among carriers versus non-carriers. The average follow-up for mutation carriers was 7.9 years versus 6.7 years for controls. The authors did not find a significant difference in IBTR between carriers and controls treated with breast-conserving surgery and radiotherapy.

Recently, Kirova and colleagues investigated whether mutation status influenced the rates of ipsilateral and contralateral breast cancer after breast-conserving treatment [70]. In patients with a family with history of breast and/or ovarian cancer treated with breast-conserving surgery and radiotherapy they found no significant difference in ipsilateral tumors among BRCA mutations carriers, non-carriers and controls.

Some authors have raised the hypothesis that BRCA carriers have a tendency toward severe radiotherapeutic complications and have questioned the safety of radiotherapy in these patients. To clarify this issue, Pierce et al. [67] compared 71 women with BRCA1/2 mutations with Stage I or II breast cancer treated with breast-conserving surgery and radiotherapy to 213 women with sporadic breast cancer. They found no evidence of increased acute and chronic skin, subcutaneous, bone or pulmonary toxicity in BRCA mutations compared to controls. Similar rates of local control and survival were observed between the genetic cohort and sporadic cohort at 5 years. Though follow-up was limited, these data demonstrate the feasibility and safety of adjuvant radiotherapy for germline mutation patients.

8 Conclusion

Considering the equivalent rates of local control for breast-conserving therapy and unilateral mastectomy among mutation carriers and given the lack of data regarding the survival benefits of prophylactic mastectomy, breast conservation in BRCA positive patients may be a viable choice provided that they are closely followed with enhanced imaging techniques such as MRI. This management strategy also depends on women and family members that have ability to coexist with the high probability of developing a breast cancer in their lifetime without it affecting their quality of life. Additionally, prophylactic mastectomy can be replaced by close follow-up in many patients provided they are well informed, motivated for close lifetime screening, and are comfortable with their decision.

Conflict of interests

There are no conflicts to disclose.

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