



## PROPHYLACTIC MASTECTOMY AND HEREDITARY BREAST CANCER

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### Summary

In the female population, breast cancer is the most common malignant disease. Breast cancers caused by mutations in the *BRCA 1* and *BRCA 2* genes are responsible for up to 10% of all cases. With advances in genetics, there is the possibility of identifying women at high risk of developing breast cancer. These women receive assistance in the form of genetic counseling, psychological support, and surgical treatments to reduce their risk of developing breast cancer. Prophylactic mastectomy can be performed as a skin-sparing mastectomy, a skin and nipples-sparing mastectomy, and a simple mastectomy, which involves the complete removal of the parenchyma, skin, and nipples of both breasts. In the same act as the prophylactic mastectomy, breast reconstruction can be performed as either a primary reconstruction within the same surgical act or as a separate surgical procedure, in which case it is referred to as secondary reconstruction. Artificial material implants are predominantly used today due to their superior aesthetic results, faster healing, and smaller scars. Such surgeries can lead to various postoperative issues, including infection, hematoma, and seroma formation, while capsular contracture, implant rupture, and anaplastic large-cell lymphoma have all been linked to the use of artificial implants.

**KEYWORDS:** *heredity; prophylactic mastectomy; breast reconstruction; implant*

### EPIDEMIOLOGY OF BREAST CARCINOMA

Breast cancer is the most commonly diagnosed malignant disease in women both in Croatia and worldwide. Statistics from 2022 reveal that over two million new cases of breast cancer were diagnosed worldwide, with the highest incidence rates seen in France. It is also noteworthy that nearly 10% of all breast cancers are hereditary, associated with *BRCA1* and *BRCA2* gene mutations, while familial breast cancers account for about 20%, and sporadic cases represent the majority at 70–80% of cases(1-4). Additionally, it is the fourth leading cause of cancer-related deaths, which is a cause for concern(3). According to data from 2021, there were 2,968 new cases of breast cancer in Croatia, resulting in an incidence rate of 145.6 cases

per 100,000 women, which is comparable to the European Union average(5).

### HEREDITARY BREAST CARCINOMA

In most hereditary breast cancers, mutations are found in the tumor suppressor genes *BRCA1* and *BRCA2*, discovered in the 1990s. These genes are involved in DNA repair and the regulation of gene transcription during DNA damage, which can result in genetic code alterations and potentially lead to cancer(6).

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Mutations of the *TP53*, *STK11*, *CD1*, and *PTEN* genes also belong to high-risk mutations for the development of breast cancer. These mutations and mutations of the *BRCA 1* and *BRCA 2* genes can explain as much as 20% of the family's tendency to develop breast cancer. Thus, heredity is imposed as one of the greatest risks for the development of breast cancer in general, and it applies to women whose relatives in the first and second generation are ill with breast cancer(7).

Mutations of certain genes, collectively known as moderate penetrance variants, account for a total of up to 5% of metastatic breast cancer. More than 180 mutations at low-risk loci have also been identified, which can account for as many as 18% of hereditary breast cancers. After all, 50% of all hereditary breast cancers are of unknown origin(7). *BRCA 1* and *BRCA 2* mutations are now known as risk factors for breast and ovarian cancer(8). The *BRCA 1* gene is located on chromosome 17q21, consists of 24 exons, and encodes a protein composed of 1863 amino acids. *BRCA 2* is located on chromosome 13q12 and consists of a total of 27 exons. Coding of the *BRCA 2* gene produces a protein composed of 3418 amino acids(9,10).

### Genetic testing for breast cancer

When conducting genetic analysis, we strive for targeted sequencing that is faster, simpler, and cheaper with high prognostic and diagnostic significance, and the panels themselves can contain from 20 to 100 genes to be analyzed. In patients who have no known mutations in the family that could correspond to a gene mutation for hereditary breast cancer, and standard genetic analysis panels have given negative results, whole genome sequencing can be performed, which remains the method of last choice due to its long duration and high of execution costs(11).

Based on the results of the genetic testing and the risk factors obtained from the anamnesis, the patients are classified into one of three risk categories for hereditary breast cancer. The high-risk category consists of individuals who carry pathogenic mutations in the *BRCA1* and *BRCA2* genes and their lifetime risk of developing breast cancer exceeds 20% (calculated using the Gail model). The intermediate-risk category includes people whose lifetime risk of developing breast cancer is 12-20% and the low-risk category includes all individuals

whose risk of developing the disease is 12%, i.e. equal to the risk general population(2,12,13).

According to the Croatian guidelines, women who fall into the high-risk category are recommended to perform regular breast self-examinations at least once a month, and after the age of 25, to have a clinical and ultrasound examination of the breasts repeated every 6 months. The first mammogram should be done 10 years before the age when first relative was diagnosed with breast cancer, at the latest by the age of 40, and it is optional to do a breast magnetic resonance once a year(14).

Chemoprophylaxis and surgical prophylaxis can be carried out in women carrying mutations in the *BRCA 1* and *BRCA 2* genes. Chemoprophylaxis is performed with tamoxifen, while surgical prophylaxis involves bilateral prophylactic mastectomy and can be performed in healthy women. In women in whom a cancer seed was found in one of the breasts, prophylactic mastectomy of the contralateral breast is performed(14).

Guidelines for prophylactic mastectomy are generally similar around the world, although there are some minor differences in emphasis and approach. In the United States, the American Society of Clinical Oncology (ASCO) suggests that prophylactic mastectomy should be considered for individuals at high risk, particularly those with *BRCA1* or *BRCA2* mutations or other pathological variants associated with an increased risk of breast cancer. Risk-reducing mastectomy is recommended for individuals who have a very high likelihood of developing breast cancer based on their family history, genetic predisposition, or other risk factors. This approach stresses the importance of genetic testing and considers bilateral prophylactic mastectomy as a preventive option when the risk is significantly elevated. European guidelines emphasize multidisciplinary evaluations, genetic counseling, and personalized risk assessments. They prioritize patient education and shared decision-making throughout the process(15).

### PROPHYLACTIC BREAST SURGERY

Prophylactic mastectomy is currently considered the most effective method for risk reduction(14,16,17). For women who have already developed breast cancer and who carry *BRCA1* and *BRCA2* gene mutations, the risk of cancer recurring in the opposite breast or the same breast after spar-

ing surgery is high. Therefore, contralateral prophylactic mastectomy is justified(16). There are several options for performing a prophylactic mastectomy. These include bilateral skin-sparing mastectomy (SSM) and bilateral mastectomy with skin and nipple sparing (SNSM). For women who do not wish to undergo breast reconstruction, a simple bilateral mastectomy can also be performed. Regardless of the chosen method, the primary goal of each procedure should be to ensure safety and achieve a satisfactory aesthetic outcome(14,16,17).

### **Bilateral skin-sparing mastectomy (SSM)**

Bilateral skin-sparing mastectomy is a surgical technique that was developed in the 1960s and over time, almost completely replaced radical mastectomy. A skin-sparing mastectomy involves removing a segment of skin from the nipple-areolar complex while preserving the surrounding skin. This technique allows for breast reconstruction using autologous grafts, implants, or tissue expanders in the same act. Preserving the skin is important for the aesthetic outcome of the procedure and helps maintain the natural contours and shape of the breasts(19).

### **Bilateral skin and nipple-sparing mastectomy (SNSM)**

The indication for this procedure can be the prevention of breast cancer or a therapeutic measure. Bilateral mastectomy with skin and nipple sparing has proven to be an excellent method of preventing the occurrence of breast cancer in women with an increased risk. The characteristic of this technique is a very high quality of life after the procedure itself, whether we are talking about an increased risk due to a *BRCA* gene mutation or numerous combined risk factors that increase the incidence of breast cancer during life by more than 20%. This procedure involves sparing the areola-nipple complex, but preserving the skin of the breast completely while the glandular tissue of the breast is completely excised. It is advisable to send the retroareolar segment of glandular tissue as a separate sample for pathohistological analysis. This procedure is often the method of choice when planning a prophylactic mastectomy because it ensures an aesthetically good outcome(19).

### **Simple prophylactic mastectomy**

Simple prophylactic mastectomy is rarely performed and is usually only done at the request of the patient after all surgical and breast reconstruction options have been explained. This procedure involves completely removing the glandular tissue of the breast within known anatomical limits. Additionally, most of the skin with the nipple is removed. The remaining skin is only enough to properly close the wound without putting excessive pressure on the sutures, thus preventing potential complications such as wound dehiscence or tissue death in the operated breasts. Excess skin may remain on the chest, resulting in a *dog ear deformity*, which can be corrected through later surgical reconstructions(19).

### **The complications of prophylactic mastectomy**

The complications of prophylactic mastectomy are similar to those of other breast surgeries. The most common complications include: skin necrosis, formation of *dog ear deformity*, sensory paresthesias, infections in the operative area, postoperative chronic pain, formation of seroma and/or hematoma, breast asymmetry, and scarring(20).

Postoperative complications are more common in patients who have breast implants placed after a mastectomy. Capsular contracture, which is the most common reason for revision surgery, typically occurs three to five years after breast reconstruction. This is caused by the formation of a thick fibrous sheath around the implant due to chronic infection, which is a result of biofilm development on the implant surface. To prevent biofilm formation, it is recommended to rinse the implant pockets with antibiotics and antiseptics and to insert them without direct contact to minimize the risk of colonization(20,21). Another potential complication is intra- or extracapsular implant rupture and in the last decade, even cases of anaplastic large cell lymphoma have been reported(20,22).

## **DISCUSSION**

Genetic testing and prophylactic mastectomy in the prevention of breast cancer present ethical challenges for patients, but also for health workers who carry out counseling and preventive programs.

The ethical dilemma surrounding prophylactic mastectomy is rooted in its name. Some suggest

replacing *prophylactic/preventive mastectomy* with *breast cancer risk reduction* to better reflect the uncertainties involved(23). While we can identify a *BRCA1* or *BRCA2* gene mutation in a woman, we cannot guarantee she will develop breast cancer. Similarly, undergoing a prophylactic mastectomy does not guarantee that a woman will not get breast cancer, despite the procedure's high effectiveness. Some argue that this raises ethical concerns about justifying prophylactic mastectomy. This is because the procedure doesn't prevent breast cancer; it aims to minimize the risk. Bilateral prophylactic mastectomy reduces the incidence of breast cancer by over 90% in individuals with *BRCA* mutations, offering strong protection against disease development. However, a residual risk of about 5% remains, likely due to undetectable residual glandular or ectopic breast tissue(24). Additionally, prophylactic mastectomy doesn't prevent death from breast cancer, but rather the occurrence of it.

Prophylactic mastectomy rates vary significantly by region. In Croatia, data on the frequency of prophylactic mastectomy is limited and remains to be fully researched. In the United States, the rates of contralateral prophylactic mastectomy among patients with unilateral breast cancer have significantly increased, with studies indicating rates as high as 49% among *BRCA* mutation carriers. In contrast, European countries generally report much lower rates, often below 10%, as evidenced by studies from Switzerland and other nations(25,26,27).

Today, preventive mammography programs that offer early detection, combined with effective treatment, lead to a high five-year survival rate of breast cancer, which is about 90% in developed countries(4,28).

## CONCLUSION

As scientific advancements and genetic testing continue to improve, more women can now be identified as being at high risk of developing breast cancer. Modern medicine offers solutions for these women through preventive programs, as well as the possibility of surgically reducing the risk of breast cancer. There are numerous surgical options available, including prophylactic mastectomy with primary or secondary breast reconstruction. Surgery is becoming an increasingly personalized branch of medicine, so mastectomy and breast reconstruction are tailored to each

woman individually, taking into consideration their lifestyle. The goal is to preserve the quality of life and achieve highly satisfactory aesthetic results. Implants can produce a pleasing aesthetic result by mimicking the natural breast tissue with their size, shape, and content. This allows the muscle tissue, previously used in breast reconstruction, to remain untouched, resulting in smaller scars and faster postoperative recovery.

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## Sažetak

## PROFILAKTIČKA MASTEKTOMIJA I NASLJEDNJI KARCINOM DOJKE

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Karcinom dojke najčešća je maligna bolest u populaciji žena. Mutacije gena *BRCA1* i *BRCA2* odgovorne su za 10% svih nastalih karcinoma dojke. Napretkom genetike postoji mogućnost identifikacije žena s visokim rizikom obolijevanja. Takvim ženama pruža se pomoć u vidu genetičkog savjetovanja, psihološke pomoći i smanjenje rizika od nastanka karcinoma dojke kirurškim metodama. Profilaktičku mastektomiju danas je moguće napraviti s poštedom kože, s poštedom kože i bradavice te jednostavnu mastektomiju koja podrazumijeva potpuno odstranjivanje parenhima, kože i bradavice obiju dojki. U istom aktu s profilaktičkom mastektomijom moguće je učiniti i rekonstrukciju dojke, tada se to naziva primarnom rekonstrukcijom. Kada se izvodi kao zaseban kirurški zahvat naziva se sekundarnom rekonstrukcijom. Danas se gotovo isključivo koriste implantati izrađeni od umjetnih materijala koji pružaju vrhunske estetske rezultate, osiguravaju brži oporavak, a ožiljak je manji. Postoperativne komplikacije ovakvih zahvata mogu biti razne; infekcija, stvaranje hematoma i seroma, dok upotrebom umjetnih implantata može nastati kapsularna kontraktura, ruptura implantata i anaplastični limfom velikih stanica.

KLJUČNE RIJEČI: nasljeđe; profilaktička mastektomija; rekonstrukcija dojke; implantat