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Mastectomia preventiva: ainda uma estratégia controversa?

Prophylactic Mastectomy: still a controversial procedure?

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RESUMO

O seguimento de portadoras de mutações nos genes *BRCA1/2* e a tomada de decisões sobre as suas estratégias de gestão de risco, desafiam a relação médico-doente classicamente estabelecida. Neste contexto, há quem advogue o aconselhamento não directivo, com discussão das várias alternativas de redução de risco de cancro, nomeadamente do cancro da mama. A evidência científica nesta área é complexa de analisar pois há falta de estudos randomizados e os critérios de selecção são complexos. Os médicos responsáveis pelo seguimento destas doentes devem estar actualizados de forma a possibilitar uma discussão informada e orientá-las na decisão que melhor se adequa aos seus factores individuais. A prevenção cirúrgica (mastectomia preventiva e/ou ooforectomia preventiva) reduz de forma significativa o risco de cancro da mama invasivo em mulheres portadoras de mutações nos genes *BRCA1* and *BRCA2*. A mastectomia preventiva é, neste contexto, a estratégia mais eficaz na redução da incidência de cancro da mama. Apesar da sua eficácia, é um procedimento controverso, principalmente porque é considerado não terapêutico e a decisão da sua realização poder ser tomada apenas baseada em critérios clínicos. Com a generalização do rastreio *BRCA1* e *BRCA2* é possível fazer uma selecção mais correcta das candidatas para mastectomia preventiva. A aceitação desta técnica cirúrgica pelas mulheres em risco e pelos profissionais de saúde é variável. A integração da gestão do risco hereditário de cancro da mama em unidades multidisciplinares é sugerida.

Palavras chave: cancro da mama, *BRCA1*, *BRCA2*, mastectomia profiláctica.

ABSTRACT

The follow up and care of *BRCA1/2* women, and the decisions concerning risk reduction strategies, challenge the classical patient-doctor relationship. Non-directive counseling with open discussion about different alternatives for breast cancer risk reduction is usually recommended. Scientific evidence in this field is complex, due to the lack of randomized data and heterogeneous selection criteria for different studies. The physicians in charge of this follow up must be aware of the latest scientific data, to allow for an informed discussion with their patients. Decisions must be tailored taking into account individual factors. Surgical prevention (prophylactic mastectomy and/or oophorectomy) reduces the risk of invasive breast cancer in *BRCA1* and *BRCA2* patients, with prophylactic mastectomy (PM) being the most effective procedure for cancer prevention, in these women. Although effective in this setting, prophylactic surgery is still criticized because it could be non-therapeutic and only decided on the family history or clinical decision. With generalization of commercial *BRCA1* and *BRCA2* screening, a more accurate selection of candidates for PM is possible. Acceptance of this procedure by women at risk and health practitioners is variable. We suggest that risk management of these high-risk women must be done by multidisciplinary teams.

Key words: breast cancer, *BRCA1*, *BRCA2*, prophylactic mastectomy.



INTRODUCTION

Women belonging to families with several cases of breast cancer were always considered at higher risk for this disease than women from the general population. Before the availability of genetic screening, mammography surveillance was started at young ages (usually 5-10 years earlier than the age of the breast cancer diagnosis in a first degree relative). Prophylactic bilateral mastectomy (PBM), a more radical approach was controversial (¹), but it was, in several cases, the choice of some women and their physicians. The results of a retrospective study, covering more than 30 years of surgical activity at the Mayo Clinic, confirmed the efficacy of this procedure (²).

A growing interest in preventive surgery has developed after commercial availability of genetic screening for *BRCA1* and *BRCA2* mutations. Women carriers of these mutations have a lifetime risk of breast cancer up to 80% (³) and they are also at high risk for ovarian cancer (⁴). Considering their high risk, *BRCA1/2* carriers are the ideal candidates for preventive surgeries, specifically PBM since breast cancer is the most frequent neoplasia diagnosed in *BRCA* families (⁴). Also, the identification of a *BRCA* mutation in one family allows the accurate selection of women at risk (those positive for the family mutation), targeting the discussion of the several risk reducing strategies to the appropriate candidates.

Although there are no randomized trials studying the benefit of prophylactic mastectomy, evidence accumulated, during the last years, concerning the benefit of PBM. But there is still controversy about this procedure and the knowledge of physicians about its indications is variable (⁵). High-risk women, potential candidates for PBM, have varying levels of acceptability of the procedure. Another issue is the generalization of prophylactic mastectomy of the contralateral breast in women with standard or moderate risk.

In here, we review the role of preventive surgery, most specifically prophylactic mastectomy in the management of women at high risk for hereditary

breast cancer, and the attitudes of these women and their physicians towards this procedure and other risk reducing strategies.

RISK REDUCING STRATEGIES FOR WOMEN AT HIGH RISK FOR HEREDITARY BREAST CANCER

Hereditary breast cancer syndromes are rare, accounting for less than 10% of all breast cancers. Most of confirmed hereditary cancer syndromes are associated with mutations in *BRCA1* and *BRCA2* genes, with a smaller proportion related with *pTEN* and *p53* gene mutations. A growing number of clearly breast cancer high-risk families, without identified pathogenic mutations in known genes, are a difficult issue emerging in breast cancer risk counseling.

Most of the literature concerning risk reducing strategies for hereditary breast cancer refers to *BRCA1/2* carriers (⁶). Strategies available for these women are: increased surveillance, prophylactic surgery and chemoprevention. The levels of evidence for the benefit of the different strategies differ. Most of the studies are retrospective or case control, and breast cancer early identification or breast cancer incidence reduction is usually the primary endpoint. Quality of life and overall survival are less studied endpoints. It's hoped that the inclusion of the growing number of identified *BRCA1/2* women in clinical studies will help to clarify these issues.

If management strategies for unaffected patients with *BRCA* mutations are continually redefined, a growing number of identified *BRCA1/2* cancer survivors also challenge health practitioners about the possibility of prevention of second cancers.

WHEN TO CONSIDER PREVENTIVE MASTECTOMY

Preventive mastectomy is an option for carriers of a mutation in a breast cancer predisposing gene



(mostly *BRCA1* and *BRCA2* carriers), either for non-affected carriers (bilateral prophylactic mastectomy or BPM) or for unilateral *BRCA1/2* breast cancer survivors (contralateral prophylactic mastectomy or CPM). This procedure has also been considered for some women belonging to high risk families without an identified cancer predisposing gene mutation, for breast cancer survivors in general (to reduce the risk of contralateral breast cancer), and for women with specific findings at breast biopsies (like lobular breast cancer in situ). Most of the data reviewed here concerns *BRCA1/2* carriers.

EFFICACY OF PROPHYLACTIC MASTECTOMY

Although radical and invasive, surgical options involving either PBM or CPM are the most effective means for primary prevention of breast cancer in high risk women, being associated with up to 85-100% reduction in breast cancer risk^(2,7,8). A prospective study about the benefit of this procedure in *BRCA* women, the Prevention an Observation of Surgical Endpoints (PROSE) study detected a 90% risk reduction in Breast cancer in a cohort of *BRCA1* and *BRCA2* women: 2% of *BRCA* women undergoing PBM were diagnosed with breast cancer compared with 49% of *BRCA* women under surveillance⁽⁹⁾. In this study, an important observation was that risk reduction was higher (95%) in women undergoing prior or concurrent bilateral prophylactic oophorectomy (BPO). BPO is another surgical option for cancer risk reducing in these *BRCA1* and *BRCA2* carriers. This procedure is recommended for the prevention of ovarian cancer in *BRCA1/2* women but, as found in the PROSE study, it is also associated with breast cancer prevention. Besides the added preventive value to prophylactic mastectomy, BPO alone can reduce the risk of breast cancer by 60%⁽¹⁰⁾. BPO has side effects related to a precocious menopausal status⁽¹¹⁾ but is the preventive surgery most acceptable by *BRCA1/2* women, since prophylactic mastectomy,

the most effective breast cancer surgical prevention, is considered too aggressive by many⁽¹²⁾.

DECISION ABOUT SURGICAL PREVENTION

More than a strong recommendation for prophylactic mastectomy, a physician should discuss with candidates for this procedure, the risks and benefits of BPM, CBP and/or BPO. Individual factors, like age, partner or marital status, reproductive and psychological issues must be taken into consideration. In cancer survivors, prognosis of the previous cancer diagnosis should also be taken into account and discussed carefully with the patient.

During the decision process, one of the relevant issues is the surgical technique the surgical team considers appropriate for each woman. Reconstruction options and related risks must also be discussed⁽⁶⁾. Until recently, the majority of PBM were performed using a simple or skin-sparing mastectomy technique, removing the nipple areola complex with all the underlying breast parenchyma. A surgical alternative is a nipple-sparing approach allowing for the removal of the breast parenchyma with preservation of the nipple areolar complex. This technique may not be indicated for all women, but may prevent the loss of areolar sensation.

It's not clear if the risk of recurrence with skin sparing mastectomy or preservation of the nipple areolar complex is higher^(13,14) than that of other techniques. Reconstruction options are also variable and selection of the optimal surgical procedures must take into account patient choice, body *habitus* and comorbidities.

Timing of preventive surgery is also an issue. The earlier onset of disease seen in mutation carriers would recommend these procedures at a young age, but risk reduction has to be balanced against the possible negative impact on body image, menopausal symptoms and reproductive issues. For BPO, it's generally recommended delaying it until completion of parturition (around 35 years of age). This surgery



is being increasingly accepted amongst BRCA mutation carriers (15, 16), maybe because women perceive a “double benefit” (6) of reducing breast and ovarian cancer risk and also because of the lesser impact on external body image. For women motivated for PBM, BPO should also be discussed and timing for the decided preventive surgery or for both procedures should be tailored as a compromise between women’s life risk and life needs.

Most studies reveal acceptance rates of PBM between 14-20% (17), with only one study reporting a 50% rate (18). BPO is usually preferred to PBM; in one study (19) 14,9% of women decide for PBM and 50,3% for BPO. Decision for BPO was also more rapid, after receiving the test results than for PBM. Patients opting for BPO were older (47 versus 42 years) and more frequently, survivors of breast cancer (19). In another study (16) 23% of carriers underwent PBM and 51% BPSO. Predictors for accepting preventing surgery were age (under 60) and a previous diagnosis of breast or ovarian cancer.

There are no conclusive data on the complication rate for prophylactic mastectomy that was reported to be as high as 64% (20). Short-term risks include bleeding, seroma formation, and infection. Also, it is not technically feasible to provide 100% risk reduction (21). Data on the psychological impact of PBM is not definite but PBM may improve quality of life by reducing emotional concern for developing breast cancer (22).

ALTERNATIVES TO PREVENTIVE MASTECTOMY

Increased surveillance and chemoprevention are considered alternatives to surgical prevention in BRCA1/2 women (6).

Increased surveillance is the least invasive risk reducing method and aims at early detection of breast cancer, not primary prevention. Risks related to increased worry about cancer and unnecessary biopsies have been described (23). This is an important

issue also with breast Magnetic Resonance (MRI), the preferred method for breast cancer screening in BRCA1/2 women (24).

Tamoxifen decreases breast cancer incidence by 50%, in women with increased risk calculated according to the Gail model (25). In *BRCA1/2*(26) mutation carriers, with a previous breast cancer diagnosis, initial treatment with tamoxifen reduces the risk of contralateral breast cancer. Inconclusive data suggests that tamoxifen may also reduce the incidence of breast cancer in *BRCA2* mutation carriers by 62% while having no effect in *BRCA1* mutation carriers (27). Aromatase inhibitors also decrease the incidence of breast cancer in women at risk, although more information is needed about the specific *BRCA1/2* population.

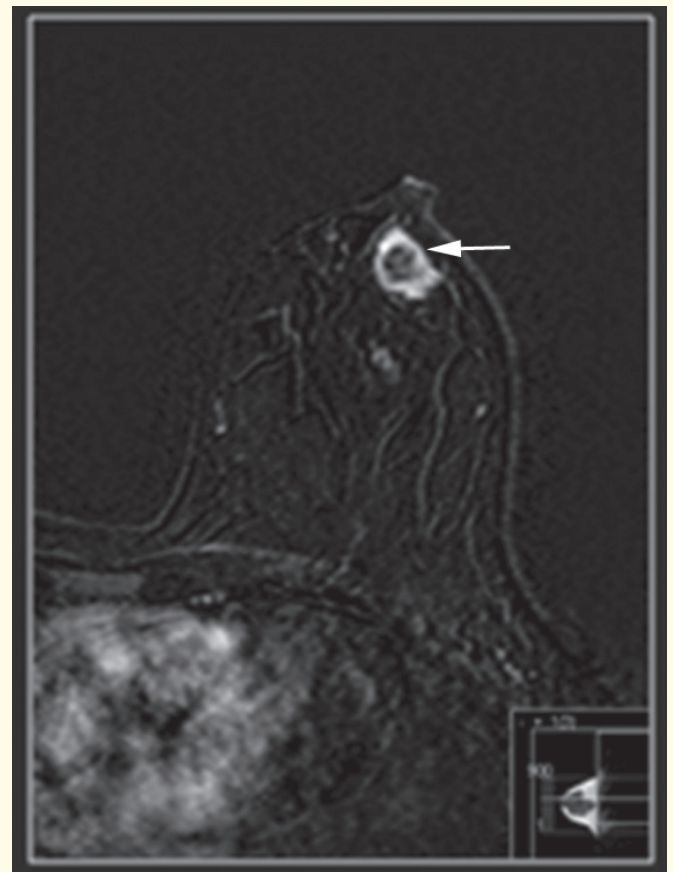


FIG. 1 – *BRCA2* carrier submitted to prophylactic mastectomy (skin-sparing mastectomy with preservation of the nipple-areolar complex) with immediate prosthetic reconstruction.



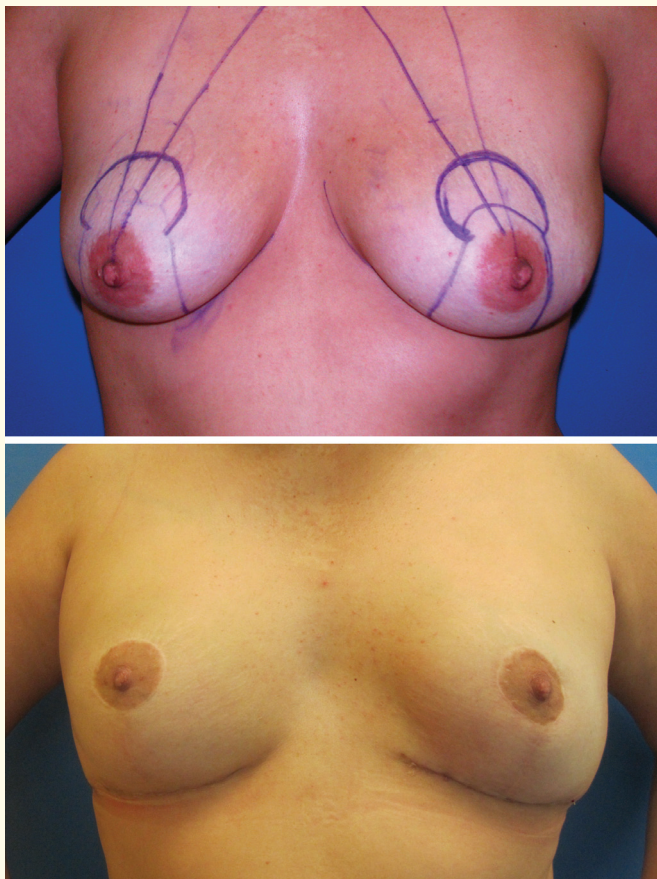


FIG. 2 – MRI detection of a breast suspicious lesion in a *BRCA1* carrier (arrow). Pathology diagnosis revealed a triple negative breast cancer.

Acceptability of different risk-reducing strategies varies among different countries ⁽¹²⁾: Mammographic screening (87%) and chemoprevention (58%) have the highest levels of acceptability by women at high risk of breast cancer, while BPO and PM were considered acceptable before 35 years, by only 19% and 16% of women included in the study ⁽¹²⁾. Besides country of origin, preferences relating to preventive attitudes vary with *BRCA* status, DCIS, breast biopsy or a family history of ovarian cancer ⁽²⁸⁾. Patients with a previous history of ovarian cancer or advanced breast cancer were more likely to undergo surveillance. Women with a family history of ovarian cancer were more likely to undergo BPO ⁽²⁸⁾.

BENEFIT OF DIFFERENT PREVENTIVE PROCEDURES

No randomized controlled trial has ever been conducted to examine the benefit of PBM over other risk-reducing procedures in *BRCA1* and *BRCA2* women. Considering the data available and the perception of risk by *BRCA1/2* women running such a trial is unlikely.

Effects on survival are also unknown. Models have been developed to estimate life gains regarding different prevention strategies. One study ⁽²⁹⁾ concluded that the most effective single intervention for *BRCA1* mutation carriers is PO at age 40 with a 15% absolute survival gain. For *BRCA2* mutation carriers, the most effective single intervention was PM, with a 7% survival gain if performed at age 40 years. The combination of PM and PO at age 40 increased survival gains (24% gain for *BRCA1* and 11% for *BRCA2* mutation carriers). PM at age 25 plus PO at age 40 years yielded the greatest survival probability but, in spite of this finding, substituting mammography plus MRI screening for PM seemed to offer comparable survival.

The similar model had been previously used for the estimation of life expectancy gains with different strategies in *BRCA1* and *BRCA2* women with previous breast cancer ⁽³⁰⁾. In that analysis, CBP and PO afforded a better survival gain than tamoxifen. This study also showed that low-penetrance, older age and poorer prognosis from primary breast cancer attenuated these gains.

BRCA1/2 MEN AND PROPHYLACTIC MASTECTOMY

BRCA1/2 men, principally *BRCA2* men are also at increased risk for breast cancers. Incidence of breast cancer in *BRCA2* men has been shown as 7.1% before age 70 ⁽³¹⁾. There is scarce data concerning the role, either of preventive mastectomy ⁽³²⁾ and of screening ⁽³³⁾ in *BRCA2* men.



CONCLUSION

Managing the risk of women at risk for hereditary cancer is a complex and rapidly changing field. Due to a lack of randomized trials, published guidelines reflect not only retrospective and prospective studies, but also expert consensus. During the decision process about risk-reducing procedures, non-directive counseling as opposed to classical directive counseling is preferable. Issues related to patient's individual preferences have to be taken into consid-

eration. Multidisciplinary teams, with a collaboration of different specialists, have been suggested as the optimal setting for the management of this high-risk group.

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