Bilateral prophylactic mastectomy in BRCA mutation carriers: what surgeons need to know.

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Aim of this paper is to allows to analyze a topic of great relevance and media interest such as the role of prophylactic mastectomy in healthy women with BRCA mutation proposing to the surgeons some useful informations for decision-making.

Less than 15% of all breast cancers are associated with germline genetic mutations. The majority of hereditary breast tumors are due to mutations in BRCA1 and BRCA2 genes that are responsible for only one third of hereditary cases. The risk estimates are extremely heterogeneous with a mean cumulative lifetime breast cancer risk of approximately 72% in BRCA1 and 69% in BRCA2 by age 80. The breast cancer is often bilateral and multicentric in BRCA mutation carriers. BRCA1 carriers have earlier-onset disease, particularly before age 50 and are more likely to develop aggressive triple-negative breast cancer than BRCA2 carriers or those who are BRCA mutation negative [1].

Multiple strategies are effective in managing the risk of breast cancer in these women, including surveillance, chemoprevention, bilateral salpingo-oophorectomy and risk-reducing mastectomy.

More intensive surveillance, including annual mammography and breast magnetic resonance imaging screening (commonly alternated every six months) beginning at age 25 or individualized based upon the earliest age of onset in the family, have significantly improved early detection of breast cancer among patients with deleterious BRCA mutations [1].

The risk-reducing benefit of chemoprevention is not as well defined; chemopreventive strategies to reduce the risk of breast cancer have focused exclusively on prevention in high-risk women and involve the use of selective estrogen receptor modulators (SERMs) and aromatase inhibitors for breast cancer prevention. Only limited data are available regarding the preventive benefit of tamoxifene in BRCA mutations carriers [1].

Risk-reducing bilateral salpingo-oophorectomy is recommended for BRCA mutation carriers by 35 to 40 or when childbearing is completed, or individualized based on age of onset of ovarian cancer in the family; bilateral salpingo-oophorectomy decreases the risk of both breast cancer and ovarian cancer in BRCA1 and BRCA2 mutation carriers and has also been associated with reduced all cause, breast cancer-specific, and ovarian cancer-specific mortality; risk-reducing bilateral salpingo-oophorectomy seems to offer an approximate 50% relative reduction in breast cancer risk [1].

Prophylactic mastectomy provides the greatest reduction in risk of breast cancer development. In both retrospective and prospective observational studies, bilateral prophylactic mastectomy decreases the incidence of breast cancer by 90 percent or more in patients with BRCA mutation; it also is able to determine a variable gain in life expectancy compared to radiological surveillance; besides risk-reducing mastectomy allows to contain the strong anxiety and the fear of getting sick that often compromise the quality of life of BRCA mutation carriers [2].

Prophylactic mastectomy could be technically performed in different ways. However, regarding the surgical technique, on the basis of current evidence, the gold standard seems to be represented by nipple-sparing mastectomy which, thanks to the preservation of the skin envelope and the nipple-areola complex, is able to optimize the oncological and aesthetic results. Nipple-sparing mastectomy provides superior cosmetic results. This procedure is usually performed through an inframmamary or

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radial or axillary incision where the skin is carefully dissected off the breast until all anatomic boundaries of the breast are reached and the gland in its entirety is excised. This technique does not seem to compromise the oncological/preventive efficacy compared to other types of mastectomy. In a multi-institution review of prophylactic 346 BRCA carriers undergoing either bilateral mastectomy or contralateral mastectomy with nipple-areola sparing there were no cases of breast cancer, whereas, based on models, 22 would have been expected [3]. However nipple-sparing mastectomy must be carried out with technical skill and maximum attention not to leave macroscopic residues of mammary gland in particular in the axillary extension, peripheral extremities of the gland and the nipple-areola complex; it is necessary to perform an accurate dissection and a meticulous preparation of the skin flaps and of the areola-nipple complex which must be reasonably thin without however compromising its vitality.

Whenever the patients opt to proceed with bilateral prophylactic mastectomy, an accurate preoperative radiological study should always be performed with mammography, ultrasound and magnetic resonance imaging to rule out the presence of suspicious breast lesions and minimize the risk of occult carcinomas by definitive histological examination.

In the absence of contraindications, all patients should be candidates for breast reconstruction in order to minimize the negative physical and psychological impact of the mastectomy; the breast reconstruction should preferably be immediate, performed at the same time of the prophylactic mastectomy, by a team of dedicated plastic surgeons, or with permanent prosthesis or autologous tissues; the choice of the most appropriate reconstructive technique depends on various factors such as the physical/anatomical structure of the woman, the morphology/degree of breast ptosis, the comorbidities but also the patient's wishes and preferences [1].

However, in the discussion on the possibility of carrying out a prophylactic mastectomy, it is always necessary to consider a series of issues related to this procedure:

– the possible oncological failure because risk-reducing mastectomy does not completely eliminate the risk of developing breast cancer; there is always a residual risk of about 5% to be related to the possible presence of residual glandular tissue or ectopic breast tissue [2];

– the surgical morbidity with overall complication rates of 15-20% such as ischemia of the skin and/or of the areola-nipple complex, haematomas, infections, implant failure, partial/total autologous flap loss; in a considerable percentage of cases there is also the need to resort after the prophylactic mastectomy to further aesthetic/plastic procedures to correct some imperfections or repair surgical complications [3-5];

– the presence of sequelae such as the loss of sensitivity of the areola-nipple complex, possible paresthesias, painful sensations and the need for re-adaptation to a different body image [2];

– the possible body image issues due to many factors, such as self-consciousness, feeling less sexually attractive and dissatisfaction with the scars [2,3].

In addition to these issues we must add that most of the studies that show a gain in life expectancy thanks to prophylactic mastectomy, are based only on mathematical models and that the few prospective cohort studies often do not show a statistically significant improvement in terms of survival among women undergoing MP and intensive radiological surveillance [1,2].

Therefore in consideration of the benefits but also of the problems that the prophylactic mastectomy involves, all the international guidelines highlight that this procedure must be *considered*, must be *discussed* with healthy BRCA women, however without giving an absolute recommendation to perform it [1]. This discussion must take place, case by case, in specialized breast centers with a dedicated risk team. A personalized multidisciplinary path should guarantee an accurate genetic and clinical counselling, adequate psychological support and detailed information about all alternative risk management strategies. Clinical decision-making about strategies to pursue for breast cancer risk reduction should involve a trade-off between life expectancy and quality of life. However if the patient and the medical team opt to proceed with prophylactic surgery, the cumulative evidence to date supports nipple sparing mastectomy with immediate reconstruction as an appropriate risk-reducing procedure to optimize the oncological and aesthetic results and improve quality of life.

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