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Impact of Prophylactic Mastectomy in *BRCA1/2* Mutation Carriers

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Keywords

BRCA1 · *BRCA2* · High-risk genes · Prophylactic mastectomy

Summary

Unlike the general decrease in invasive oncologic care, the trend for prophylactic bilateral mastectomy in healthy women and prophylactic contralateral mastectomy in women with unilateral breast cancer is steadily rising. This is even more surprising when considering that for e.g. prophylactic contralateral mastectomy no clear survival benefit has been demonstrated so far. The decision-making process around risk-reducing surgery may be influenced by several conflicting parameters such as the patient's fears and desire to achieve a survival advantage, the surgeon's financial motivations, or the oncologist's paternalistic approach to the above trend. Physicians should support their patients throughout the decision-making process, guide them through the dense fog of information, and encourage them to reconsider all options and alternatives before embarking on an irreversible surgical intervention. Healthy and diseased women should be comprehensively informed about their absolute individual risks for cancer, the benefits and harms of the surgery, alternative preventive strategies, and last but not least the competing risks of preceding carcinomas and cancer in general. Within the framework of non-directive counseling in the specialized centers of the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC), decision-making aids are being developed with grants from the Federal Ministry of Health and the German Cancer Aid to support women in making conclusive and satisfactory decisions.

Introduction

Rates of prophylactic bilateral mastectomy (PBM) and particularly prophylactic contralateral mastectomy (PCM) have been increasing even prior to the coming-out of Angelina Jolie [1]. This trend is affected by multiple factors: On the one hand, one can assume that the increase in the use of breast magnetic resonance imaging at the time of diagnosis, the advances in immediate breast reconstruction, and 'surgeon bias' may influence a patient's decisions. On the other hand, healthy women just like breast cancer patients wish to decrease their individual lifetime risk for breast cancer. Several prospective trials have shown a dramatic risk reduction in breast and ovarian cancer incidence and mortality for healthy *BRCA1* and *BRCA2* mutation carriers after PBM and prophylactic bilateral salpingo-oophorectomy (PBSO). The prerequisite for an informed consent should be non-directive counseling about the individual cancer risks in specialized centers for hereditary breast and ovarian cancer.

Cancer Risks of *BRCA1* and *2* Mutation Carriers and Preventive Measures

Women carrying deleterious *BRCA1* and *BRCA2* mutations face an elevated lifetime risk for breast, contralateral breast, and ovarian cancer. In a recent prospective analysis (Epidemiological Study of Familial Breast Cancer, EMBRACE) [2] using a cohort of 978 *BRCA1* and 909 *BRCA2* mutation carriers, the average cumulative risks by age 70 for *BRCA1* carriers were estimated to be 60% (95% confidence interval (CI) 44–75%) for breast cancer, 59% (95% CI 43–76%) for ovarian cancer, and 83% (95% CI 69–94%) for contralateral breast cancer. For *BRCA2* carriers, the corresponding risks were 55% (95% CI 41–70%) for breast cancer,

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16.5% (95% CI 7.5–34%) for ovarian cancer, and 62% (95% CI 44–79.5%) for contralateral breast cancer. Risk-reducing strategies comprise structured breast cancer surveillance, chemoprevention, and prophylactic surgery. The portfolio of risk-reducing surgery includes PBM, PCM, and PBSO. For healthy *BRCA1/2* mutation carriers, a reduction in the incidence of breast cancer of at least 90% and of breast cancer mortality after PBM was reported [3–5]. PBSO is highly effective in reducing cancer incidence and mortality of ovarian and fallopian tube cancer in *BRCA* mutation carriers without a history of breast cancer [4, 6]. Moreover, PBSO in premenopausal women leads to a 50% breast cancer risk reduction for healthy women and presumably also for patients with a history of unilateral breast cancer [7]. Therefore, PBSO is recommended for women with a known *BRCA1/2* mutation around the age of 40 years and upon completion of childbearing [8]. Within an intensified breast cancer surveillance program [8], over 82% of breast carcinomas will be diagnosed as stage 0–I tumors (unpublished data of the GC-HBOC).

Women should be optimally supported throughout the complex decision-making process to weigh up the pros and cons of risk-reducing surgery. Non-directive counseling within specialized centers should be the basis for deciding between the 2 sides of the coin: the decreased likelihood of developing a (second) primary carcinoma on the one hand and the downsides such as risk of surgery, impairment of a woman's self-image, as well as short-term and long-term morbidities on the other hand.

Genetic Testing and Genotype/Phenotype Correlation

Genetic testing for deleterious mutations in the *BRCA* genes enables members of a family with a strong cancer history to estimate their individual lifetime risk for breast and ovarian cancer. Individuals testing negative for known familial *BRCA* mutations carry similar cancer risks as the general population. Those women do usually not benefit from risk-reducing surgery or intensified breast cancer surveillance. The diagnosis of a deleterious *BRCA* mutation, however, only allows rough risk estimation due to incomplete penetrance and influence of modifying factors. Experienced counselors contrast the individual cancer risks with the benefits and harms of the different preventive options. In particular, the comprehensive consideration of an individual situation includes the phenotype of *BRCA*-associated carcinomas. Patients with *BRCA1* germline mutations predominantly develop high-grade invasive ductal carcinomas of no specific type with frequent medullary-like morphology and in 70–75% negative for estrogen receptor, progesterone receptor, and HER2 overexpression or amplification (triple-negative) [9]. In contrast, *BRCA2*-associated breast carcinomas are very heterogeneous [10, 11]. Although no specific phenotype is as yet predictive of *BRCA2*-associated tumors, the majority comprise estrogen receptor-positive and HER2-negative features and show low or intermediate histological grade [12]. In particular, 2 morphological features are significant in *BRCA2*-associated breast cancer: pushing margins and lack of tubule formation [13]. The 10-year survival in *BRCA1* and *BRCA2* mutation carriers is similar to the survival of women with sporadic cancer, in particular if the mutation carriers were treated with chemotherapy [14].

The Individual Decision-Making Process

This information together with the personal experience of families with a strong cancer history contributes to the decision-making process. As an example, a 42-year-old healthy *BRCA2* mutation carrier decided to undergo PBSO and participate in the intensified breast cancer surveillance, but declined to undergo PBM. The rationale for her decision was based on her mother's story, who also carries a *BRCA2* mutation and was diagnosed with ductal carcinoma in situ (DCIS) at the age of 66 years. She underwent breast-conserving therapy followed by adjuvant radiation with a very satisfactory cosmetic outcome. The 42-year-old daughter bisected her breast cancer risk by undergoing PBSO last year after having finished family planning. She has little fear of the prospect of a breast cancer diagnosis after having been informed of her model-based calculated risk of 6% for the next 5 years, and would anticipate a 'typical' *BRCA2* carcinoma (grade 2, hormone receptor-positive) or a diagnosis of DCIS. It is possible that in the case of an early diagnosis, she will not have to undergo chemotherapy.

In contrast, a 31-year-old *BRCA1* mutation carrier with a model-based risk calculation of 1% for breast cancer in the next year decided to undergo a risk-reducing mastectomy with primary reconstruction immediately after detection of a *BRCA1* mutation. Her mother and grandmother both suffered from breast cancer from the ages of 38 and 41 years, respectively. Both women died from breast cancer within 2 and 5 years, respectively. The 31-year-old woman is planning to have a family in the next 4 years, and is anxious about an early breast cancer diagnosis. She expects a typical *BRCA1*-associated breast cancer (triple-negative), and wants to avoid chemotherapy which is recommended even for early-stage tumors within the intensified surveillance program. PBSO is planned to be carried out at the age of 40 years.

Informed consent should be based on the individual cancer risk evaluation in the setting of comprehensive pretest and posttest counseling including all preventive medical management strategies for specific genes. Well-educated specialists can encourage patients to undergo genetic testing and increase their understanding of their situation. Interestingly, women from families with multiple breast and ovarian cancer cases commonly overestimate their cancer risks [15]. For ex-

ample, for patients participating in chemoprevention trials, the mean lifetime calculated risk using the Gail model was 15%; however, the median risk perceived by patients was 50% [16]. A survey carried out in the USA found that although 75% of Americans were aware of Angelina Jolie's double mastectomy, fewer than 10% of respondents had the information necessary to accurately interpret her risk of developing cancer relative to a woman unaffected by the *BRCA* gene mutation [17]. There is without a doubt a high need to respond to such experiences and news with more target-oriented communication efforts by specialists in order to increase public awareness. Communicating lifetime risks for cancer is not a helpful tool to support the decision-making process for or against prophylactic surgery. The combination of a 3-generation pedigree together with a model-based calculation including the deleterious *BRCA* mutation allows for an individual risk prediction for breast and ovarian cancer for each upcoming year of life. This calculation enables women to make a decision based on her current situation, presumably leading to a more satisfactory outcome because an intervention at the wrong time is certainly worse than no intervention at all. Moreover, the decision-making process should consider tremendously important aspects such as residual risks after prophylactic mastectomy, limited evidence for the different surgical techniques related to safety and outcome (e.g. cosmetics), and increased risk for associated cancers such as pancreatic and colon cancer. Patients with a history of unilateral breast cancer should be informed about their competing risks (e.g. prognosis of the first breast cancer) to avoid unnecessary surgery where there is low risk of developing contralateral breast cancer compared to high risk of developing metastases. Last but not least, the competing common cancer risk (e.g. lifetime risk for women to suffer from some form of cancer = 43%) [18] should be integrated in the discussion.

Risk-Reducing Options for *BRCA1/2* Mutation Carriers

Prophylactic Bilateral Mastectomy in Healthy BRCA1/2 Mutation Carriers

Specialists within the centers of the GC-HBOC offer risk-adapted preventive measures and therapies to *BRCA* mutation carriers and women at high risk. The interdisciplinary team informs women about these items, and the measures are evaluated. Preventive strategies include participation in the intensified breast cancer surveillance program, different risk-reducing surgical options, and targeted therapies (e.g. PARP inhibitors) [8, 19, 20]. Risk-reducing surgeries for *BRCA1/2* mutation carriers include PBM, PCM, and PBSO. The GC-HBOC has established evidence-based guidelines for these risk-reducing operations [8]. PBM reduces breast cancer risk in *BRCA1/2* mutation carriers to approximately 2%, and breast cancer mortality to less than 10% [5]. Prospective data have shown radical mastectomy including the nipple areola complex to be the most efficient surgical technique for reducing breast cancer risk, while after other methods such as subcutaneous mastectomy women still developed breast cancer [5].

The main facts that have to be discussed in preparation for a risk-reducing mastectomy are the individual breast cancer risk and the surgical technique best suitable to minimize the residual cancer risk. Moreover, patients have to be informed about alternative strategies (e.g. intensified breast cancer surveillance) and other risk-reducing concepts (e.g. PBSO, endocrine therapy). Accurate information and comprehensive communication within the shared decision-making process should enable patients to come to a concrete decision for or against PBM. Non-directive counseling acts on the maxim that PBM is an option, not a recommendation. Several open questions should be addressed by further prospective studies, including residual cancer risk after different surgical techniques of PBM, patient satisfaction and quality of life, safety and cosmetic outcome after the use of different materials (acellular dermal matrices), acute and chronic postsurgical pain, physical integrity, sexuality, and partnership.

Prophylactic Contralateral Mastectomy in BRCA1/2 Mutations Carriers after Unilateral Breast Cancer

High-risk patients without breast cancer may take months or years to obtain accurate information on the pros and cons of PBM. In contrast, women with newly diagnosed unilateral breast cancer often decide to undergo PCM within a few days. This decision may be compromised by the stress of being diagnosed with breast cancer and the assumption that only the most aggressive surgical measure will achieve a significant survival benefit. Patients presume that PBM of the affected breast is the ideal chance to be cured from their current breast cancer and to protect the contralateral breast from the unavoidable risk of synchronous or future cancer. Moreover, most patients want to eliminate the risk of having to undergo a second chemotherapy. Therefore, the rate of patients who opt for PCM has almost tripled, independent of *BRCA* mutations or a strong family cancer history [1, 20]. King et al. [1] interestingly showed that a greater awareness of genetic risk was not responsible for increasing rates of PCM as previously proposed. Only 29% of the patients in their study who opted for a PCM underwent genetic testing.

While there is evidence for the risk-reducing effect of PCM on the development of contralateral breast cancer [21–23], outcome reports refute patients' assumptions by showing limited evidence for decreased mortality after PCM. These data support the view that prognosis for patients with unilateral cancer is determined by the primary lesion that has a lead-time advantage to generate distant metastases. A recent retrospec-

tive study described an improved survival for *BRCA* mutation carriers after bilateral mastectomy compared to unilateral mastectomy in patients with unilateral breast cancer [24]. The survival rate after 20 years for women who underwent mastectomy of the contralateral breast was 88% (95% CI 83–93%) and for those who did not 66% (95% CI 59–73%). Limitations of this particular study are the severe differences between the 2 groups of patients with unilateral and bilateral mastectomy concerning significantly more favorable tumor stages (pT and pN) and more efficient chemotherapeutic regimens (1994 compared to 1987) in the PCM group. Given the small number of events in the study cohort and the improvement in survival after more than 10 years of observation time, further research generating prospective data should be awaited before the efficacy of PCM can be reliably estimated.

A study by the GC-HBOC [25] provided data that was able to influence the decision-making process of women with unilateral breast cancer. The retrospective, multicenter cohort study was performed from 1996 to 2011 and comprised 6,235 women with unilateral breast cancer from 6,230 high-risk families that had either tested positive for *BRCA1* (n = 1,154) or *BRCA2* (n = 575) mutations or tested negative (n = 4,501). The study showed that contralateral breast cancer risk depends on mutation status and age at first breast cancer diagnosis. The cumulative risk of contralateral breast cancer 25 years after first breast cancer diagnosis was 44.1% (95% CI 37.6–50.6%) for patients from *BRCA1*-positive families, 33.5% (95% CI 22.4–44.7%) for patients from *BRCA2*-positive families, and 17.2% (95% CI 14.5–19.9%) for patients from families that tested negative for *BRCA1/2* mutations. Younger age at first breast cancer diagnosis was associated with a higher risk of contralateral breast cancer. For women who had their first breast cancer before the age of 40 years, the cumulative risk of contralateral breast cancer after 25 years was 55.1% for *BRCA1*, 38.4% for *BRCA2*, and 28.4% for patients from *BRCA1/2*-negative families. These data support the risk for mutation carriers shown in a previous study by the GC-HBOC [26], and confirm a contralateral breast cancer risk for *BRCA1/2*-negative women comparable to that of women without a strong family history.

It is indisputable that the discussion for or against PBM should include the risk for recurrence and metastasis of the primary breast cancer and other important individual competing risk factors, particularly if the risk for a severe course of the current disease is higher (e.g. several positive axillary lymph nodes) compared to the course of an early contralateral breast cancer (e.g. pT1b, pN0, hormone receptor-positive, HER2/neu-negative) diagnosed within the intensified surveillance program. Moreover, PBSO reduces the risk for (contralateral) breast cancer in *BRCA* mutation carriers to 30–50% [4, 6]. Without an efficient ovarian cancer surveillance program as an alternative to PBSO, specialists recommend PBSO to be carried out around the age of 40 years or 5 years before the age at first ovarian cancer diagnosis within the family and after family planning is completed [8, 27]. Moreover, PBSO reduces ovarian cancer risk to 1–2% in healthy mutation carriers and overall mortality to 25% [4, 6]. A prophylactic hysterectomy is not indicated, and hormone replacement until the age of 50 years is recommended without affecting the (contralateral) bisection of breast cancer risk. In summary, a risk-reducing effect is only documented for PBSO in *BRCA*1/2 mutation carriers. Limited data exist for efficiency of other prophylactic surgeries in healthy and affected *BRCA* mutation carriers as well as individuals at high risk. Therefore, women should decide whether or not to undergo irreversible prophylactic surgery based on a shared decision-making process with comprehensive and transparent discussion of the individual risks. The GC-HBOC accompanies the complex shared decision-making process of *BRCA1/2* mutation carriers within a prospective trial supported by the German Ministry of Health. The trial investigates ethical, legal, socioeconomic, and psychological aspects of the decision-making process. The psychological counseling considers the complex composition of such a life-changing decision due to different influencing factors such as fear of cancer and the wish for health but also partnership, family and other future plans.

Conclusion

Except for PBSO in the case of *BRCA1/2* mutation carriers, there is no reliable data regarding the efficacy of risk-reducing surgery, either for mutation carriers who have already developed cancer or for *BRCA1/2*-negative healthy or affected women. With this in mind, prophylactic operations should only be discussed with the greatest possible caution and following extensive and comprehensive non-directive counseling as an integral part of the shared decision-making process. This is in stark contrast to the current steep rise in prophylactic mastectomies, which can most readily be explained by a lack of knowledge of the risks on the part of both physicians and patients. For this reason, the GC-HBOC has made it one of its central tasks to communicate this data with a view to counteracting the tendency to uncritically carry out prophylactic procedures. The goals are to establish a structured, open-ended risk consultation, to decide on criteria for a prophylactic procedure, and to settle ethical and legal principles of the issue without forgetting the patient's needs which are to be identified within the framework of a national cancer plan financed by the German Health Ministry.

Disclosure Statement

The authors declare no conflicts of interest.

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