

ORIGINAL ARTICLE

Risk reducing mastectomy in patients with and without gene mutation: experience in an Italian Breast Unit

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Summary

Purpose: Risk reducing mastectomy (RRM) is a recommended clinical practice in cases of a serious increased risk of developing breast cancer. Current guidelines are considering such a practice in the presence of BRCA 1/2 genetic mutations even if in clinical practice other factors are involved in the choice for RRM. In this work we tried to investigate the factors that can intervene in the decision of women to have a RRM.

Methods: We analyzed the characteristics of a consecutive series of women who received RRM in the National Cancer Institute of Bari from 2015 to 2018; in particular, information on BRCA test, family history, age at the time of surgery, concomitant or delayed prophylactic surgery were compared to curative cancer surgery, imaging findings and histology.

Results: A consecutive series of 60 women (8 bilateral RRM, 52 contralateral RRM) receiving RRM was retrospectively selected. The decision to receive RRM was based on the pres-

ence of a genetic pathogenic variant in 51.6% of cases, but the 48.4% of women decided for such surgery despite a negative or unavailable test. Bilateral RRM was chosen only by women carrying a germline BRCA mutation. Multivariate analysis confirmed BRCA test stronger but not unique factor influencing the decision for RRM.

Conclusions: We revealed the prevalent role played by BRCA test in the decision of women to have a RRM, but other factors also seem to be relevant. In order to reduce the heterogeneity of approach to such practice, we suggest that: a) a multidisciplinary approach should be guaranteed; b) a clear intra-hospital clinical pathways should be adopted; c) social education attenuating the perception of risk and expectations for such preventive practice should be activated.

Key words: risk reducing mastectomy, BRCA, decision making process

Introduction

Prophylactic mastectomy is an increasing practice typically chosen to reduce an unacceptably high risk of breast cancer.

Current clinical guidelines suggest that Risk Reducing Mastectomy (RRM) should be taken into consideration on the basis of suggestive family history and/or results of genetic testing [1]. However, most women consider this practice because

of greater awareness of the treatment option or because of psychological factors [2].

The relevance of various factors in the decision making process of the woman to choose RRM has been widely investigated from the clinical genetic and psychological point of view [3,4]. Even more interesting, surgeon attitudes about recommendation for RRM has been also stressed as a relevance fac-

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tor influencing the likelihood of women to receive RRM [5]. Furthermore, geographical and cultural characteristics of the women have been reported [6]. It can then be asserted that reasons on the basis of this decision process in the routine clinical practice are still a topic of discussion.

BRCA-carriers patients have a risk of developing breast cancer up to 72%, much higher than the average risk present in the female population which is around 12%. RRM produces important benefits such as the reduction of the risk of 90-95% despite the absence of significant survival benefits [7]. Furthermore, RRM presents a non-negligible number of surgical complications and psychological damage in the short and long term [3].

For this reason, the choice of planning a RRM intervention must be well weighed by the surgeon and the patient who must be made aware of the advantages and potential risks associated with the intervention.

RRM has been utilized as a cancer preventive practice first of all in United States but suddenly spread all over the world also after Angelina Jolie experience [8]. Information concerning utilization of RRM in Europe is less numerous and, in particular, data concerning Italian experience are scanty and reporting only exploratory approaches [9].

The purpose of the present study was to review the characteristics of the women who received RRM in the Senology Department of an Italian reference cancer center consecutively between 2015-2018. Information on timing of surgery, BRCA genetic test, family history, histological and diagnostic imaging were analyzed.

Methods

The records of all women who underwent prophylactic breast surgery (PBS) at our Institute between January 2015 and May 2018 were reviewed.

Each patient underwent a genetic test for the search of the BRCA1-2 genes mutation and was found to be positive. All women underwent a preoperative evaluation with mammography in our Institute. Each case was also classified on the basis of breast density according to the BIRADS categories and then distinguished in high or low density breast according to Recthman et al [10].

Among 2156 women treated with breast surgery, of which 1651 for malignant neoplasm, 60 records were selected due to breast removal (monolateral n=52; bilateral n=8) without any histocytologic of presence of carcinoma.

For the mastectomies performed for prophylactic purpose (RRM) we mean all those mastectomies performed without preoperative radiologic evidence of malignant neoplasm and/or with a preoperative microhistologic sampling with outcome from B1 to B3 without atypia.

All women receiving a monolateral reducing risk mastectomy (controlateral RRM, CRRM) had a breast cancer surgery in the other breast synchronously or before the CRRM. Information on timing of CRRM, availability of a BRCA test for cancer risk, pre-surgery imaging characteristics of the breast and histologic lesions in healthy breast were collected.

All surgical and personal information were collected directly from clinical records of each woman and in particular age, timing of CRRM, timing of primary surgery and TNM of the primary tumour. The study was approved by the Scientific Board of the Institute as Ricerca Corrente RC 2020. All patients have given their consent to the processing of data for scientific purposes.

In order to evaluate the association between BRCA 1/2 status and risk reducing mastectomy, we used the χ^2 test. A result was considered statistically significant when the p value was <0.05.

Results

The main characteristics of the sixty women included in the analysis are reported in Table 1.

The median age of the patients resulted 49 years (range 31-71), significantly lower than in the overall series of women (59 years; range 25-99) who were subjected to primary breast cancer surgery in the same period in our Institute. Eighty percent (48/60) of women had a BRCA test before their RRM. All 8 women who were operated

Table 1. Clinical characteristics of 60 women receiving risk reducing mastectomy (RRM)

Characteristics	Number (%)
Women receiving RRM	60
Monolateral RRM	52 (86.6)
One time with breast cancer surgery	32(53.3)
Delayed with breast cancer surgery	20 (33.3)
Bilateral RRM	8 (13.3)
Median age (years, range)	46.5 (31-71)
Germline BRCA 1/2 test	
Presence of pathogenic variant	31
Absence of pathogenic variant	17
Not performed	12

Table 2. BRCA 1/2 status and risk reducing mastectomy

Germline Women BRCA status	Contralateral RRM (%)	Bilateral RRM (%)
BRCA 1/2 mutation	31 (51.6)	8 (100)
BRCA 1/2 wild type	17 (28.3)	0
BRCA test not performed	12 (20)*	0

*no test

with bilateral CRRM had a positive test for BRCA mutation but RRM was performed in 17 women (28.33%) with BRCA test negative for mutation and in 12 (20%) with BRCA test not performed at all.

In conclusion, 48.33% of CRRM were not performed irrespective to BRCA test result.

BRCA status in relation to RRM is summarized in Table 2. BRCA 1/2 status and risk reducing mastectomy were significantly independent (χ^2 , $p < 0.005$).

The mammography and MRI images were also retrospectively reviewed to verify if there were findings capable of justifying mastectomies. All the findings displayed on the images were presented in BIRADS 2 or 3 (benign or probably benign, with indication for follow-up). Therefore, in no case did the imaging characteristics justified RRM.

The individuals with healthy breasts undergoing RRM showed moderate-high mammographic density in 60% of the cases. Some examples are shown in Figures 1 and 2.

Results concerning the histologic study of health breasts removed with RRM are reported in Table 3.

Invasive carcinoma was never found while in 4 (6.6%) *in situ* breast carcinoma was diagnosed (3 in the group of patients BRCA-carriers); however, high grade atypia lesions were described in 16 (26.6%) breasts, 8 among BRCA-carriers and 8 among BRCA-non-carriers. In the reported lesions with high grade of atypia there were flat atypia ($n=2$), atypical ductal or lobular hyperplasia ($n=7$), radial scar ($n=3$), LIN1-2 ($n=3$) and papillomatosis with atypia ($n=1$).

All of the patients with genetic mutation ($n = 31$) had bilateral mastectomies (100%) with a total of 62 breasts removed: 23 of them were removed for a tumor (curative mastectomy, 37.1%) and 39 for prophylactic purposes (CRRM, 62.9%). 8/31 patients (25.8%) were subjected to double prophylactic mastectomy whereas the remaining (23/31 74.2%) had a contralateral prophylactic mastectomy associated with curative mastectomy. 20/31 patients (64.5%) had synchronous surgery to the primary tumor, while 11/31 patients (35.5%) metachronous one, i.e. deferred with respect to the curative intervention; the range of deferral of the second intervention in the latter was 2-175 months [13.1 and 33.32, mean and standard deviation respectively].

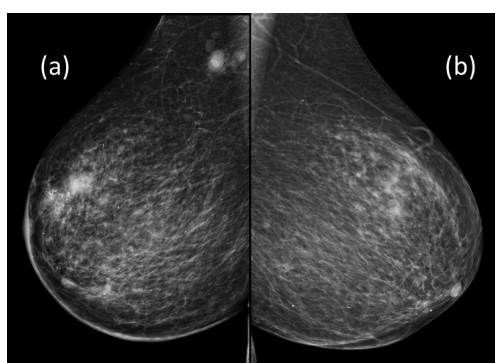


Figure 1. Bilateral mastectomy, curative on the right breast (a) with upper quadrant neoplasm. RRM on the left breast (b) due to the presence of scattered microcalcifications with characters of benignity. Mammography density is low. Conclusive mammography report: BIRADS 5 (right), BIRADS 3 (left). Histology: infiltrating ductal carcinoma B5 (right), foci of flat atypia B3 (left).

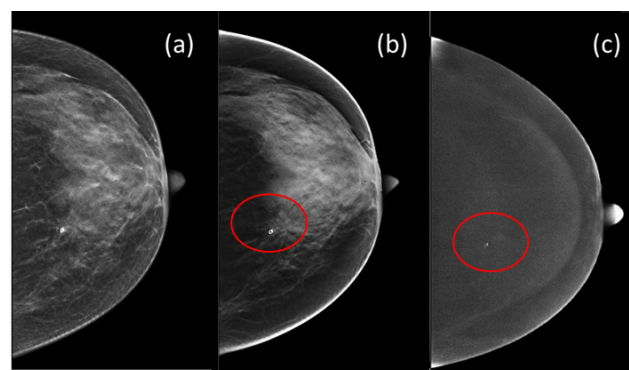


Figure 1. (a) In 2D mammography, stereotactic biopsy clips are detected in the left inner quadrants. (b) in tomosynthesis the distortion area is highlighted in the same location. (c) in CESM after a light contrast medium and modest impregnation. Mammography density is high. Conclusive mammography report: BIRADS 3. Histology: radial scar B3.

Table 3. BRCA 1/2 status and histopathological diagnosis in healthy breasts removed for RRM

Germline BRCA status	Number Women ($n=60$)*	Number of Breasts removed as RRM ($n=68$ *)			
		Invasive carcinomas	In situ carcinomas	High grade atypia	Absence of lesions
BRCA 1/2 mutation	31	0	3	8	20
BRCA 1/2 wild type	17	0	1	5	11
BRCA test not performed	12	0	0	3	9

*8 women receiving bilateral RRM

Mammography density was high in 18/31 patients (58%), similar in the 2 groups who had decided for synchronous surgery (60/40% high / low) or for metachronous surgery (54.4 / 46.6% high / low). In 9/31 patients there was also a finding judged as BIRADS 3 before surgery and in 6/31 a biopsy with B3 was performed in the follow up. The definitive histology of the 39 prophylactic mastectomies in BRCA-carrier patients highlighted 3 cases (7.69%) of DCIS and 8 cases (20.5%) of lesions at risk (4 atypical ductal hyperplasia, 2 LIN1-2, 1 radial scar and 1 papillomatosis with atypia). Among patients with no known mutation (n = 29) 27 (93.1%) had bilateral mastectomy (27 prophylactic + curative) and 2 (6.9%) unilateral mastectomy (judged prophylactic in both cases due to absence radio-histological evidence of carcinoma). Among the 27 patients with a bilateral mastectomy, there were 18 subjected to synchronous surgery (18 curative + prophylactic at the same time of intervention) and 9 metachronous with a range of postponement of the second surgery varying from 6 to 36 months (10.9 and 5.7, mean and standard deviation respectively). The mammographic pattern was judged as high density overall in 18/29 patients (62%): 14/18 patients (77.7%) who had opted for synchronous surgery with curative intervention and 4 / 9 patients (44.4%) who had opted for deferred metachronous surgery.

Discussion

We retrospectively analyzed a series of women who underwent RRM at our Institute in the last years. Among all women who were subjected to mastectomy, we selected 60 women with bilateral (n=8) or CRRM (n=52) breast risk-reducing surgery.

This first evidence that emerges from our study highlights the fact that the only factor that makes healthy women to possibly opt for bilateral RRM is the presence of a pathogenic variant in BRCA gene. This evidence is in agreement with what was previously reported by Park et al [11]. The concern to have a high probability for breast cancer is justifying such an approach now widely suggested in main international guidelines [1].

The other information coming from our series concerns the performance of CRRM in women treated for cancer in the other breast. The probability to have a contralateral breast cancer in subjects who already had a cancer in the other breast is particularly higher (range 63-82% of the life-long probability) in women carrying a BRCA mutation [12], a risk clearly justifying a preventive breast surgery [13]. However, 51.67% of our women decided for such an operation independently from BRCA status. In particular, only 48.33% of women knew at the time of

CRRM the positive test result, while 20% of women received CRRM without having performed a genetic test before surgery or, even, with a not informative test (in 28.33% of cases). Goldhirsch and Gelber [14] stressed that some imaging characteristics, such as breast density, could induce surgeons to go ahead with CRRM, but in our series this it appeared relevant only in the group of non-BRCA carriers patients who performed tumor synchronous surgery. It is likely that automatic aids to radiologist reporting can help improve the diagnostic performance even in dense breasts as it is observed in radiomics studies, reducing this amount of uncertainty [15-18]. Significant variations in the attitude of physicians towards prophylactic mastectomy has been demonstrated among different countries [6]. Rosenberg et al [19] demonstrated that many patients overestimate their personal risk and benefit on survival of CRRM.

The choice of CRRM in our series might therefore reflect the increased public emphasis on prevention [20] and attendant increase in fear of breast cancer due to cancer screenings. These facts are of major relevance in a population with less or poor cultural level, thus stressing that the problem of empowerment of patients specifically on this topic is first of all mandatory in some social teams.

The discussion in our Institute on how to optimally counsel women about this surgical option is ongoing.

One more comment involves the timing for the CRRM with respect to breast surgery of the primary cancer. Of the women receiving CRRM 63.3% did it in one time with respect to primary breast cancer surgery, while the remaining delayed the surgery of the healthy breast. The choice of women for a simultaneous or delayed CRRM did not depend on tumor size, histology, ER status or Her2/neu score. The reason why delayed surgery remains less clear demands further studies investigating the womens' psychosocial status, attitude of surgeons, characteristics of the hospital where they received primary surgery, the presence of a multidisciplinary team, etc.

Within the population of women with an established genetic mutation, it is interesting to note that 20/31 patients had performed an RRS simultaneously with the contralateral curative intervention and 11/31 deferred compared to the intervention for carcinoma. Second surgery varied between 2 and 175 months (13.1 and 33.32, mean and standard deviation, respectively) but, excluding two cases with prophylactic mastectomy performed at 8 and 13 years, the range of the remaining patients was shortened to 2-30 months (8.4 and 6.42, mean and standard deviation respectively). In this group of patients, genetic mutation was the

only variable that really affected the choice of the intervention, as the others were equally divided between patients who have opted for synchronous and metachronous surgery, including mammographic density. A similar situation was also observed in non-mutated cases that presented the majority of cases of synchronous mastectomies (18/29) and the minority of prophylactic mastectomies deferred with respect to the curative intervention (9/29): in the first group the observation of a mostly dense (77.7%) would suggest an impact of mammographic density on the decision-making process in performing prophylactic mastectomy in the absence of genetic positivity at an early time.

Conclusion

In conclusion, it appears that we can confirm the growing trend of prophylactic surgery among patients at risk of breast cancer. Several factors seem to contribute to this trend. Our observations confirmed the positive genetic test data as the main input to the decision-making process. In the context of non-BRCA carriers, the mammographic density seems to influence the attitude towards an early prophylactic surgery synchronous to the oncological treatment.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author contributions

D.L. designed the study, collected and analyzed diagnostic breast images and wrote the manuscript. A.F. analyzed data with uni and multivariate analyses and wrote the manuscript.

S.D., N.C. and R.A. analyzed the retrospective clinical series.

M.P. and M.D. collected all information and organized the database and data analysis.

R.M. and A.V.P. revised the manuscript.

Conflict of interests

The authors declare no conflict of interests.

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