



Risk-reducing Mastectomy along with Breast Reconstruction – the Current State of Knowledge

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Abstract

Risk-reducing mastectomy (RRM) with breast reconstruction is performed in women at high risk and highest risk of breast cancer incidence. The objective of this work is to discuss current recommendations with regard to performance of such a type of surgeries based on recommendations accepted both in Western Europe, as well as in the United States and recently, also in Poland. The work presents principles of qualification for RRM, the types of performed surgeries of breast removal and reconstruction as well as complications related to them. Risk-reducing mastectomy consists in bilateral breast removal in women at high and highest risk of the disease and is a form of primary prevention. After RRM performance there is a possibility of surgical restorative treatment - breast reconstruction.

Reconstruction may be carried out using implants, tissues of a patient (most often musculocutaneous flap) or a combination of these methods, either in a deferred mode or immediately after breast amputation. An informed decision is taken by a patient after a very detailed and in-depth analysis of pros and risks related to the surgery presented to her by a team consisting of: an oncologist surgeon, a medical geneticist, a psychologist and a rehabilitator. The scope of psychological and rehabilitation care of women after the RRM has not been clearly defined yet. Discussion with regard to other methods of primary prevention of breast cancer goes beyond the scope of this work.

Key words: risk-reducing mastectomy, breast reconstruction, breast cancer

Introduction

Women in the case of who the lifetime risk of breast cancer incidence is estimated at the level of >20% according to the National Comprehensive Cancer Network or >30% according to the National Institute for Health and Care Excellence, should be informed about a procedure that reduces the risk of breast cancer incidence, such as: removal of ovaries and fallopian tubes, taking hormonal drugs (e.g. tamoxifen, exemestan) or bilateral breast amputation (RRM) with the possibility of a surgical restorative treatment (breast reconstruction).

Surgeries reducing the risk of breast cancer incidence may be carried out only in women older than 18 years of age, who are at high or very high lifetime risk of this cancer incidence and their life expectancy is ≥ 10 years. A decision to choose this method of conduct should always be conscious [1,2,3,4,5].

Determination of the groups of a high and very high risk of breast cancer incidence

Selecting women with risk factors for breast and/or ovarian cancer incidence from the general population requires performance of genetic analyses. Women from families with a history of breast and/or ovarian cancer (including male breast cancer) and other malignancies, especially those diagnosed when <50 years of age, are eligible for the examinations.

Carriers of pathogenic gene mutations should have preventive examinations aimed at early detection of breast and/or ovarian cancer or other malignant neoplasms performed more frequently and they should be informed about surgical and conservative procedures reducing the risk of developing these neoplasms.

Based on statistical methods and the theory of probability, a division into three groups of a risk of breast cancer incidence was developed and it is presented in Tables 1 and 2.

The lifetime and accumulated risk (within the age range from 0-79 years) of breast cancer incidence in Poland, in 2010, amounted to 6,3% [6]. Women from the groups of a very high and high risk of breast cancer incidence are qualified for RRM. The analysis of genetic and family predispositions is presented in Tables 3 and 4 [7,8,9,10,11,12].

Table 1. A moderate, high and very high risk of breast cancer incidence expressed as a chance of the disease occurrence (%) (National Institute for Health and Care Excellence, 2013, updated 2017) [13,14]

A woman's age	A moderate risk (indirect)	A high risk	A very high risk (the highest risk)
Accumulated risk of incidence 40-50 years of age	3%-8%	>8%	8%-30%
Lifetime risk of incidence*	17-30%	>30%	≥50%

*The lifetime risk of breast cancer incidence, assuming the age of 20 as the lower limit, and the upper limit for the age close to the average life expectancy of women in the Polish population (mainly includes women who are at risk of developing cancer being a new case in the population).

Table 2. A moderate, high and very high risk of breast cancer incidence expressed as a number (a relative risk) defining the risk of the disease development in the group of women exposed to a potentially pathogenic agent compared to the group of women who are not exposed (understood as the general population) [13,14]

A woman's age	A moderate relative risk** (indirect)	A high relative risk	A very high relative risk (the highest risk)
0-79 years	2-3	~5	≥10

**The risk of breast cancer incidence in the group of women exposed to a potentially pathogenic agent in comparison with the non-exposed group (understood as the general population).

Table 3. The group of a very high lifetime risk of breast cancer incidence ($\geq 50\%$) [13,14]

The group of the highest risk of breast cancer incidence includes individuals with a defined:	
Genetic factor and/or	A pathogenic mutation of the BRCA1 or BRCA2 or TP53 or PTEN*** gene confirmed in a molecular study
Family factor and/or	≥ 3 breast cancer cases in the 1st or 2nd degree relatives (including a female probant) in one family line regardless of the age at which the disease occurred
	Female probants whose first degree relatives had breast and ovarian cancer (synchronous or metachronic disease)
	Female probants whose first-degree relatives had a few (≥ 2) primary cancer of the pancreas, prostate, endometrium, thyroid, leukemia or malignant brain tumor
Other	Chest radiation below 30 years of age (relative risk: 7.0-17.0)

***A lifetime risk of breast cancer incidence among carriers of PTEN gene mutation amounts to 25%-85% and depends on the kind of mutation and the frequency of breast cancer incidence among relatives of the mutation carrier.

Table 4. The group of a high lifetime risk of breast cancer incidence ($> 30\%$) [15,16]

The group of a high risk of breast cancer incidence includes individuals with a defined:	
Genetic factor and/or	Pathogenic mutation of the CDH1 or STK11 gene confirmed in molecular studies (the risk is also referred to as elevated or equivocal) or PALB2 or NF1
Family factor and/or	Female probants who had two breast cancer cases among the first or second degree relatives in the same family line (i.e. on the paternal or maternal side), with at least one incidence < 50 years old
	Female probants whose first and/or second degree relatives suffered from bilateral breast cancer
	Probants whose mothers or sisters had breast cancer before the age of 40
Other	A history of atypical ductal hyperplasia or lobular, or lobular carcinoma (LCIS) in situ (relative risk: 4.0-5.0)

Rules for quantifying woman for genetic testing

Before qualification for genetic testing it is recommended to assess an individual risk of carrying pathogenic mutations of specific genes in a gi-

ven probant. The minimum probability of detecting irregularities of genetic material, authorizing the person to have genetic tests performed, is considered to be equal to or above 10%. Determination of the probability of detecting a pathogenic mutation is based on the pedigree analysis and clinical-pathomorphological data if a probant suffers from breast cancer. Risk assessment programmes the sensitivity of which amounts to 80%-90% may also be used. They are a kind of mathematical models in which selected individual-clinical-pathomorphological parameters are assigned a specific score. The simplest and clinically useful programmes for predicting detection of BRCA1/2 gene mutation are the Manchester Scoring system and Referral Screening Tool allowing for determination of the likelihood of detecting BRCA1/2 gene mutation both in breast and/or ovarian cancer patients and healthy women with aggravating family factor. One of the most important parameters for qualification for genetic testing is the age of the onset of a malignant neoplasm (the age of the probant and/or her relatives) – the younger the age, the higher the risk of carrying a mutation. Correct estimation of the risk of carrying BRCA1/2 genes in a patient with breast and/or ovarian cancer should also include at least one parameter of pathomorphological assessment. A person with a high probability of carrying BRCA1/2 gene mutation (> 25%) is a woman/man with primary invasive breast cancer without a special type (NOS), neither expressing estrogen and progesterone (ER-/PgR-) steroid receptors nor overexpression receptor for human epidermal growth factor type 2 (HER-2), with a high degree of histological malignancy (grade 3 or 2), diagnosed before the age of 40 in the case of women or – regardless of age – in the case of men. Positive results of molecular tests constitute the final confirmation of carrying BRCA1/2 genes mutation (<http://annals.org/on07/29/2018>). Therefore, they should be performed in women who have been diagnosed with metachronic or synchronous breast and ovarian cancer or breast and endometrial (or cervical or pancreatic cancer or melanoma), in those whose first-degree relatives had

breast and ovarian cancer, women with primary ovarian cancer, men with primary breast cancer as well as in people at highest and high risk of breast and/or ovarian cancer incidence based on the pedigree analysis, supported by appropriate medical documentation [17,18,19,20,21].

Bilateral risk-reducing mastectomy – BRRM

Bilateral risk-reducing mastectomy lowering the risk of breast cancer in healthy women with a high and highest risk of its occurrence should be considered for all carriers of the pathogenic mutation of BRCA1 and/or BRCA2 gene.

It is also recommended for all young women below 30 years of age who have received therapeutic chest irradiation and have an expected life expectancy of >10 years. Scientific reports describe breast cancer cases in patients with Hodgkin's lymphoma, who were radically irradiated in the mediastinal area and the area of axillary pits. This risk increases especially when a high dose is used – above 40Gy, showing a linear relationship between the dose and the tumor development [22,23]. Modern irradiation techniques as well as multi-drug chemotherapy have improved the prognosis of patients with Hodgkin's lymphoma significantly, extended the survival time at the same time increasing the risk of secondary cancers, including breast cancer by about 10% [24].

Bilateral breast amputation in a healthy woman is not only a mutilating procedure, but it also involves a risk of complications, which is why the decision to perform it should be carefully considered, with taking into account primarily a patient's well-being. In each case it is necessary to weigh the benefits against the risks, taking into account, among others a patient's age and individual risk factors for a malignant neoplasm. Every woman before being subjected to BRRM should undergo a genetic and psychological consultation.

Before taking the final decision, a patient must be informed about the possibility of breast reconstruction and about the methods (e.g. implant, musculocutaneous flap) and the time of its performance (immediate, de-

ferred). Pros and cons of each type of amputation should be explained to a patient and she should have a free and independent choice of it.

A decision whether mastectomy and reconstruction are to be performed simultaneously (an immediate reconstruction), or as a two-stage procedure with prior placement of an expander, or as a multi-stage procedure with a deferred reconstruction and reconstruction of the papilla-areola complex, is taken by a patient herself.

Regular preventive examinations constitute an alternative to RRM. A patient should be clearly informed about the benefits of oncological surveillance and its effectiveness compared to performing a risk-reducing mastectomy (RRM). A patient should be also informed about other methods of primary prevention of breast cancer, i.e. ovariectomy or the use of hormonal drugs [25,26].

Studies have shown that different ethnic groups of women perceive the risk of breast cancer incidence differently, which translates into the choice of different options for its reduction. In an ethnically and racially heterogeneous population of 1,700 healthy women aged 40 to 74 years who underwent mammography, Caucasian women were more open to discussion about breast cancer prevention than women of other races. Detection of primary breast lesions during mammography significantly increased their interest in the issue of reducing breast cancer risk, including the possibility of having RRM [27].

Contralateral risk-reducing mastectomy in women with primary breast cancer from the groups of a high and the highest risk of breast cancer incidence

Patients with primary breast cancer diagnosed before the age of 50, who at the same time are also carriers of pathogenic mutations of the BRCA1/2, PALB2, TP53, PTEN, CDH1, STK11, NF1, CHECK2 genes have a 40% risk of developing second breast cancer.

Such patients should be offered a contralateral risk-reducing mastectomy to reduce the risk of second breast cancer (CRRM). Candidates for

this type of treatment may also be patients who are not carriers of pathogenic mutations, but who have a positive family history of -2 or more documented cases of breast and/or ovarian cancer [AGCA, Wright recommendations from 2017 and by ESMO and SEOM].

The Polish Society of Clinical Oncology extends indications for CRRM in patients with infiltrating breast cancer detected before the age of 40 or in situ lobular carcinoma (LCIS) if it has been diagnosed before the age of 40 and, in addition, the patient is a carrier of the BRCA1/2 gene pathogen aggravating family history: multiple cases of breast and/or ovarian cancer or breast cancer in a first degree relative below 40 years of age or male breast cancer regardless of age.

It has been indicated that the risk of second breast cancer incidence within 10 years from the first diagnosis is estimated to be at the level of 32% in carriers of BRCA1 gene mutation and 24.5% in carriers of BRCA2 gene mutation [28]. The risk increase has been associated with the age of patients at the moment of the first diagnosis of breast cancer and amounted to 31% and 23.5% for the patients below and over 50 years of age, respectively. Similar observations have been reported by Menes et al., though they have not confirmed the association for carriers of BRCA2 gene mutation. The risk of second breast cancer incidence in a 10-year follow-up amounted to 21% for patients diagnosed with breast cancer before the age of 40 and 11% for patients with breast cancer diagnosed after 40 years of age.

A meta-analysis of Molina-Montes et al. has shown that in the case of carriers of mutations in the BRCA1 and/or BRCA2 genes the risk of second breast cancer incidence during 5 years of follow-up was 15% and 9%, respectively, and it increased with time, reaching 27% and 19% after 10 years. In patients without a detected BRCA1/2 genes mutation, the risk of second breast cancer incidence in a 5-year and a 10-year follow-up was significantly lower and amounted to 3% and 5%, respectively [29]. In a study of 506 women with unilateral breast cancer without a confirmed BRCA1/BRCA2 gene mutation, 112 of them (22.1%) selected a contralateral risk-reducing mastectomy. Women who chose CLRRM were youn-

ger; the second breast cancer had a non-invasive nature; they had less pre-operative satisfaction associated with the appearance of their breasts and a lower level of optimism [30].

Types of risk-reducing mastectomy

Research conducted by Hartmann LC, Schaid DJ, Woods JE has shown that preventive mastectomy provides a 90-94% risk reduction for patients at high risk of breast cancer incidence and 89.5% risk reduction for patients at medium risk of breast cancer incidence. The data correlate with the current recommendations of NCCN and Wright 2017. No differences have been indicated between clinical efficacy and the applied surgical method [31]. The cosmetic effect of a properly performed surgery is satisfactory, acceptable by a patient and does not disturb anatomical proportions. Also the influence on the level of self-esteem, quality of life and sexual activity of a woman is not without significance¹.

Breast reconstruction is performed at the same time as mastectomy or as a deferred/ two-stage procedure, using an artificial implant or own tissues.

Patients qualifying for RRM can be offered a choice of one of the described below surgery methods:

1. Simple mastectomy – consists in the removal of the mammary gland along with the areola-papilla complex and excess skin. The end result of it is a transverse scar at the site of the removed gland. This method does not allow simultaneous reconstruction, but it is possible to postpone breast reconstruction by the use of skin-muscular flaps or an expander and an implant. This technique is rarely chosen by a surgeon in the case of women qualified for preventive mastectomy, it is more often chosen by the patients themselves.
2. Nipple sparing mastectomy, NSM – consists in the removal of the mammary gland with saving the skin above the gland and the areola-papilla complex and formation of the so-called “skin envelope” for the applied implant. This method is proposed to patients in the

case of who simultaneous breast reconstruction using an expander, implant or autologous fat transplant is planned. In the case of preventive mastectomy, the risk of Paget's cancer or cancer that occurs locally is minimalized. Safety of this procedure has been assessed in a multicenter study conducted in 55 healthy women at high risk of breast cancer incidence and 27 patients with primary breast cancer who were qualified for preventive mastectomy of the other breast. It has been shown that breast cancer occurred in two cases – 61.8 and 24.4 months after the surgery, but none of them was located in the spared papilla-areola complex. Studies by other authors have shown that NSM, despite saving the terminal ductal lobular unit (TDLUs), does not increase the risk of cancer development in the saved nipple, even in the case of carriers of pathogenic BRCA1/2 gene mutations [31,32]. The most serious complication of this method is the risk of necrosis of the saved areola-papilla complex, which affects about 10% of the operated women, while minimal necrosis (<1/3 of the wart) concerns about 60% of the cases. Other possible complications include: separation of sutures, various degrees of necrosis of the skin over the implant and abnormal wound healing. The risk of necrosis and deterioration of cosmetic effect increases with a decrease in the thickness of the left skin and glandular flap, while the risk of breast cancer after sparing mastectomy increases along with the volume of the spared glandular tissue. Possibility of performing endoscopic mastectomies that save the areola-papilla complex, the effect of which is a smaller scar, a better cosmetic effect and a lower incidence of complications should also be mentioned [33,34].

3. Skin sparing mastectomy, SSM – consists in the removal of glandular tissue along with a partial or complete removal of the papilla-areola complex. This procedure allows simultaneous reconstruction with low skin tension, leaving a small scar and restoring the natural shape of breast. At a later stage, patients are proposed a reconstruction of the nipple and micropigmentation of the

nipple areola. In the study conducted over the years 2001-2005 by Garwood et al. in a group of 170 patients subjected to skin sparing mastectomy, the following complications occurred: papillary-areola necrosis 5-15%, surrounding tissues necrosis 13-30%, implant loss 10-31%, skin flap necrosis 11-16%, wound infection 9-17%. The risk of failure in a form of necrosis decreases with the use of an expander, but increases with reconstruction using a patient's own tissues and removal of >30% of the papilla-areola complex [33].

Methods of breast reconstruction after risk-reducing mastectomy

The methods of breast reconstruction after risk-reducing mastectomy divided depending on type of material presented in Table 5.

Patients who do not decide to undergo breast reconstruction may use external prostheses classified as medical devices and issued upon the request of an oncologist.

Implementation of the procedure of risk-reducing mastectomy: the types of risk-reducing mastectomy and breast reconstruction carried out in accordance with the regulation of the Ministry of Health.

According to the ordinance of the Minister of Health of January 9, 2019 preventive mastectomy is a benefit reimbursed by the National Health Fund, including the procedure of unilateral or bilateral breast amputation and the procedure of unilateral or bilateral reconstruction, simultaneous or deferred. The Regulation unifies the conditions for benefit performance. The document standardizes qualification of patients for the surgery. It is recommended that the process of including patients into the treatment including risk-reducing mastectomy is carried out by a multidisciplinary team consisting of a psychologist, a physician specializing in clinical genetics and a physician specializing in the field of oncological surgery or plastic surgery. In the Regulation, it is recommended that the procedure should be performed in breast unit centers by physicians certified in the field of breast reconstruction.

Table 5. Methods of breast reconstruction after risk-reducing mastectomy

Reconstruction using an implant	Reconstruction using autologous adipose tissue	Reconstruction using musculocutaneous flap
One step Two stages using an expander	Lipofilling/lipotransfer Directly to the major pectoral muscle, lateral fascia of the chest and under the skin left after removal of the mammary gland [33].	DIEP flap (deep inferior epigastric perforators) LD flap (latissimus dorsi flap) TRAM flap (transverse rectus abdominis muscle flap) I-GAP flap (inferior gluteal artery perforator) S-GAP flap (superior gluteal artery perforator) TUG flap (transverse upper gracilis) TDAP flap (toracodorsal artery perforator flap) LICAP flap (lateral intercostal artery perforator flap)
Possible with SSM and NSM or with a simple mastectomy expander. An implant can be inserted prepectorally or subpectorally.	As an independent reconstruction method, complementary to the reconstruction using an implant to improve the cosmetic effect. The regenerative properties of adipose tissue enable formation of the desired shape of breast. They prevent skin over the implant necrosis and increase the success of the procedure [34].	After a simple mastectomy or inability to use an implant or after unsuccessful reconstruction by the use of an implant. As an independent reconstruction method or complementary to reconstruction using an implant.

Source: own elaboration based on data from:

Stark RY, Mirzabeigi MN, Vonderhaar RJ, Bucky LP. Utilizing large volume fat grafting in breast reconstruction after nipple sparing mastectomies. *Gland Surg* 2018; 7(3): 337-346.
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The paper contains a review of the current guidelines of the National Comprehensive Cancer Network (NCCN), the Polish Society of Clinical Oncology (PTOK), European Society of Medical Oncology (ESMO), Wright 2017.

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