

# Risk Reduction Strategies in Breast Cancer Prevention

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## ABSTRACT

Evaluating the risk of breast cancer makes it possible to identify women with a high risk of developing breast cancer in the future. Adopting a healthier lifestyle, involving diet and exercise, is one way of reducing this risk-but there are other, non-modifiable risk factors, such as family history, genetics and diagnosis of premalignant lesions. In this high-risk population, the tracking must be rigorous and involve the participation of the patient herself, earlier and more frequent clinical assessment, and the use of imaging screening. Agents such as tamoxifen, raloxifene and aromatase inhibitors may be used in chemoprevention and may reduce the risk substantially. The risks and benefits must be assessed, and one must discuss with the patient her adverse events and the decision regarding the best treatment. Women who carry the BRCA1/2 mutation (very high risk) can benefit from prophylactic surgical interventions, such as bilateral mastectomy and/or bilateral salpingo-oophorectomy. This group of patients must be monitored by a multidisciplinary team, providing explanations prior to surgery regarding the surgical treatment offered, the reconstruction techniques, and the risks and complications.

**Keywords:** Breast, risk, mastectomy, serm oophorectomy

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## Introduction

The strategies for reducing the risk of breast cancer have been increasingly studied, principally for the group of women considered to be at high risk.

The main risk factors are genetic and family factors, reproductive history, lifestyle, dense breasts, previous chest wall radiotherapy prior to the age of 30 and/or breast biopsies with a diagnosis of atypical hyperplasia or lobular neoplasia (Table 1) (1).

The availability of means of identifying women at high risk, such as genetic tests for identifying the mutations in the BRCA1 and BRCA2 oncogenes, and statistical epidemiological indexes such as the Gail model, intensify the need to define the risks and benefits of protective measures for these women.

Approximately 10%-30% of all cases of breast cancer are attributed to hereditary factors; of these, only 5%-10% correlate with hereditary factors linked with high penetrance. Only a small fraction of these cases (4%-5%) is explained by mutations in high penetrance genes transmitted in an autosomal dominant manner (2).

Germinative mutations in the BRCA1 and BRCA2 genes are responsible for approximately 50% of the total risk for hereditary breast cancer. The prevalences estimated for carriers of mutations in BRCA1/2 are, respectively, 0.11% and 0.12% in the general population, and between 12.8%-16% in high risk families with three or more cases of breast or ovarian cancer (Table 2) (3).

These are associated with tumors in younger women. The risk in the general population is of 1/800, although among Ashkenazi Jews it is 2.3% (4).

Recent technological advances in the area of large-scale parallel sequencing have identified that the remaining 50% of cases of breast cancer are due to a combination of the effects produced by mutations in genes of high,

moderate and low penetrance (5). Several of these genes have been identified and associated with other neoplasias (Table 3).

**Clinical and research implications**

The preventive measures for women at high risk are:

**1- Tracking by imaging**

The screening of these patients is based initially in the risk assessment (6).

- A) Women with previous history of breast cancer: Clinical assessment every 4-6 months in the first 5 years, and annual mammogram. Additional imaging scans follow the same recommendations as for normal risk (7).
- B) ≥35 years old, presenting a risk of invasive breast cancer in 5 years ≥1.7% according to the Gail Method: Clinical assessment each 6-12 months with a specialist, and annual mammogram (8, 9).
- C) Women with a lifetime risk of breast cancer of >20%, based in dependent models of the family history (Claus, Tyrer-Cuzick) (10): Clinical assessment with a specialist each 6-12 months after the

**Table 1. Risk factors - family and personal history**

1. Family history: women with first-degree relatives who had breast cancer prior to the age of 50, bilateral or multiple relatives with breast cancer or ovarian cancer.
2. Personal history of cancer: women who had breast cancer have a greater risk of developing cancer in the contralateral breast.
3. Presence of genetic mutation in the BRCA1 or BRCA2 genes.
4. Multiple breast biopsies with diagnosis of precursor lesions with atypia and principally in situ lobular carcinoma.
5. Diffuse changes in dense breasts, principally microcalcifications, hinder follow-up, but in isolation do not characterize indication for surgery.
6. History of chest wall radiotherapy before the age of 30, principally for treatment of Hodgkin lymphoma.
7. Two or more first-degree relatives with breast cancer
8. One first-degree relative and two or more second-degree relatives or third-degree relatives with breast cancer
9. One first-degree relative with breast cancer prior to the age of 45, and another relative with breast cancer
10. One first-degree relative with breast cancer and one or more with ovarian cancer

**Table 2. Risk factors from the family history due to being a BRCA1/2 mutation carrier**

- Known BRCA1 and 2 mutation
- Breast cancer and ovarian cancer
- 2 or more cases of breast cancer < 50 years old in the family
- Male breast cancer
- One or more cases of cancer in the family when of Ashkenazi descent
- Ovarian cancer in person of Ashkenazi descent

**Table 3. Syndrome gene or locus associated neoplasia genes with high penetrance mutations**

	<b>Biochemical Mechanisms</b>	
Hereditary breast and ovarian cancer syndrome (HBOC)	BRCA1 (17q12-21) BRCA2 (13q12)	Female breast, ovarian cancer prostate and pancreatic cancers
Li-Fraumeni Syndrome	TP53 (17p13.1)	Breast, sarcomas, leukemias, brain tumors, adrenocortical carcinoma and lung cancers
Cowden Syndrome	PTEN (10q23.3)	Breast, thyroid, endometrium, benign hamartomas and megalencephalies
Peutz-Jeghers Syndrome testicles and colon	STK11(19013.3)	Cancers of the breast, cervix, uterus, ovaries, uterus,
Hereditary gastric cancer	CDH1 (16q22.1)	Hereditary diffuse gastric cancer, breast, lobular and colorectal cancers
	<b>Genes with moderate penetrance mutations</b>	
Syndromes related to ATM	ATM (11q22.3)	Breast and ovarian cancers
Syndromes related to CHEK2	CHEK2 (22q12.1)	Breast, colorectal, ovarian and bladder cancers
Syndromes related to PALB2	PALB2 (16p12.1)	Breast, pancreatic, ovarian, male breast cancers
Moderate risk of Breast and Ovarian Cancer	BARD1, MRE11A, NBN, RAD 50, 51C e 51D XRCC2	Breast and ovarian cancers

Table 4. Biochemical and molecular association between diabetes mellitus Type II and breast cancer

Biochemical Mechanisms	
Insulin	Insulin, which is secreted in increased amounts in type 2 diabetes, was shown to be mitogenic in breast tissue. This is compounded by the fact that insulin receptors tend to be over-expressed in breast cancer cells. In fact, circulating level of C-peptide as a marker for insulin secretion has been shown to be positively associated with risk of breast cancer in some studies
Insulin-like growth factor-1 (IGF-1)	Increase in insulin secretion is accompanied by an increase in the serum level of IGF-1, which may also contribute to tumor growth and thus can predict the risk of breast cancer in premenopausal women.
Estrogens and androgens	Increased levels of insulin also lead to higher levels of serum estrogens and androgens through inhibition of sex hormone-binding globulin. Increased levels of estrogen and testosterone have been associated with an increased risk of breast cancer in post-menopausal women.
Molecular Mechanisms	
Insulin Receptor (IR)	IR is a heterotetrameric protein consisting of four subunits; two subunits bind insulin, while the other two subunits span the membrane, protrude into the cytosol, and have tyrosine kinase activity. Two isoforms of the insulin receptor are produced by alternative splicing: IR-A (the fetal isoform) and IR-B. In most cancers, fetal IR-A predominates because it mediates mitogenic rather than metabolic effects.
Insulin-like growth factor-1 receptor (IGF-1R)	(IGF-1R) is 60% homologous with IR and also has tyrosine kinase activity upon ligand binding by IGF-1. It promotes mitogenic, metastatic, and anti-apoptotic processes in breast cancer cells through the PI3K/Akt pathway. Because insulin and IGF-1 can bind to both IR and IGF-1R with different affinities, both ligands can enhance growth and survival
Insulin receptor substrate-1 (IRS-1)	In type 2 diabetes, insulin resistance arises from the up-regulation of cytokines and derivatives of free fatty acids. These lead to activation of protein kinase C-zeta (PKC-zeta), which phosphorylates insulin receptor substrate-1 (IRS-1), impairing its ability to activate the PI3K/Akt pathway upon ligand binding (39). It is possible that hyperglycemia and high insulin levels develop. Activation of IGF-1R by these high insulin levels can therefore lead to activation of the mitogenic and anti-apoptotic pathways, leading to an increased risk of cancer. Metabolic syndrome very often results in these patients; this is characterized by hypertension, insulin resistance, obesity, and dyslipidemia
IGF-1: insulin-like growth factor-1; IR: insulin receptor; IR-A: insulin receptor isoform A (fetal); IR-B: insulin receptor isoform B; IGF-1R: insulin-like growth factor-1 receptor; PI3K: phosphatidylinositol 3-kinase; Akt: protein kinase B; IRS-1: insulin receptor substrate-1; PKC-zeta: protein kinase C-zeta	

age of 30, and an annual mammogram – also, consider annual magnetic resonance imaging (11).

- D) Previous history of chest wall radiotherapy between the ages of 10-30 years old (12) ≥25 years: annual mammogram, annual magnetic resonance imaging, clinical assessment with a specialist each 6-12 months, beginning 8 to 10 years after exposure to chest wall radiotherapy, or from the age of 40 (whichever comes first). <25 years old: risk counseling and annual clinical assessment with a specialist, 8 to 10 years after exposure (13, 14).
- E) Diagnosis of in situ lobular carcinoma (ISLC) or atypical hyperplasia: Clinical assessment each 6-12 months and an annual mammogram subsequent to diagnosis. One retrospective study assessed the use of magnetic resonance imaging associated with mammograms in this group of patients. Breast cancer was detected by the MRI in 4% of the patients for whom the mammograms were normal and diagnosis of ISLC and had no impact on patients with atypical hyperplasia. The routine use of screening with magnetic resonance imaging, therefore, is not indicated (15, 16).
- F) Suggestive or known genetic predisposition (BRCA1/2): Clinical assessment each 6-12 months after the age of 25, annual mammogram and magnetic resonance imaging after the age of 25 or based on the earliest age of diagnosis for breast cancer in the family (11, 17-19).

## Mammography

The sensitivity of mammograms in women with dense breasts has a significant decrease of <48% (>97% in fatty breasts), culminating in failure to diagnose cases of breast cancer in this population in 37-70% of cases (20). For this reason, and based in the fact that women with

dense breasts are considered high risk, the use of imaging examinations in addition to mammograms is sometimes necessary.

Although some studies have suggested the use of ultrasound in conjunction with mammograms in tracking breast cancer in women with dense breasts, there are as yet insufficient studies providing evidence for the routine use of this, when there are no other associated risk factors (6, 21).

## Automated breast ultrasound system (ABUS)

A new technology has been developed as an alternative to traditional ultrasound, the aim being to increase its accuracy and reduce the duration of the examination (7 minutes vs. 30 minutes), and the human failure rate (22).

Siemens Healthcare, U-Systems Inc. and SonoCiné developed ABUS, which involves the use of high-frequency waves and 3-D volumetric imaging technology for the entire breast. This 3-D image benefits the population with dense breasts, as it allows the radiologist to assess the breast from various angles, and to produce a better interpretation of the examination. At the time of writing, there are three systems in use worldwide.

Automated breast ultrasound produces a 97% increase in sensitivity when used in conjunction with mammography. As this is a new technology, further studies are necessary, as is the training of the radiologists and the operators (23).

## 2- Changes in lifestyle

Undertaking physical exercise and changing one's diet are the factors explored most in studies. In the major cities, greater sedentariness and a poor diet have been observed.

Studies assessing the interaction with physical activity have been increasing in frequency, and have already demonstrated a reduction in the levels of insulin and in the inflammatory reaction, and an improvement in cellular immunity, in such a way as to reduce the risk of breast cancer. When the disease is already present, physical activity has been associated with modification of the disease's staging, the body mass index, and the status of the estrogenic receptors (24).

START (Supervised Trial of Aerobic versus Resistance Training) was a Canadian study, involving the participation of 242 women diagnosed with breast cancer that were recruited between 2003 and 2005, and monitored over a minimum period of 7.5 years. They were divided into 3 groups with the objective of assessing the effect of physical exercise during chemotherapy. In the first group, the patients remained with their usual care alone, the second group was composed of those who received supervised aerobic exercise, and the third was made up of women carrying out resistance exercises. This study's main objective was to assess the disease-free survival (DSF), while its secondary objectives were to assess global survival, disease-free survival and the recurrence free interval.

Exercise during chemotherapy helps in the treatment completion rate, without need for changes in the drugs and/or their dosages. Physical activity seems to strengthen the effect of the drugs used in the chemotherapy, due to influence in the distribution and metabolism of the same.

Resistance exercises increase muscular force by 25-30%, and the lean body mass, which has been proven to be linked to lower rates of mortality in the general population. The aerobic exercises, besides leading to weight loss, prevent weight gain. Weight gain-more precisely, the increase in body fat-in patients diagnosed with breast cancer, is associated with the early recurrence of the disease and lower rates of survival. The difficulty of this type of study lies in the recruitment and adherence of the patients, due to the side effects of the chemotherapy treatment.

The daily practice of exercise, consumption of low-calorie food rich in greens, fruits and vegetables, not smoking, not drinking alcohol to excess and keeping oneself within the ideal weight for one's age are simple measures which can make all the difference (25).

### 3- Chemoprevention (26)

Chemoprevention (tamoxifen, raloxifene, anastrozole, exemestane) is recommended for women  $\geq 35$ . Its usefulness in women  $< 35$  years old is unknown.

The importance of estrogen in the pathophysiology of breast cancer, confirmed by clinical, laboratory and epidemiological evidence, means that chemoprevention-through the use of anti-estrogenic medications, or medications that have an antagonist action on estrogen-is an important alternative in this type of approach.

The selective estrogen receptor modulators (SERMs) are medications which bind to the estrogen receptors and act as estrogenic agonists in specified tissues (e.g. bone tissue) and as antagonists of estrogen in others (the uterus and breasts). Due to the fact that they antagonize the estrogenic effect in the breast, the SERMs are excellent candidates for use in the chemoprevention of breast cancer.

Tamoxifen, a first generation SERM, reduces the risk of breast cancer in women at high risk of this disease. The use of tamoxifen in the

prevention of breast cancer has been evaluated in four main clinical studies: the Breast cancer prevention trial (BCPT) undertaken by the National Surgical Adjuvant Breast and Bowel Project (NSABP P-1), the Royal Marsden Trial (RMT), the Italian National Trial (INT) and the International Breast Cancer Intervention Study (IBIS study) (27, 28, 29).

The NSABP P-1 study assessed 13.388 women, and the results showed a reduction in the incidence of invasive and noninvasive breast cancer in approximately 50% of women at high risk, which led to the drug's approval in 1998 by the Food and Drug Administration (FDA), as indicated for the reduction of the incidence of breast cancer in this population. Furthermore, this study showed a reduction of approximately 80% in the risk of invasive breast cancer in those patients with a previous diagnosis of atypical hyperplasia. However, women aged more than 50 years old, using tamoxifen, presented a risk of developing endometrial cancer which was 2.5 times greater, and a threefold increase in the relative risk of pulmonary thromboembolism (28).

The European studies-the Royal Marsden Trial and the Italian National Trial – did not reproduce the results obtained in the NSABP P-1, which was explained by the sample size of the population selected (low risk for breast cancer). A reduction in the risk of breast cancer in the subgroup of women receiving hormone replacement therapy (HRT) when the study began, or who initiated HRT during the study, was observed. In a meta- analysis of three clinical studies, a statistically significant reduction of 38% in the risk of breast cancer, with tamoxifen, was evidenced (30).

The use of tamoxifen for 5 years leads to a statistically significant reduction in the incidence of breast cancer in women at high risk of the disease. This reduction took place through the lower incidence of estrogen-receptor-positive tumors, there being no difference in comparison with placebo in those cases which did not express estrogen receptors. However, the toxicity and the presence of adverse events, such as hot flushes and increase in the risk of pulmonary embolism and endometrial cancer make it important to select patients among whom the benefits should be clearly greater than the possible risks.

Recent studies suggest that the rate of abandonment of chemotherapy with tamoxifen is high, reaching 46% after 4.5 years of use (30).

Raloxifene hydrochloride is a second generation SERM which binds with high affinity to the estrogenic receptors, in particular the alpha receptors, and presents intense antiestrogenic activity in the uterus and breasts, and estrogenic activity in the bone tissue (6, 7). Raloxifene is a well-tolerated drug, and does not increase the incidence of mastalgia, vaginal bleeding or carcinoma of the endometrium. The principal adverse events are vasomotor symptoms (hot flushes), thromboembolism and cramps. There is a threefold increase in the relative risk of thromboembolism related to the use of raloxifene, the absolute risk being of 0.8%.

The MORE (Multiple Outcomes of Raloxifene Evaluation) study was a multicenter study undertaken in 25 countries. It was randomized, double-blind and placebo-controlled, and included 7.705 postmenopausal women. The study's primary objective was to assess the efficacy of raloxifene in the reduction of the risk of vertebral fractures. The reduction in the risk of breast cancer was one of the study's secondary objectives. The patients who participated in the MORE study also underwent annual mammograms. A statistically significant reduction of 76% was observed in cases of invasive breast cancer with positive estrogen receptor, in the

women in the raloxifene group, in comparison with the placebo group. When only the cases of tumors with positive estrogen receptors were analyzed, the reduction in relative risk was 84%. There was no reduction in estrogen receptor negative tumors after three years of treatment. The study's follow-up period was four years (31).

The CORE (Continuing Outcomes Relevant to Evista) study was a multicenter study which evaluated the efficacy of the use of raloxifene for over 4 years for preventing invasive breast cancer. A total of 4,011 patients were recruited, who had already participated in the MORE study, totaling 8 years. At the end of the study, a 66% reduction in the risk of invasive breast cancer (independently of the presence of estrogenic receptors in the tumor) was observed among the patients using raloxifene 60 mg/day, in comparison with the placebo group. When the analysis was undertaken separately, taking into account the presence of estrogen receptors in the tumor, the reduction in the risk was of 76% in patients using raloxifene, in comparison with those using placebo. The two analyses were shown to be statistically significant ( $p < 0.01$ ) (32).

The effect of raloxifene on breast density was assessed in one study involving 280 postmenopausal women with osteopenia or osteoporosis, divided into two groups: combined hormone therapy (CHT) and raloxifene. In the CHT group, 27.4% of the women presented an increase in breast density in the mammogram, as opposed to 0.9% of the women in the group taking raloxifene. It follows that in postmenopausal women with low bone mass, therapy with raloxifene for 12 months does not increase breast density in the mammography, while CHT leads to a significant increase.

In the MORE study, the incidence of vaginal bleeding and of endometrial cancer among women taking raloxifene was similar to the group using placebos, this data being compatible with the antagonist action of estrogen in the endometrium (31).

The STAR (Study of Tamoxifen and Raloxifene) study was sponsored National Cancer Institute (NCI) and undertaken by a multicenter group of investigators. It included more than 19,000 women who presented a higher risk of invasive breast cancer and who were randomly assigned to take either raloxifene 60 mg/day or tamoxifen 20 mg/day. The study aimed to evaluate raloxifene's efficacy in reducing the risk of developing invasive breast cancer, as well as its safety in the long-term, in comparison with tamoxifen. The women who participated in the STAR study were postmenopausal, were aged at least 35 years old, and had a higher risk of breast cancer. Both raloxifene and tamoxifen reduced

-in a similar manner-the risk of developing invasive breast cancer by approximately 50%. In addition to this, the women using raloxifene had a 36% lower risk of uterine cancer and 29% fewer episodes of deep vein thrombosis and pulmonary embolism in comparison with the women in the group using tamoxifen (33).

Raloxifene was shown to be a drug as efficacious as tamoxifen in reducing the risk of breast cancer in women at high risk of this disease, with fewer adverse events such as uterine cancer.

### Aromatase inhibitors

Aromatase inhibitors (AIs) potentially suppress the conversion of androgen to estrogen and block the production of estrogen not only in the normal tissues, but also in the neoplastic cells (29). Due to their different mechanism of action, AIs are better tolerated than tamoxifen and present a lower cardiovascular and endometrial risk. The AIs' safe-

ty profile is superior to tamoxifen's, with the exception of the potential increase in osteoporosis due to estrogen depletion.

The results of 5 years of anastrozole in adjuvant therapy for breast cancer demonstrated a striking reduction in the incidence of contralateral breast cancer in comparison with tamoxifen, particularly in patients with positive hormonal receptors (reduction of 53%, CI 95% 25-71,  $p = 0.0001$ ). As tamoxifen was capable of reducing contralateral cancer by 50% in comparison with the placebo, one can imagine that anastrozole reduces or delays the risk of developing breast cancer by up to 80% (31).

These results have been reproduced with other AIs, raising the possibility of use of AIs as chemoprevention for breast cancer.

Controlled studies with placebos, exemestane and anastrozole in postmenopausal women with risk factors for breast cancer have demonstrated at least 50% efficacy in reducing invasive breast cancer and that they were well-tolerated. Vasomotor symptoms were experienced, and differences were not observed in fractures or cardiovascular events. The AIs are an alternative for postmenopausal women at high risk who want chemoprevention, but who are contraindicated for SERM.

The data showing a lower incidence of breast cancer with raloxifene, both in postmenopausal women and in the high-risk population analyzed in the STAR study, provide a new perspective in reducing the risk of breast cancer. Tamoxifen continues to be the drug of choice for secondary prevention in the contralateral breast in women who have already undergone mastectomy, as this was not the population evaluated in the STAR study (33).

The use of aromatase inhibitors is restricted to postmenopausal women. We await data from prospective multicenter studies so as to include its use in our practice.

### Metformin and new clinical trials

In one meta-analysis with 20 studies, the association between diabetes mellitus and increase in the risk (20%) of developing breast cancer was demonstrated; this increase can reach 23% in menopausal women. An increase in mortality from breast cancer was also evaluated (34).

Biochemical and molecular association between type II diabetes mellitus and breast cancer Table 4 (35).

Recent studies have shown a reduction of 50% in the incidence of cancer among patients using metformin for more than 4 years. The mechanisms explaining metformin's action are complex and as yet difficult to understand. Metformin seems to directly and indirectly regulate (through the insulin) the proliferation rate of tumor progenitor cells in premalignant lesions, preventing or delaying tumor formation. One can also prevent the recurrence of cancer through this regulation in the proliferation of the latent cancer stem cells (36).

Cancer is the second most common cause of death worldwide, with diabetes being the 12th. The use of metformin as an antidiabetic drug and for chemoprevention of breast cancer will bring numerous benefits and positive results.

### Risk-reduction surgery

The surgical resources for reducing a woman's risk of developing breast cancer are the prophylactic mastectomy, skin-sparing mastectomy, and salpingo-oophorectomy.

The prophylactic mastectomy may be applied in two situations: contralateral mastectomy synchronous with the treatment of the primary tumor and as a bilateral procedure in women at high risk of developing this disease.

An evaluation by the multidisciplinary team-specialist in breast disease, oncologist, plastic surgeon, psychologist and geneticist-must be undertaken in order to define if surgery is indicated, to ascertain whether the patient is prepared for the possibility of a dissatisfactory esthetic result, and to define the best surgical technique and best option for reconstruction. The individualized selection of the patient is fundamental.

The risk-reduction or prophylactic mastectomy is the surgical removal of the breast tissue. It is worth emphasizing that no mastectomy technique can guarantee the total removal of the mammary gland, due to the impossibility of establishing its real limits, given that it is close to the skin and extends to the axilla. It is estimated that surgery can provide a reduction of 90% in the risk-therefore, the more radical the surgery, the greater the protection it affords (37).

The benefit of prophylactic surgery varies according to the risk of developing the disease: in women with a risk of 40% during their lifetime, prophylactic surgery adds a further 3 years of life; in women for whom the risk is 85%, this number rises to over 5 years (38).

In the case of a woman with a first-degree relative with breast cancer, the ideal is that the mastectomy should be undertaken before the patient reaches the age at which the relative was diagnosed. However, physicians recommend preventive mastectomy only for women who have already finished having children.

### Techniques

The techniques consist of: Simple mastectomy (removal of the entire gland and PAC), skin and papillary-areolar complex sparing adenomastectomy (removal of the gland while preserving the skin and PAC)-this technique is the one that leaves the highest

proportion of residual breast tissue, and skin-sparing adenomastectomy (removal of the gland while preserving the skin).

Some patients must be considered to be at greater risk of occult carcinoma-such as those who present with abnormal findings in their mammogram and/or preoperative MRI, those who have not undergone a previous biopsy, or those who have a family history and did not undertake resonance prior to surgery. In these cases, the undertaking of a sentinel lymph node biopsy would be indicated in order to obtain the axillary staging (39, 40).

The reconstruction can be done with silicon prostheses, tissue expanders, or dermo-muscular flaps from the abdomen or back. In some cases, both may be used. The papillary-areolar complex can be reconstructed either with tissue from the vulvar region or through tattooing (Figures 1, 2, 3).

It is important to inform the patient regarding the risks of complications, and to emphasize the possible sequelae such as change in temperature, sensitivity and shape. For women who smoke, one must reinforce the importance of stopping smoking so as to prevent complications.

Currently, there is the possibility of autonomization of the nipple-areola complex. This technique involves dissection through a small

incision of 0.5 cm on the inferior margin of the areola, the nipple is detached from the mammary gland, but remains attached to the skin, through which it receives all of its vascularization. The tissue behind the nipple is sent for biopsy. This procedure must be undertaken 15 days prior to the surgery (Figure 4).

While the rate of mastectomy has declined in recent years, more and more women with unilateral breast cancer are opting to have both breasts removed. Researchers have questioned whether the contralateral prophylactic mastectomy has been used more than necessary (41).

In one recent study held in the Sloan-Kettering Memorial Hospital, an increase was observed in the indication of contralateral prophylactic mastectomy, from 6.7% to 24.2% over a period of 8 years. In a genetic study of these 407 women, only 13% were genuinely at greater risk of developing a second breast cancer.

One study published in the National Cancer Institute's Journal (30) showed an improvement in the cancer-specific survival at 5 years in women who had undergone contralateral prophylactic mastectomy in young women with initial breast cancer and negative hormonal receptors (88.5% vs. 83.7%). In contrast, older women-with more advanced disease and with positive hormonal receptors-were not shown to have benefited from contralateral prophylactic surgery.



Figure 1. Inframammary incision with implants



Figure 2. Radial incision and PAC. Immediate post-operative period



**Figure 3.** Autonomization of the PAC



**Figure 4.** Risk reduction and sentinel lymph node surgery in the breast, with autonomization of the PAC

In 2011, Dr. Morrow presented a study (42) at the ASCO which demonstrated that women with greater anxiety regarding local recurrence were three times more likely to opt for radical surgery. She questioned whether it is ethical to treat anxiety with surgery, and concluded that further prospective studies were necessary to answer the question of whether the contralateral mastectomy had real benefits, and for which subgroup of patients.

### Salpingo-oophorectomy

Prophylactic salpingo-oophorectomy is commonly recommended for carriers of the BRCA1 and BRCA2 mutations, in order to reduce the risk of breast cancer and ovarian cancer. In Canada, approximately 60% of women with the BRCA1 and BRCA2 mutations undergo prophylactic oophorectomy within 1 year of being diagnosed as having a BRCA mutation.

One case-control study in the general population showed that the bilateral oophorectomy in menopausal women is associated with a significant reduction in the risk of breast cancer. Several studies have also shown that the oophorectomy is efficacious in reducing the primary risk and the risk of contralateral breast cancer in BRCA1 and BRCA2 carriers. In that study, among women with the BRCA1 and BRCA2 mutations, the bilateral oophorectomy was associated with a highly significant reduction in the risk of subsequent breast cancer. The oophorectomy provided a substantial reduction in the risk for 15 years after the operation. Further studies will be necessary to establish whether the protection persists for longer than that. These results confirm the findings reported previously, in much smaller studies of women with hereditary susceptibility to breast

cancer and ovarian cancer. The results of these studies support the hypothesis that the suppression of estrogen reduces the risk of breast cancer, whether this is sporadic or hereditary. This result was rather unexpected, given that the majority of the tumors associated with BRCA1 are estrogen receptor negative, but there are various other hormonal modifiers related to the risk of breast cancer in which BRCA1 was identified (3).

The reduction in the risk of breast cancer seemed to be greater for carriers of the BRCA1 mutation who underwent oophorectomy prior to the age of 40, although a protective effect has also been observed in older women. The lowest magnitude in reduction of the risk was observed in BRCA2. It is probable that the lower global effect in BRCA2 is due to the patient's age at diagnosis and, consequently, on average, a greater period of time occurs between the oophorectomy and breast cancer for BRCA2 than for carriers of BRCA1 (10.5 years for BRCA2, as against 7.2 years for carriers of BRCA1). A total of 31% of carriers of BRCA2, who underwent oophorectomy, underwent this procedure 15 years or more before the appearance of their breast cancer, in comparison with 21% of carriers of BRCA1. However, during the 15 year period after oophorectomy, the level of the reduction of risk was similar for both mutation subgroups, although the BRCA2 sample size was far lower, and the result was of borderline significance. It is possible that the difference observed in the risk of breast cancer after the oophorectomy in BRCA1 as against BRCA2 may reflect biological differences in carcinogenesis (43).

Prophylactic oophorectomy is associated with a lower risk of surgical complications, but may result in the sudden beginning of the symptoms of the menopause. The long-term complications of the early surgical menopause include an increased risk of diseases of the heart, and

of osteoporosis, in conjunction with a reduction in libido. Hormone replacement therapy up to 50 years of age is frequently recommended in order to prevent these complications. However, hormone replacement has not been shown to reduce the risk of cardiovascular diseases and it is not yet known to which point hormone replacement reduces oophorectomy's protective effect in relation to the risk of breast cancer (44, 45).

In summary, a significant degree of protection against breast cancer was ascertained among carriers of BRCA1, but no similar significant reduction was observed for BRCA2. The protective effect may be limited to the period of 15 years after the operation. The strongest effects were observed for patients aged 40 years old and for early-age-onset breast cancers (diagnosed before 40 years of age) in carriers of BRCA1. In view of the normally early onset of hereditary breast cancers, we recommend that preventive oophorectomy should be considered for women carrying the BRCA1 or BRCA2 mutations, who are 35 years old and over. This operation is also envisaged to avoid ovarian cancers in this high-risk group.

Recent studies have suggested that ovarian cancer may originate in stem cells located in the distal portion of the fallopian tubes, and recommend salpingectomy as efficient for premenopausal women, leaving the oophorectomy for after the menopause (46).

### Possible risks and complications

The complications which can occur are inherent to any surgical procedure-such as infection, hemorrhages, inflammation and breaking of sutures. The surgery can cause emotional sequelae due to the trauma of having the breast removed as-even with the reconstruction-the feeling of loss, and drop in self-esteem, must be worked upon. More specific risks involve the necrosis of the breast and areola and deformation of the silicon prosthesis.

There is also the chance that the patient may not be satisfied with the result of the preventive mastectomy. Patients who have a greater post-operative risk, such as smokers, the obese, or people with comorbidities such as diabetes or hypertension have provisos for undertaking the preventive mastectomy, as a result of which it may be contraindicated in some cases.

The preventive mastectomy surgery is carried out by a specialist in breast disease. However, a multidisciplinary team as indicated, which must include a plastic surgeon, to do the breast reconstruction, and a psychologist to accompany the entire process of removal of the breasts, from the medical consultation through to the postsurgical follow-up, so as to mitigate possible emotional sequelae for the patient.

### Conclusions

Prophylactic mastectomy is a good option for prevention of breast cancer in women at high risk of this disease, but the method's efficacy is not totally known. Women who are candidates for the surgery must listen to specialists and gain a thorough understanding of the benefits and limits of the technique. The clinical studies undertaken have shown a reduction in the incidence of breast cancer of 90% in women who undergo the operation the same studies demonstrated a reduction from 81% to 94% in the risk of death from breast cancer.

In the Johns Hopkins University, only 10% of patients who were offered the surgery accepted it. Long-term studies of satisfaction have

evidenced that 4% of patients regretted having the operation, and that 44% said that they should have done it 10 years earlier.

In the clinical decision to undertake the surgery, the following factors need to be taken into account:

- The need for reconstructive surgery
- The effect of the surgery on body image and sexuality
- The irreversibility of the decision
- Clarification that not all women who undergo the operation would have had breast cancer.

In relation to the risk-reduction Salpingo-oophorectomy

- These reduce the incidence of breast cancer and ovarian cancer
- They reduce mortality from breast cancer and ovarian cancer
- They present the best results when undertaken prior to the age of 40

**Informed Consent:** Informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - M.C.; Design - M.C.; Supervision - M.C., P.S.; Resources - M.C., P.S.; Materials - P.S.; Data Collection and/or Processing - M.C.; Analysis and/or Interpretation - M.C., P.S.; Literature Search - P.S.; Writing Manuscript - M.C., P.S.; Critical Review - M.C.

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