

Decision Making Process for Risk Reducing Mastectomy in a Comprehensive Cancer Center

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Abstract

Background: Risk Reducing Mastectomy (RRM) is a rising practice chosen by the woman to reduce an unacceptable high breast cancer risk. Current guidelines are considering such a practice in presence of suggestive family history and/or *BRCA* 1/2 genetic pathogenic mutations. However, it has been reported that in clinical practice other factors (surgeon attitude, women psychological traits, cultural/geographical aspects) are playing a role in the decision process for RRM.

Method: We analyzed the characteristics of a consecutive series of women who received RRM in the Comprehensive Cancer Institute of Bari; in particular information on *BRCA* test, family history, diagnostic imaging, clinical pathological factors were collected.

Results: A consecutive series of 59 women receiving RRM was retrospectively selected. No Mammographic/NMR breast characteristics supporting the need for RRM were present. 8 (14% had a bilateral RRM while 51 (86%) a contralateral RRM (CRRM). The decision to receive a RRM was based on the presence of a *BRCA* alteration in 31/59 (53%) of cases, but, interestingly, 47% of women decided for such a surgery even with a genetic test negative for *BRCA* mutations (17%) or with *BRCA* genetic test not performed (30%). Bilateral RRM was chosen only by women carrying a germline *BRCA* mutation. The decision for a CRRM was not based on specific primary tumor characteristics and performed in one time with respect to primary surgery in 26/51 cases while in the remaining subgroup of women in a delayed time. The multivariate analysis confirmed *BRCA* test stronger but not unique factor influencing the decision for RRM.

Conclusion: We confirm the prevalent role played by *BRCA* test in the decision of women to have a RRM but other factors seem to be able to suggest this practice also when no clear clinical benefit could be expected. 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.

Keywords: Risk reducing mastectomy; *BRCA*; Decision making process; Mammographic; Mutations

Introduction

Removal of healthy breast to reduce the risk of cancer is a rising practice [1] generally chosen by woman who consider the breast cancer risk unacceptably high [2]. 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 [3] however, most women consider this practice because of greater awareness of the treatment option or because of psychological factors [4]. The relevance of various factors in the decision-making process of the woman to choose RRM has been widely investigated from the clinical [5], genetic [6] and psychological point of view [7]. Even more interesting, surgeon attitudes about recommendation for RRM has been also stressed as a relevance factor influencing the likelihood of women to receive RRM [8]. Furthermore, geographical and cultural characteristics of the women have been reported [9]. We can then to assert that reasons on the basis of this decision process in the routine clinical practice are still topic of discussion [10].

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 [11]. Information concerning utilization of RRM in Europe is less numerous and, in particular, data concerning Italian experiences are scanty and reporting only exploratory approaches [12]. The aim of the present study was to review the characteristics of the women who received RRM in the Senology Department of

a comprehensive cancer center, Istituto Tumori G Paolo II of Bari, consecutively between 2015-2017. Information on timing of surgery, *BRCA* genetic test, family history, histological and diagnostic imaging were analyzed.

Materials and Methods

Records of all women who received prophylactic breast surgery at our Institute between January 2015 and March 2017 were reviewed. Among 1350 women treated for breast surgery, 59 records were selected because concerning a breast removal (monolateral n=51; bilateral n=8) without any cytohistological or imaging doubt of presence of a carcinoma. All Women receiving a monolateral reducing risk mastectomy (ControlateralRRM, 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, presurgery

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Received April 15, 2019; Accepted June 01, 2019; Published June 07, 2019

Citation: Forgiaa DL, Fanizzia A, Diotaiuti S, Altierib R, Patrunoc M, et al. (2019) Decision Making Process for Risk Reducing Mastectomy in a Comprehensive Cancer Center. J Cancer Sci Ther 11: 188-191.

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imaging characteristics of the breast (s), histological lesions in healthy breast were collected.

All surgical and personal information were collected directly from clinical diaries of each woman and in particular: age, timing of CRRM, timing of primary surgery, TNM of the primary tumour. The study was approved by the IAB of the Institute as RC2017.

BRCA test

Information on *BRCA* genetic test availability and test results were obtained from Centro Studi Tumori Eredo-Familiari of the Institute; the test was classified as informative when a pathogenic mutation or a class 3 unclassified variant in *BRCA 1/2* genes was found; molecular analysis was performed by direct sequencing and MLPA in Laboratory of Molecular Diagnostics of our Institute [13].

Pre - surgery imaging

All women had a presurgery evaluation by Mammography and/or NMR at Senology Radiology of our Institute. Each case was classified as with absence of any lesion at imaging or presence of benign lesion. Furthermore, breast density was evaluated and classified as High or Low dense breast according to Reethman [14].

Histopathological diagnosis

All removed healthy breasts had histological diagnosis performed in pathological anatomy of our Institute and classified as Breast with a) Invasive carcinoma; b) *In situ* carcinoma; c) High grade Atypia; d) Absence of any lesion.

Statistical analysis

Clinical information of the entire series was preliminarily analyzed; in specific, age of women at time of prophylactic surgery, timing of RRM, results of genetic test, imaging and histological diagnosis descriptions were analyzed. Furthermore, in order to identify the characteristics associated with RRM, we performed a multivariate statistical analysis aimed at evaluate characteristics becoming more homogeneous the series of women. The characteristics included in the model were *BRCA* genetic test result (categories: informative vs not informative vs test not performed), timing of RRM (categories:

Characteristics	Number (%)
Women receiving RRM	59
Monolateral RRM	51 (86)
One Time with breast cancer surgery	28 (47)
Delayed with breast cancer surgery	23 (39)
Bilateral RRM	8 (14)
Median Age (range)	49 yrs (33-71)
Germline BRCA 1/2 TEST	
Presence of pathogenic mutation*	31 (53)
Absence of pathogenic mutation	11 (17%)
Not performed	17 (30)
*BRCA 1/2 Unclassified class 3 variants included.	

Table 1: Clinical characteristics of 59 women receiving risk reducing mastectomy (RRM).

Germline Women BRCA status	Contralateral RRM	Bilateral RRM
BRCA 1/2 mutation*	23 (45%)	8 (100%)
BRCA 1/2 wild type	11 (22%)	0
BRCA test not performed	17 (33%)	0
*BRCA 1/2 Unclassified class 3 variants included.		

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

synchronous vs delayed), presurgery imaging (categories: negative imaging vs. presence of benign lesions), age at surgery (category: old vs young; cut-off median age of the series). A stepwise algorithm was developed that at each interaction inserted or eliminated iteratively the characteristics that, more than any other, minimizes the dissimilarity within the group, up to the saturated model (i.e., with all 4 variables considered). To this end, at each step, a coefficient of inconsistency was calculated (12-13); the higher the value of this index, the less similar are the objects belonging to the adjacent groups. Given the qualitative nature of the features detected, the metric used to evaluate the dissimilarity between single units in the hierarchical analysis was the distance from Manhattan, while the distance between two groups of units was the average distance between the elements of these.

Results

Main characteristics of the 59 women included in the analysis are reported in Table 1. Median age of the series resulted 49 yrs (range 33-71) significantly lower than in the overall series of women (59 yrs; range 25-99) who received primary breast cancer surgery in the same period in our Institute (data unpublished). Height women had a bilateral RRM without any clinical history of breast cancer. Fifty-one women had a CRRM. Twenty-five women decided to undergo CRRM at a variable time after primary surgery (delayed CRRM) for breast cancer in the other breast (mean time elapsing from primary surgery 4 yrs), while 26 received CRRM together with primary surgery for breast cancer in the contralateral breast (one time CRRM) [15,16].

The availability of an informative *BRCA* test was higher in women receiving bilateral RRM than in those who received CRRM (8/8 women vs 23/51, respectively). Women who underwent CRRM, did not show different pathological characteristics in cancer of the other breast (mean tumour size, histological type ER status or Grade) with respect to women treated for primary breast cancer surgery and not receiving CRRM in the same period at our Institute (data not shown). When the probability of women to receive a one time or delayed CRRM was analyzed, we showed that that decision was not associated with a different tumour size (52% of women with tumour diameter >2 cm choose one time CRRM), invasive histology (57% of women with ductal

Germline BRCA status	Number Women (n=59)	Number of Breasts removed as RRM (n=67)			
		Invasive carcinoma	In situ carcinomas	High Grade Atypia	Absence of lesions
BRCA 1/2 mutation [§]	31	0	3	8	28
BRCA 1/2 wild type	11	0	1	2	8
BRCA test not performed	17	0	0	10	7
*8 Women receiving Bilateral RRM					
§BRCA 1/2 Unclassified class 3 variants included.					

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

Steps	Variables				Inconsistency
	1	2	3	4	
Step 1	BRCA test			--	0.90
Step 2	BRCA test	One time surgery	Negative imaging	--	1.11
Step 3	BRCA test	One time surgery	Negative imaging	Age at RRM	1.13
Step 3	BRCA test	One time surgery		--	1.14

*See M&M for details

Table 4: Multivariate stepwise analysis with RRM as dependent variable*.

ca. choose one time CRRM). Furthermore, biological characteristics (ER status, Cytological Grade, Her2/neu status) did not influence the choice of woman to have a one time or delayed CRRM. 42/59 (71%) women had a *BRCA* test before their RRM. All 8 women who received bilateral CRRM had a positive test for *BRCA* mutation but RRM was performed in 11 (22%) in women with *BRCA* test negative for mutation and in 17(33%) with *BRCA* test not performed at all. In conclusion, 55% of CRRM were performed irrespective to *BRCA* test result (Table 2). To try to understand if any clinical doubt was on the basis of RRM, pre-surgery NMR and/or Mammography imaging were also reviewed. In no case, diagnostic imaging characteristics justifying the utilization of RRM was observed. The healthy breasts undergoing RRM showed high mammographic density in 44% of cases.

Results concerning the histological study of health breasts removed with RRM are reported in Table 3. Invasive carcinoma was never found while in 4 (6%) breasts *in situ* carcinoma was diagnosed; however, high grade atypia lesions were described in 20 (30%) breasts. When histological diagnoses were analyzed with respect to *BRCA* test information, we showed that *in situ* lesions were only present in patients with *BRCA* test performed. Conversely high grade atypia was more frequent in breasts of women who did not perform a *BRCA* test.

Table 4 summarizes the results of the multivariate stepwise analysis showing the features inserted or eliminated at each iteration and the associated inconsistency coefficient. *BRCA* status is the first selected variable; indeed, in correspondence with this iteration we observe the lowest value of the coefficient of inconsistency. Therefore, among all the characteristics considered, *BRCA* status defines a more homogeneous sample. The introduction of other features in the model, however, generates a certain variability making the group less homogeneous. We found a second minimum of the inconsistency coefficient when *BRCA* status, time of surgery and absence of any diagnostic doubt were jointly considered. Age at time of RRM does not seem to influence the model.

Discussion

We retrospectively analyzed the series of woman who underwent Prophylactic mastectomy at our Institute in the last years. Among all women who received mastectomy at our Institute, we selected 59 woman who received bilateral (n=8) or CRRM (n=51) breast risk reducing surgery. The primary finding emerging from our analysis is that bilateral mastectomy in healthy people is precisely of women with *BRCA* mutated gene. This first evidence is stressing the fact that the only factor inducing healthy women, eventually to bilateral RRM is the presence of a pathogenic mutation in *BRCA* gene. This evidence is in agreement with what previously reported by Park [17]. The concern to have an high probability for breast cancer is justifying such approach now widely comprised in main international guidelines (NCCN, 2018).

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 82%-63% of probability all along the life) in women carrying a *BRCA* mutation [18], a risk clearly justifying a preventive breast surgery [19]. However, 55% of our women decided for such a surgery independently from *BRCA* status; in particular, only 45% of women knew at the time of CRRM the positive test result while 33% of women received CRRM without having performed a genetic test before surgery or, even, with a test not informative (in 22% of cases). The multivariate analysis confirmed that *BRCA* test is the main driver of the decision but also timing of CRRM seems to play some relevance (Table 4).

This data is in complete agreement with what reported by other AA who stressed that women decide about CRRM irrespective of genetic test [20]. What are the known elements till here analyzed able to induce women to accept CRRM? Goldirsch [21] stressed that some imaging characteristics such as breast density could induce surgeons to go ahead with CRRM but in our series this characteristic seems not relevant. Significant variations in attitude of physicians towards prophylactic mastectomy has been demonstrated among different countries. Rosenberg [22] demonstrated that many patients overestimate their personal risk and benefit on survival of CRRM. The choice of CRRM in our series might therefore reflect increased public emphasis on prevention [23] 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 mandatory first of all in some social realities. 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. Only about 50% of women receiving CRRM practice did it in one time with respect primary breast cancer surgery while the remaining ones 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 reasons why of delayed surgery remain less clear and further studies are investigating psychosocial habit of the women, attitude of surgeons, characteristics of the hospital where they received primary surgery, the presence of a multidisciplinary team, etc.

Conclusion

In conclusion, it seems we can confirm the increasing trend of prophylactic surgery among patients at risk for breast cancer. Several factors seem to contribute to generate this trend. For sure, the availability of a genetic test like *BRCA* test for breast cancer susceptibility individualization is the main driver for this process. The role of the test is not only direct but seems to play also several associated effects such as increase awareness of the risk, increase anxiety in specific subjects, etc. This situation calls for some specific actions in different directions:

- The topic should be up only to specialized centers able to provide a multidisciplinary approach to the women;
- The attitude of surgeon should be mitigated through the adoption of clear intra-hospital clinical pathways;
- A clear action for social education should be activating to attenuate the role that social determinants play in the game.

References

- Jerome D'Emilia B, Kushary D, Supplee PD (2019) Rising rates of contralateral prophylactic mastectomy as a treatment for early-stage breast cancer. *Cancer Nurs* 42: 12-19.
- Mau C, Untch M (2017) Prophylactic surgery: For whom, when and how? *Breast Care* 12: 379-384.
- https://www.nccn.org/professionals/physician_gls/pdf/geneticsscreening.pdf
- Rosenberg SM, Sepucha K, Ruddy KJ, Tamimi RM, Gelber S, et al. (2015) Local therapy decision-making and contralateral prophylactic mastectomy in young women with early-stage breast cancer. *Ann Surg Oncol* 22: 3809-3815.
- Carbine NE, Lostumbo L, Wallace J, Ko H (2018) Risk-reducing mastectomy for the prevention of primary breast cancer. *Cochrane Database Syst Rev* 4: CD002748.
- Krontiras H, Farmer M, Whatley J (2018) Breast cancer genetics and indications for prophylactic mastectomy. *Surg Clin North Am* 98: 677-685.

7. Greener JR, Bass SB, Lepore SJ (2018) Contralateral prophylactic mastectomy: A qualitative approach to exploring the decision-making process. *J Psychosoc Oncol* 36: 145-158.
8. Katz SJ, Hawley ST, Hamilton AS, Ward KC, Morrow M, et al. (2018) Surgeon influence on variation in receipt of contralateral prophylactic mastectomy for women with breast cancer. *JAMA Surg* 153: 29-36.
9. Julian-Reynier CM, Bouchard LJ, Evans DG, Eisinger FA, Foulkes WD, et al. (2001) Women's attitudes toward preventive strategies for hereditary breast or ovarian carcinoma differ from one country to another: Differences among English, French, and Canadian women. *Cancer* 92: 959-968.
10. Den Heijer M, Van Asperen CJ, Harris H, Nippert I, Schmidtke J, et al. (2013) International variation in physicians' attitudes towards prophylactic mastectomy - comparison between France, Germany, the Netherlands and the United Kingdom. *Eur J Cancer* 49: 2798-2805.
11. Liede A, Cai M, Crouter TF, Niepel D, Callaghan F, et al. (2018) Risk-reducing mastectomy rates in the US: A closer examination of the Angelina Jolie effect. *Breast Cancer Res Treat* 171: 435-442.
12. Dionigi F, Maffoni M, Ferrari A, Garcia-Etienne CA, Ricciardi A, et al. (2017) What about prophylactic surgery in BRCA1/BRCA2 mutation carriers? Observations from an Italian pilot study. *Breast J* 23: 766-767.
13. Digennaro M, Sambiasi D, Tommasi S, Pilato B, Diotaiuti S, et al. (2017) Hereditary and non-hereditary branches of family eligible for BRCA test: Cancers in other sites. *Hered Cancer Clin Pract* 15: 7.
14. Rechtman LR, Lenihan MJ, Lieberman JH, Teal CB, Torrente J, et al. (2014) Breast-specific gamma imaging for the detection of breast cancer in dense versus nondense breasts. *AJR Am J Roentgenol* 202: 293-298.
15. Jain AK, Dubes RC (1988) Algorithms for clustering data. Upper Saddle River, NJ: Prentice-Hall, USA.
16. Zahn CT (1971) Graph-theoretical methods for detecting and describing Gestalt clusters." *IEEE Transactions on Computers* 20: 68-86.
17. Park S, Lee JE, Ryu JM, Kim I, Bae SY, et al. (2018) Genetic diagnosis before surgery has an impact on surgical decision in BRCA mutation carriers with breast cancer. *World J Surg* 42: 1384-1390.
18. Mavaddat N, Peock S, Frost D, Ellis S, Platte R, et al. (2013) Cancer risks for BRCA1 and BRCA2 mutation carriers: Results from prospective analysis of EMBRACE. *J Natl Cancer Inst* 105: 812-822.
19. Kenny R, Reed M, Subramanian A (2018) Mastectomy for risk reduction or symmetry in women without high risk gene mutation: A review. *Int J Surg* 50: 60-64.
20. Hawley ST, Jagsi R, Morrow M, Janz NK, Hamilton A, et al. (2014) Social and clinical determinants of contralateral prophylactic mastectomy. *JAMA Surg* 149: 582-589.
21. Goldhirsch A, Gelber S (2014) Breast cancer: Why do women opt for contralateral prophylactic mastectomy? *Nat Rev Clin Oncol* 11: 443-444.
22. Rosenberg SM, Tracy MS, Meyer ME, Sepucha K, Gelber S, et al. (2013) Perceptions, knowledge, and satisfaction with contralateral prophylactic mastectomy among young women with breast cancer: A cross-sectional survey. *Ann Intern Med* 159: 373-381.
23. Boccardo C, Gentilini O (2016) Contralateral risk reducing mastectomy in patients with sporadic breast cancer. Benefits and hazards. *Eur J Surg Oncol* 42: 913-918.