

## Prophylactic Mastectomies in Patients with Breast Cancer and Known Germline Pathogenetic Variants: An Austrian Registry

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### Abstract

**Objectives:** Risk-reducing surgeries are common in patients with germline mutations. Some patients develop breast cancer before they decide to receive for these surgeries. We aimed to examine the frequency of risk-reducing mastectomies and salpingo-oophorectomy among Austrian patients with breast cancer and known germline pathogenetic variants (GPV).

**Methods:** In 2014, we established an Austrian registry of patients with (GPV). From the onset until 2018, 111 patients were recruited from four breast cancer centers. Data on the type of mastectomy, reconstructions, and complications were collected.

**Results:** Of all patients, 13.5% discovered bilateral breast cancer. Among patients with unilateral breast cancer, the majority (86.8%) opted for prophylactic mastectomy on the contralateral side. Those who underwent modified radical mastectomy were more likely to choose prophylactic surgery

( $p = 0.001$ ). 19.4% of patients had cancer relapse postoperatively. Immediate reconstructions were performed in 71.3% of the patients. In addition, patients undergoing immediate reconstruction were more likely to choose a prophylactic operation on the contralateral side than those with delayed reconstruction ( $p = 0.001$ ). A mesh was used in 47.8% of all reconstructions. The subpectoral implant was used in 75.6% of patients and the pre-pectoral in 13.3%. A mesh was inserted in all patients with pre-pectoral implants.

**Conclusion:** The results indicate that the willingness to undergo risk-reducing surgeries is high and the option to receive immediate reconstruction is preferred by patients with breast cancer.

**Keywords:** Prophylactic mastectomy, bilateral salpingo-oophorectomy, breast cancer, BRCA, Austria

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### 1. Introduction

Mutations in germline breast cancer genes 1 and 2 (*BRCA1* and *BRCA2*) and other germline pathogenetic

variants (GPV) confer a high lifetime risk for breast and ovarian cancer. In the United States, the lifetime risk of breast cancer among the general population is estimated at 15.2% [1], as opposed to 69-72% in

women harboring pathogenic *BRCA1* or *BRCA2* mutations [2]. The treatment of early *BRCA*-deficient breast cancer can differ from the treatment of breast cancer that is without genetic background. Patients with hereditary *BRCA1*-associated breast cancer are better at responding to platinum agents and have a reduced response to taxanes [3]. Although this work used a small cohort of patients, the pathologic complete remission (pCR) for cisplatin was 83%, while women treated with doxorubicin and docetaxel presented 8% of pCR. In the adjuvant setting PARP inhibitors are associated with significantly longer survival free of invasive or distant disease [4]. The best pCR was achieved with platin derivatives in association with anthracyclines ± taxanes. However, there is no difference between PARP inhibitor alone, compared to PARP inhibitors with standard chemotherapy [5].

According to the current guidelines such as those provided in NCCN or ESMO, patients are informed about their options when having a mutation in a high-risk gene, including opting for risk-reducing surgeries, such as bilateral salpingo-oophorectomy (BSO), which also reduces the risk for breast cancer [6, 7], and prophylactic bilateral mastectomy (PME), regular screening, or chemopreventive medication [8]. PME is the most effective method to reduce the risk of breast cancer; however, the risk remains [9]. Although contralateral PME did not delay adjuvant therapy in breast cancer and GPV [10], possible complications should be discussed with the patients [11, 12]. Nonetheless, the complication rate in the diseased breast is higher than that in the prophylactically operated breast [10]. The rate of PME in the contralateral breast in patients with cancer continues to rise [13]. The highest rate of prophylactic mastectomy is reported in the United States (36.3%), whereas Poland has the lowest rate (2.7%) [14].

There are three main options for performing a mastectomy. The first is a simple modified radical mastectomy (MRM), which allows the use of an expander for reconstruction or autologous tissue. The second option is skin-sparing mastectomy (SSM). This option is preferred for larger and ptotic breasts during skin reduction, often resulting in an inverted T-shaped scar. In small breasts, a scar from removing the areola

is visible. In younger individuals, the preferred option, if possible, is a nipple-sparing mastectomy (NSM). When this procedure is performed on non-ptotic breasts, a single scar appears mostly in the under-breast fold. When performed on ptotic breasts, skin reduction replaces the areola-free flapping or tanging. These options are preferred based on literature supporting their oncological safety [15, 16].

We developed a registry of the different types of procedures and recorded possible complications owing to the lack of data in this field.

## 2. Methods

Using data from our four breast cancer centers in Austria (Medical University of Vienna, Wilhelminen Hospital, University Hospital Salzburg, and Kepler University Hospital Linz), we established a registry for patients with hereditary breast and ovarian cancer syndrome (HBOCS) who underwent oncologic and prophylactic operations. In Austria these types of operations are performed by general surgeons, plastic surgeons, and gynecologists. In the present study, we included patients with breast cancer and HBOCS who underwent surgery from 2014 to 2018. We recorded data retrospectively in 80.2% of patients and prospectively in 19.8%. All operations were recorded using the same case report form. Retrospectively, we searched for the results in the hospital databases. In the prospective situation, the ethics committee opted for informed consent; therefore, the patient was asked for a written agreement, the recruiter of the center filled out the case report form, and then reported any complications about 6-12 months after.

The data showed the different types of ablations and reconstructions. We recorded the type of autologous reconstruction, the type and placement of the implant, and the mesh used (Table 1). In addition, we collected data on surgical complications, such as revision, skin or nipple necrosis, hematoma, capsular fibrosis, inflammation, fistula, dehiscence, and implant loss. All major variables are described as percentages (nominal variables), means, medians, and standard deviations (metric variables). The Chi-square test was employed to assess the effect of certain variables on

the complication rate for nominal variables, whereas logistic regression analysis was used for metric variables. Statistical significance was set at  $p < 0.05$ .

Due to the exploratory nature of the first analysis, no correction for multiple testing was applied.

**TABLE 1.** Nearly all types of ablations are done with the same frequency. When opting for an implant-based reconstruction, in 64.9% direct-to-implant operation was chosen. Under 20% of patients prefer flap reconstruction over an implant-based reconstruction. Not all patients who are reconstructed with an implant receive a mesh for stabilization.

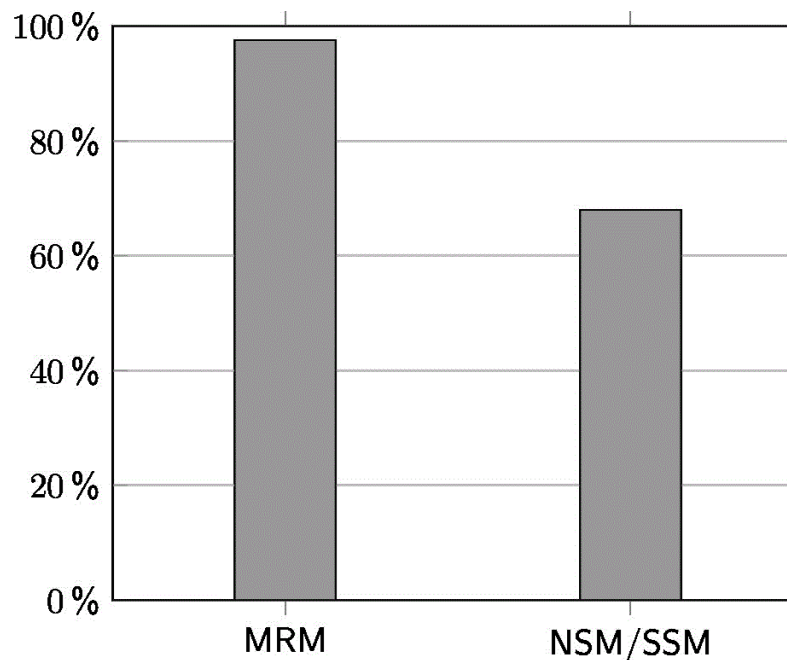
Types of reconstruction	number of patients	% of all patients
MRM	41	36.9 %
SSM	31	27.9%
NSM	36	32.4%
Implants	72	64.9%
Expander	36	32.4%
titanized mesh	13	11.7%
ADM	30	27.0%
TRAM	4	3.6%
DIEP	4	3.6%
Gracilis	5	4.5%
Latissimus	5	4.5%
IGAP	1	0.9%
Lipofilling	7	6.3%
Nipple reconstruction	10	9.0%

MRM: Modified Radical Mastectomy; SSM: Skin-Sparing Mastectomy; NSM: Nipple-Sparing Mastectomy; ADM: Acellular Dermal Matrix; TRAM: transverse rectus abdominus myocutaneous; DIEP: Deep Inferior Epigastric Perforators; IGAP: Inferior Gluteal Artery Perforator.

### 3. Results

A total of 111 patients were included in the study during the follow-up period. Most patients (78.2 %) underwent surgery at the Medical University of Vienna, 10% of patients underwent surgery at Wilhelminen Hospital, 9.1% at University Hospital Salzburg, 1.8% at Kepler University Hospital Linz, and 1.8% at an unknown hospital. The majority of the patients (100) were carriers of germline mutations in *BRCA*. The remaining patients had other germline

mutations, which were associated with a higher breast or ovarian cancer risk (ATM: 3, CHEK2: 4, PALB2: 4). The mean age of patients who underwent mastectomy was 45 years, and that of patients who underwent PBSO was 46.4 years. While most of the patients had unilateral cancer (86.5%), only 13.5% had bilateral breast cancer. Among patients with unilateral breast cancer, the majority (86.8%) opted for PME on the contralateral side. Patients with MRM were more likely to choose contralateral PME (Figure 1).



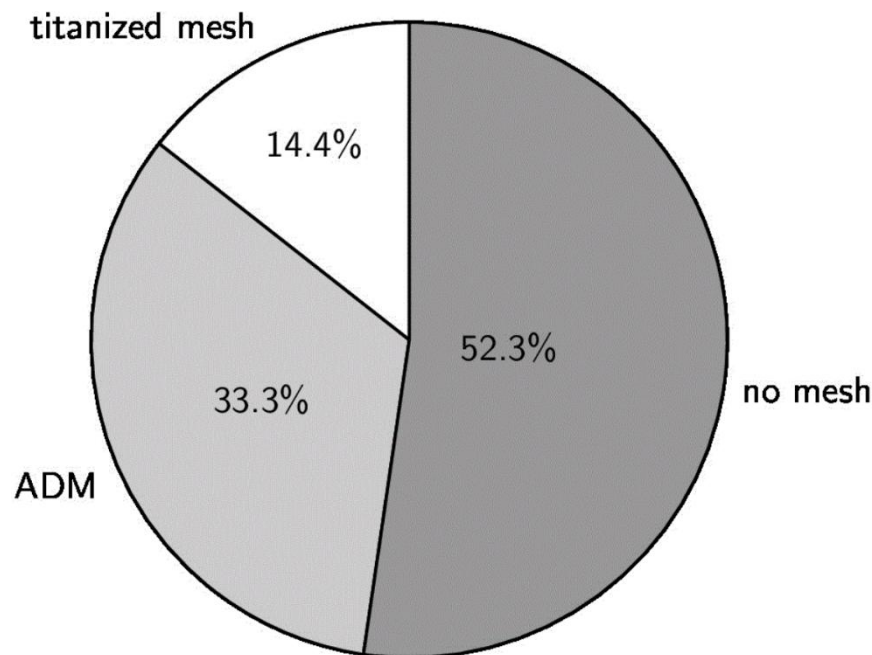
**FIGURE 1.** Patients with unilateral breast cancer undergoing modified radical mastectomy (97.6%) are more likely opting for a prophylactic mastectomy than those undergoing skin-sparing mastectomy or nipple-sparing mastectomy (68%) ( $p > 0.001$ ).

All three types of mastectomies were used in a similar number of patients. MRM was used in 36.9%, NSM in 32.4% and SSM in 27.9% of patients. Radiation was administered to 42 patients. Out of all patients, 21 had a relapse or new primary breast cancer. Data on relapse and mastectomy were not available in three patients. PBSO was performed in 51 patients, and 4 had ovarian cancer. Patients who underwent prophylactic mastectomy were less likely to undergo PBSO ( $p = 0.001$ ). Implant-based reconstruction was performed in 81.1% of patients, however there was no data on reconstruction for 3% of patients. We recorded immediate reconstructions in 77 of 108 patients (71.3%), delayed reconstructions in 4.6%, and both reconstruction methods in 7.4%.

Autologous reconstruction accounted for 28.9% of all reconstructions (gracilis and latissimus dorsi flap in five patients, transverse rectus abdominus myocutaneous [TRAM] and deep inferior epigastric perforators [DIEP] in five, and inferior gluteal artery perforator [IGAP] in one). Autologous reconstruction was compared to an implant or expander in 16 patients.

The remaining patients opted for no reconstructions. In addition to reconstruction, 7 patients received lipofilling, and 10 underwent operative nipple reconstruction. All patients with operative nipple reconstruction had previously undergone MRM, and none had undergone SSM ( $p = 0.0001$ ).

Among those with immediate reconstruction, 93.1% chose prophylactic treatment of the contralateral side, as opposed to only 44.4% in delayed reconstruction. This difference was statistically significant ( $p = 0.001$ ). Silicone implants were mainly used (44 of 72 patients) in immediate reconstructions; however, sodium-based implants were used in 13 patients. There were no records of the filling used in 15 patients. Half of the expanders used were Becker expanders. A mesh was used in 47.8% of all reconstructions, with 30.2% comprising tetanized mesh and 69.8% acellular dermal matrices (Figure 2). The subpectoral implant was present in 75.6% of patients and the pre-pectoral in 13.3%; the implant position in three patients remained unknown. A mesh was inserted in all patients with pre-pectoral implants.



**FIGURE 2.** In reconstructions, acellular dermal matrices were used in 33.3% of patients, 14.4% received a titanized mesh. Most surgeons opted for no mesh (52.3%).

The most documented complication was the need for revision in 28.7% of the cases, followed by necrosis and implant loss (both with 16.8%). Inflammation occurred in 14.8% of patients, and 13% experienced dehiscence. Fibrosis was recorded in 9.3% of patients, and fistulas in 2.8%. There was no statistically significant difference in complication rates associated with immediate or delayed reconstruction, implant size, pre- or retro-pectoral implant, or the type of mesh used.

#### 4. Discussion

The data presented in this study showed preliminary results from a multicenter registry-based study conducted among Austrian patients with HBOCS and breast cancer. The majority of our patients opted for risk reducing surgery of the contralateral side. In contrast, a study from Memorial Sloan Kettering Cancer Center showed that in 39% of the cases patients with moderate-risk genes were willing to undergo contralateral prophylactic mastectomies [17]. Since the 10-year cumulative rate of contralateral breast cancer and *BRCA* mutation is 30%, the higher rate of contralateral mastectomies is a good choice [18].

In our cohort, all three types of mastectomies were used at nearly the same rate; however, MRM was used in a slightly higher number of patients. Compared to a study including patients who underwent prophylactic breast operations [19], we observed a lower number of patients who underwent NSM. This could be due to the tumor infiltrating the nipple or a surgeon-affected impact, although NSM has been proven to be oncologically safe [16, 20]. In addition, we could not prove that NSM was associated with fewer complications [21, 22]; however, this could be due to higher complication rates in patients with diseased breasts [13]. Similar to previous studies, we did not observe any difference in complication rates between sub- and pre-pectoral implant-based reconstruction [22-25]. A higher rate of implant-based reconstruction and lower rates of autologous reconstruction have been reported [16], which aligns with our results.

We observed a high number of revisions, a pattern that became apparent upon evaluating all complications. To prevent this, it has been suggested that healthcare professionals increase blood pressure to a high-normal level and ensure meticulous intraoperative hemostasis [26]. Notably, the replacement of an expander with an implant was considered as an event to be expected and,

therefore, not regarded as a complication. The study is limited by the small sample size and the different surgical techniques used. In addition, there are no data on the available resources and training background of the surgeons. For further studies, tumor-specific data should be collected.

In conclusion, the results indicated that the patients understood the procedures considering their willingness for risk-reducing surgeries and the expectation of good cosmetic outcomes in immediate reconstructions.

### Ethics Approval and Consent to Participate

The study was approved by the ethics commission of Medical University Vienna, with approval number 1833/2014. All procedures performed in this study were in accordance with the ethical standards of the institutional review board and with the 1964 Helsinki Declaration and its later amendments. All study participants included prospectively provided written informed consent.

### Consent to Publish

Not applicable.

### Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

### Conflicts of Interest

None.

### Funding

None.

### Author Contributions

All procedures performed in this study were in accordance with the ethical standards of the institutional review board and with the 1964 Helsinki Declaration and its later amendments. D.C., A.S.,

S.M., R.R. and L.C. recruited the patients. L.C. wrote the main manuscript. D.C. prepared the figures. D.G. conducted the statistical analysis. G-K. D. and S.C. oversaw the entire research. All authors read and approved the final manuscript.

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