

History and actual indications of prophylactic mastectomy

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Abstract

Breast cancer is one of the most common causes of death in women worldwide. Although in the last few decades attention was focused on discovering the most efficient method to prevent this malignancy, it seems that the only potential way to decrease the breast cancer risk is performing a prophylactic mastectomy. This type of surgical approach is efficient especially in breast cancer gene ½ mutation carriers as well in patients who had been already submitted to surgery for contralateral breast cancer. This is a literature review regarding the history, the types of performed surgical procedures and the actual indications of prophylactic mastectomy.

Keywords: breast cancer, prophylactic mastectomy, contralateral prophylactic mastectomy

Introduction

Breast cancer is a relatively often discussed subject in different social areas, therefore many women begin to develop fear of breast cancer⁽¹⁾. Although recently this disease started to be popular in media field, practitioners are studying it for decades and surgical treatment such as bilateral prophylactic mastectomy followed by reconstruction is mentioned since 1960⁽²⁾.

Breast cancer is the most common cancer diagnosed in women and the second most common cause of death from cancer in women after lung cancer in Great Britain⁽³⁾. Due to the high incidence of breast cancer strategies for identification of women at great risk for breast cancer have been developed. Several methods for breast cancer prevention are described such as surveillance, chemoprevention therapy (i.e. tamoxifen), bilateral oophorectomy and eventotal or subcutaneous bilateral prophylactic mastectomy.

Types of mastectomy

There are several techniques in which a mastectomy can be performed. In simple mastectomy or non-skin-sparing mastectomy breast parenchyma, skin and nipple-areola complex are en block removed. Only a small amount of skin is left just to close the incision without tension. This surgical approach is recommended in women who will not immediately undergo breast reconstruction. The skin-sparing mastectomy is a technique described by Toth and Lappertin^(3,4). The breast parenchyma and nipple-areola complex are removed with minimal skin excision. Nipple-sparing mastectomy was first described by Freeman in 1960 as subcutaneous mastectomy⁽⁵⁾. In 1969 Freeman mentions the indications for subcutaneous mastectomy with immediate or delayed implants. Benign tumors of the breast, certified malignancy of one breast and mammographic suspicion of the other one or positive familial history of breast cancer in association with progressive lesions and increasing anxiety were inte-

grated as indications for subcutaneous mastectomy⁽⁶⁾. Nipple-sparing mastectomy removes breast parenchyma with minimal skin excision while the nipple-areolar complex is preserved.

The role of prophylactic mastectomy

In 1975 in San Francisco at Saint Francis Memorial Hospital a Subcutaneous Mastectomy Data Evaluation Center was constituted. Data from 1500 women with high risk factors who underwent subcutaneous mastectomy were reviewed. After 9 years follow-up only 0.4% (6 cases) developed breast cancer. Three of them died of disease while the other three were still alive. This study suggested this surgical procedure might provide an efficient prophylaxis of breast cancer⁽⁷⁾.

Like other malignancies, breast cancer has also a hereditary component. Due to these findings practitioners have tried to identify women at very high risk on the basis of family history or genetic analysis. Hartmann and contributors established two categories of risk in women with family history of breast cancer: high-risk and moderate-risk patients. Criteria for high-risk status include the following: one or more relatives with breast cancer, early age at the diagnosis of cancer and a family history of ovarian cancer, bilateral breast cancer, or breast cancer in male members. Women enrolled in the study who did not meet high-risk criteria were included in moderate-risk group. Prophylactic mastectomy (90% nipple-sparing mastectomy, 10% simple mastectomy) in women with a moderate risk of breast cancer reduced the risk of breast cancer with 89.5% and in women with a high risk of breast cancer with 90-94%. The reduction in the risk of death among the moderate-risk group was 100% and in high-risk group was 81-94%. Two of the women in the high-risk group developed ovarian cancer. Breast cancer was developed in women who underwent subcutaneous prophylactic mastectomy. However the incidence was not statistically significant. Approximately 50% of the women

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included in this study underwent bilateral prophylactic mastectomy, although they did not meet the criteria for family history. The decision was made by several findings such as nodular breasts, multiple prior breast biopsies, and refractory mastodynia⁽²⁾.

Breast cancer risk prediction models

The Gail model 2 is a risk-assessment model used in individual estimation of the absolute risk of invasive breast cancer developed in 1989⁽⁸⁾ and validated in Western studies⁽⁹⁾ but not accepted in developed Asian countries, where it over-predicts the risk of invasive breast cancer⁽¹⁰⁾. Risk factors in Gail model were taken from a screening questionnaire and included: age at menarche (i.e. at least 14 years, 12 to 13 years, or fewer than 12 years), age at first live birth (i.e. nulliparous, fewer than 20 years, 20 to 24 years, 25 to 29 years, or at least 30 years), previous breast biopsy (i.e. none, one, two or more), and number of first-degree relatives with breast cancer especially mother and sister/s (i.e. none, one, two or more). The main breast cancer predictors were: early menarche, a late age at first childbirth, multiple previous benign breast biopsies and first-degree relative with breast cancer history⁽⁸⁾. Initially mammography screening was done in all cases. The cohort had an average 5 years of follow-up. The model had a good global agreement between expected and observed counts. The Gail model has some limitations; it predicts a woman's risk only until the age of 80 years and it can't be used in women with strong family history. The Gail model has been modified over the years. Nowadays the Gail model is the basis for the Breast Cancer Risk Assessment Tool, a computer program that is available from the National Cancer Institute⁽¹¹⁾.

The Claus model is another risk-assessment model used in individual estimation of the absolute risk of invasive breast cancer developed in 1994. This model estimates the probability that a woman will develop breast cancer based on her family history of cancer, while others risk factors, like in Gail model, are excluded. This model can be used in women who have at least one female first- or second-degree relative with breast cancer. Paternal and maternal history, age at onset of breast cancer, family history of ovarian cancer along with the age of the woman is variable included in the Claus model. The model estimates the risk of developing cancer as lifetime probability or over 10-year intervals⁽¹²⁾.

A retrospective case-cohort study collected data from 6 different health plans which enrolled 666800 women with at least one of the following risk factors to develop breast cancer (with no bilateral prophylactic mastectomy): family history of breast cancer (i.e. two or more first-degree relatives, one first-degree relative with other affected relatives, one first-degree relative without other affected relatives, one second-degree relative, two or more second-degree relatives, any third-degree or more distant relative affected), a personal history of atypical hyperplasia, and one or

more breast biopsies with benign findings, lobular carcinoma *in situ*, microcalcifications or ovarian cancer and 276 women with risk factors who underwent a bilateral subcutaneous or more extensive mastectomy. Breast cancer was developed in only one (0.4%) of 276 women after bilateral prophylactic mastectomy during a 6 years follow-up, while in the unexposed women group (666.800) in 26 800 (4.0%). Using Gail model⁽⁸⁾ Geiger et al.⁽¹²⁾ estimated to have prevented 15 breast cancers in the group studied and also found that bilateral prophylactic mastectomy reduced by approximately 95% or more the risk of breast cancer among women with breast cancer risk factors⁽¹³⁾.

The place of genetic testing

An autosomal dominant predisposition to breast cancer has been suggested in high-risk groups. In 1990 breast cancer (BRCA)1 gene was identified and associated with breast cancer hereditary and few years later, in 1994 BRCA2 was mapped. Genetic testing for BRCA1 and BRCA2 mutations are available to the public since 1996. The carriers of BRCA gene form a clinical syndrome known as the Hereditary Breast/Ovarian Cancer (HBOC) syndrome and it is associated with high risk of breast and other cancers. Female carriers of mutations in BRCA1 or BRCA2 have a lifetime risk of breast cancer of 45%-85% (i.e. the higher percent in shown in Ashkenazi Jewish women^(7,14)) while male carriers of BRCA2 have a 5-10% estimated increased risk of breast cancer (higher than BRCA1 carriers). BRCA1 carriers have an estimated lifetime risk of 10-40% of ovarian cancer while in BRCA2 carrier the risk ranges between 10-20%⁽¹²⁾. BRCA1 and BRCA2 genes are responsible for approximately 15% of familial breast cancers, but there are also other highly penetrant genes which are usually associated with rare cancer syndromes that includes breast cancer (i.e. Li-Fraumeni, Cowden or Peutz-Jeghers syndromes)⁽¹⁵⁾. Women with strong family history are advised to undergo a genetic test for mutations. Models to predict the probability of identifying multiple genes mutations are currently available for breast cancer risk analyses. The performance of the models depends on the ethnic group⁽¹⁵⁾.

The role of prophylactic mastectomy among BRCA 1/2 mutation carriers

Hartmann and contributors⁽²⁾ identified 26 women with an alteration in BRCA1 or BRCA2 among patients included and estimated that the risk of breast cancer is reduced by 89.5%-100.0% in BRCA1 or BRCA2 mutation carriers after prophylactic mastectomy⁽¹⁶⁾. In a prospective study 139 women with a BRCA1 or BRCA2 mutation were monitored for approximately 3 years. Seventy-six out of the 139 women underwent bilateral prophylactic mastectomy. There was no case of breast cancer occurred among patients submitted to prophylactic mastectomy, while 8 patients who opted for surveillance developed breast cancer⁽²⁾. Rebbeck and contributors⁽¹⁶⁾ conducted a study on 483 women with

germline BRCA1/2 mutations. A total of 105 women underwent one of the following types of bilateral prophylactic mastectomy: total (i.e. simple) mastectomy (i.e. removal of both breasts and overlying skin without axillary dissections), subcutaneous mastectomy (i.e. removal of both breasts with preservation of overlying skin and nipple-areolar complex), modified radical mastectomy (i.e. removal of both breasts with overlying skin and axillary contents) and radical mastectomy (i.e. removal of both breasts with overlying skin, pectoralis muscles, and axillary contents). Breast cancer was diagnosed in two women among patients submitted to subcutaneous mastectomy and in 184 of 378 group control who did not have the procedure. Another two women developed breast cancer after subcutaneous bilateral prophylactic mastectomy after 2, 3, respectively 9 and 2 years. This study estimates that bilateral prophylactic mastectomy reduces the risk of breast cancer by approximately 90% in BRCA1/2 mutation carriers^(16,17).

Prophylactic skin-sparing mastectomy followed by nipple-areola complex reconstruction is a standard of care, but recently nipple-sparing mastectomy has begun to be performed more often. Different studies suggest that preservation of nipple-areola complex may increase the patient's satisfaction and can improve the cosmetic effect as well as the emotional health⁽¹⁸⁾. However important complications such as nipple necrosis or sloughing might develop⁽¹⁹⁾. The main problem faced in nipple-sparing mastectomy is the oncologic safety. The number of terminal duct lobular units that remain behind the nipple-areola complex is greater than in those behind the skin flap and this may increase the risk of breast cancer, but further studies are still required to estimate the residual risk level⁽²⁰⁻²²⁾.

The role of contralateral prophylactic mastectomy

Another population subgroup that can benefit from prophylactic mastectomy is represented by patients with unilateral breast cancer who opt for contralateral prophylactic mastectomy in order to prevent cancer in the contralateral breast. Ductal carcinoma *in situ* after initial lumpectomy usually develops at the same site where the previous one has been and in 40% of second ipsilateral breast tumors is an invasive cancer with a mortality of only 1.6% at 8 years⁽²³⁾. Other characteristics such as comedo type and the degree of comedo necrosis, micropapillary histologic tumor type or multifocality are associated with higher rates of recurrence⁽²⁴⁾. Women with lobular carcinoma *in situ* have a 8-9 times higher risk of developing an invasive carcinoma. The use of contralateral prophylactic mastectomy in patients with stage I, II, or III breast cancer increased from 1.8% in 1998 to 4.5% in 2003⁽²⁵⁾ while in patients with ductal carcinoma *in situ* the rate increased from 2.1% in 1998 to 5.2% in 2005⁽²⁶⁾. It is estimated that the annual risk of developing contralateral breast cancer ranges between 0.5%-0.75%^(27,28),

but increases to 3% in carriers of a BRCA1 or BRCA2 mutation⁽²⁹⁾. Into another meta-analysis the 15-year incidence of contralateral breast cancer was 6.5% in women with oestrogen (ER)-positive disease and 7.1% in women with ER-negative disease regardless of use of hormone therapy⁽³⁰⁾. Herrinton et al.⁽³⁰⁾ conducted a retrospective cohort study in which he included 50,000 women, 1,072 of them being submitted to contralateral prophylactic mastectomy (i.e. after either lumpectomy or mastectomy alone or in different combinations with chemotherapy, hormone therapy and radiation) and 317 women who did not. The study demonstrated that the risk of subsequent contralateral breast cancer was reduced by 97% in women who underwent contralateral prophylactic mastectomy and so did the breast cancer related mortality; however, the risk of metastatic breast cancer in other locations other than the contralateral breast was not influenced^(30,31). In a recent study a risk reduction of 95% was achieved. However the mortality rate remained unchanged⁽²⁹⁾. Although contralateral prophylactic mastectomy reduces the risk of contralateral breast cancer, it may not provide a significant gain in overall survival, therefore alternative therapies are mentioned such as the use of tamoxifen for women with ER positive tumors with a risk reduction of 50%⁽³²⁾. It seems that the higher incidence of contralateral breast cancer is among women with strong family histories, young ages (<35 years) at diagnosis and with ER-negative tumors⁽³³⁾. Beneficial survival was seen among younger women, stage I, and ER-negative breast cancer⁽³⁴⁾. Patients who underwent contralateral prophylactic mastectomy under 50 years of age with stage I or II, ER-negative had a 4.3% improvement in breast cancer survival compared to those with ER-positive breast cancer⁽³⁵⁾. Due to the fact that there is an increased trend for contralateral prophylactic mastectomy among women with low-to-moderate risk of developing a secondary cancer in the contralateral breast, there is a significant need to develop decision models to better identify the patients who are most likely to benefit from this surgical procedure.

Although randomized controlled trials to support recommendations of prophylactic surgery are still not available, prospective cohort studies on prophylactic surgery, like those presented above, have shown a consistent reduced risk in BRCA mutation carriers. European Society for Medical Oncology (ESMO) considers that prophylactic bilateral mastectomy is the most effective strategy available for risk reduction of breast cancer in this population, the recommendation being classified as a III, B one (i.e. prospective cohort studies, strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended). As presented before different surgical techniques have been used. Total mastectomy has been considered the standard surgical procedure in case of prophylaxis, because the skin-sparing mastectomy technique (III, B) and nipple-sparing mastectomy (i.e. III, C, grade C mentioned as insufficient evidence for efficacy or be-

nefit does not outweigh the risk or the disadvantages (adverse events and optional) could leave a substantial amount of breast tissue⁽³⁶⁾. Women at very high risk, without BRCA mutations, are considered by ESMO those with previous chest wall irradiation (i.e. lymphoma) and recommend bilateral prophylactic mastectomy for risk-reducing (i.e. III, A, grade A as strong evidence for efficacy with a substantial clinical benefit, strongly recommended). Contralateral prophylactic mastectomy is considered an option in BRCA mutation carriers with early breast cancer and unilateral mastectomy (i.e. IV,

C, level IV, retrospective cohort studies or case-control studies)⁽³⁶⁾.

Conclusions

Prophylactic mastectomy seems to be the most efficient way to prevent breast cancer development in high risk patients including BRCA1, 2 mutations carriers or in cases who had already been submitted to breast cancer surgery of the contralateral breast. Other cases such as patients who had been previously submitted to chest wall irradiation might also benefit from this surgical approach. ■

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