Breast Care

Review Article

Breast Care 2021;16:144–148
DOI: 10.1159/000507503

Received: December 14, 2019
Accepted: March 25, 2020
Published online: May 11, 2020

# Nonsurgical Prevention Strategies in *BRCA1* and *BRCA2* Mutation Carriers

Christian F. Singer

Department of Obstetrics and Gynecology, and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria

**Keywords**

Primary prevention · Breast cancer · Denosumab · *BRCA1* mutation

**Abstract**

***Background:*** Female carriers of a *BRCA1* or *2* germline mutation face a high lifetime risk to develop breast and ovarian cancer. Risk-reducing surgery, such as prophylactic bilateral mastectomy and prophylactic bilateral salpingo-oophorectomy, are proven strategies to prevent breast and ovarian cancer. These procedures are, however, associated with considerable side effects, and the uptake of these highly effective interventions is therefore low in many countries. This highlights the need for alternative and noninvasive strategies for risk reduction in mutation carriers. ***Summary:*** While endocrine treatments with tamoxifen and aromatase inhibitors (AI) have been shown to be effective in secondary prevention, their benefit in primary prevention has never been prospectively evaluated. Moreover, their side effect profile makes them inappropriate candidates for chemoprevention in healthy premenopausal women. Recently, denosumab, a well-tolerated osteoprotective drug, has been shown to have an antitumoral effect on RANK+, *BRCA1*-deficient luminal progenitor cells in vitro, and has been demonstrated to abrogate tumors in *BRCA1*-deficient mouse models. ***Key Message:*** The prospectively randomized, double-blind BRCA-P trial is currently investigating the preventative effect of denosumab in healthy *BRCA1* germline mutation carriers.



## Introduction

Female carriers of a BRCA1 or BRCA2 germline mutation have a more than 70% lifetime risk to develop breast cancer and a cumulative incidence of 30–50% to develop ovarian cancer, with a particularly young age at disease onset [1]. In principle, three strategies have been recommended in the management of female carriers: surveillance, chemoprevention, and risk-reducing surgery. The aim of this study is to provide a review on the therapeutic options, and to discuss advantages and caveats for each of the options. Until now, prophylactic surgery (bilateral mastectomy, bilateral salpingo-oophorectomy [BSO], or a combination of both procedures) has been considered to be most effective in preventing the disease occurrence. These procedures are associated with a substantially reduced risk of breast cancer. However, a significant benefit of risk-reducing breast surgery on overall and breast cancer-specific survival has only been demonstrated in female *BRCA1* mutation carriers. For *BRCA2* mutation carriers, risk-reducing bilateral mastectomy appears to lead to a similar breast cancer-specific and overall survival as surveillance alone [2]. Of note, prophylactic BSO (PBSO) had initially been shown to reduce breast cancer risk by 50%, irrespective of whether the *BRCA1* or *BRCA2* genes are affected. However, a re-analysis which has addressed potential biases that had not been considered in previous analyses, has challenged studies evaluating the effect of PBSO on breast cancer risk in *BRCA1* mutation carriers and in *BRCA2* carriers older than 50 years. Only *BRCA2*

karger@karger.com
www.karger.com/brc



Christian F. Singer, MD, MPH
Department of Obstetrics and Gynecology, and
Comprehensive Cancer Center, Medical University of Vienna
Waehringer Guertel 18–20, AT–1090 Vienna (Austria)
Christian.singer@meduniwien.ac.at

mutation carriers, who are younger than 50 appear to have some benefit from PBSO but the preventive effect is weaker than shown earlier [3].

Also, the uptake of these highly effective prevention strategies is low in many cultures and is compromised by a high postoperative complications rate and suboptimal cosmetic outcome for bilateral prophylactic mastectomy [4]. This highlights the need for additional, nonsurgical alternatives for breast cancer prevention.

## Endocrine Prevention Strategies in BRCA1 and BRCA2 Mutation Carriers

*Tamoxifen*

Tamoxifen is an oral selective estrogen receptor (ER) modulator, which, if taken at a dose of 20 mg daily for 5 years, substantially reduces breast cancer risk for women who are at increased risk owing to their family cancer history, reproductive risk factors, or personal history of atypical hyperplasia or lobular carcinoma in situ. The benefit is maintained for up to 15 years after the actual tamoxifen treatment [5]. There is some evidence, which suggests that tamoxifen may be equally efficacious for the prevention of breast cancer for *BRCA1* and *BRCA2* mutation carriers. Prevention data from both primary and secondary prevention are available, although limited and retrospective in nature. Regarding primary prevention (i.e., prevention of breast cancer in unaffected women), the only published data on the efficacy of tamoxifen for *BRCA1* and *BRCA2* mutation carriers come from a subgroup analysis of the prospectively randomized NSABP-P1 breast cancer prevention trial. NSABP-P1 followed 13,388 women at increased risk of breast cancer who had either received tamoxifen 20 mg daily or placebo for 5 years. The risk ratio for disease occurrence with tamoxifen was 1.67 (95% CI: 0.32–10.7) for *BRCA1* mutation carriers and 0.38 (95% CI: 0.06–1.56) for *BRCA2* mutation carriers. It has, however, to be noted that the mutation status was only available in a very small number of women: only eight *BRCA1* and 11 *BRCA2* mutation carriers had been identified among the 288 study participants who developed breast cancer, which leads to wide confidence intervals. Nevertheless, the publication of this retrospective subgroup analysis raised the possibility that tamoxifen could modulate breast cancer risk, at least for *BRCA2* mutation carriers [6].

More data are available for the secondary prevention setting (i.e., in the prevention of a second malignancy in women who had already developed breast cancer and in whom tamoxifen was prescribed as adjuvant endocrine treatment). Due to the need for endocrine treatment in estrogen-responsive primary tumors, a randomization in a placebo arm was not feasible and thus all of these studies were observational in nature. The largest study analyzed data from 2,464 mutation carriers and demonstrated that tamoxifen use after a first breast cancer was associated with a risk reduction for contralateral breast cancer. The hazard ratio was 0.38 (95% CI: 0.27–0.55; $p < 0.001$) for *BRCA1* mutation carriers and 0.33 (95% CI: 0.22–0.50; $p < 0.001$) for *BRCA2* mutation carriers [7]. Several earlier studies had also examined the association between tamoxifen use and contralateral breast cancer in *BRCA1* and *BRCA2* mutation carriers. Although the comparatively small study size limited the statistical power considerably, the point estimates for the hazard ratios for the risk of contralateral breast cancer with tamoxifen use were consistently less than 1 for all studies and for both genes, which is consistent with tamoxifen being efficacious for contralateral breast cancer prevention for both *BRCA1* and *BRCA2* mutation carriers [8].

The differing hormonal phenotype of breast cancers arising in *BRCA1* and *BRCA2* mutation carriers is an issue that often arises in discussions about whether tamoxifen might provide benefit as a prevention agent. While the majority of breast cancers arising in *BRCA2* mutation carriers are ER positive, most breast cancers in *BRCA1* mutation carriers are ER and progesterone receptor (PR) negative, as well as HER2 negative (thus the term "triple negative breast cancer", TNBC) at the time of diagnosis [9]. Data from the randomized primary prevention studies suggested that the benefit of tamoxifen was confined to the prevention of ER-positive breast cancer. Paradoxically, however, the observational studies described above suggest that tamoxifen can reduce hormone receptor-negative tumors in *BRCA1* mutation carriers, consistent with the prevention properties afforded by PBSO. In fact, there is strong evidence that female hormones play a critical role in the early ontogeny of *BRCA1*-associated breast cancer. *BRCA1* has been shown to repress ERα-mediated transcription and may therefore alter estrogenic response [10]. Furthermore, PR expression is increasingly believed to play a crucial role in the development of solid tumors in mutation carriers. Total PR expression was reported to be elevated in *Brca1/p53*-deficient mice where the progesterone antagonist mifepristone (RU486) appeared to ameliorate mammary tumorigenesis [11].

*Aromatase Inhibitors*

To date, we do not have clinical data regarding the efficacy of aromatase inhibitors on cancer prevention in BRCA carriers from any prospective trials. It seems likely, however, that they would confer similar chemoprevention properties to tamoxifen, although aromatase inhibitors can only be used in the postmenopausal setting. The French LIBER Trial (NCT00673335) is a randomized phase III trial which is investigating whether letrozole,

compared to placebo, is able to prevent breast cancer in postmenopausal women with a *BRCA1* or *BRCA2* mutation. The study has a planned sample size of 386 participants and its primary endpoint is survival without invasive cancer at 5 years. The clinical applicability of a drug that can only be offered to postmenopausal women, however, somewhat limits the benefit in women who are particularly young and thus premenopausal at the time of disease onset [12].

## RANK Ligand Inhibition as Preventive Strategy in *BRCA1/BRCA2* Mutation Carriers

The emerging importance of progesterone/RANK ligand (RANKL) signaling as a key mediator of normal breast function raises the possibility that RANKL inhibition, using agents such as denosumab, could offer a novel approach for breast cancer prevention, although this has not been systematically evaluated in the clinic [13]. The scientific rationale for the use of RANKL inhibitors is the fact that female steroid hormones profoundly affect mammary epithelial cell function by both direct and indirect means. A recent report has found that premenopausal *BRCA1* and *BRCA2* carriers have higher serum levels of estrogen and progestin across the menstrual cycle [14]. Indeed, mammary stem cells (which lack ERα and PR) appear to be indirectly activated by female sex steroids via paracrine signaling, which is mediated by RANKL, a progestin target [15]. These findings raise the possibility that PBSO and tamoxifen reduce breast cancer risk (at least in part) by the indirect inactivation of stem and/or progenitor cells in the breast. This observation has potential relevance to *BRCA1* mutation carriers, in whom breast tumors are believed to arise from aberrant luminal progenitor cells.

Widschwendter et al. [16] have recently examined serum RANKL and osteoprotegerin (OPG) levels across the menstrual cycle and their associations with hormonal responsiveness in the mammary gland. OPG was dysregulated in *BRCA* mutation carriers and inversely associated with breast cancer risk and mammary epithelial proliferation. In comparison to women without a *BRCA* mutation, OPG levels were particularly low through most of the menstrual cycle in mutation carriers, and there was an inverse correlation between serum OPG and luteal phase progesterone levels that was more marked in *BRCA*-mutation carriers. Low serum OPG levels in an animal model were, in turn, associated with increased mammary epithelial cell proliferation, and significantly higher OPG levels were seen in the absence of functional ovaries. Interestingly, while OPG levels in breast and serum were both decreased in the presence of progesterone, RANKL serum levels did not appear to reflect local increases in breast tissue [16]. These data suggest that the net magnitude of RANK signaling in the breast upon progesterone exposure may be regulated by a local increase of RANKL which is paralleled by a decrease in both local and systemic OPG, thereby ultimately increasing the RANKL:OPG ratio in the breast tissue of mutation carriers.

There is additional evidence from animal experiments which suggests a role of the RANK/RANKL pathway in breast carcinogenesis irrespective of the *BRCA* mutation status. RANK pathway activation by progesterone-mediated RANKL upregulation can contribute to mammary carcinogenesis by increasing the mammary stem/progenitor cell proliferation. Indeed, deleting *RANK* from the mammary epithelium decreases the incidence and delays the onset of progesterone-mediated mammary cancer, indicating that RANK signaling suppression might be an excellent strategy for breast cancer prevention [17]. While, in principle, anti-progestin treatment has been demonstrated to decrease ductal branching and alveolar proliferation, and to promote differentiation in animal experiments, long-term treatment of premenopausal women with selective PgR modulators has not been tested sufficiently in humans and could potentially lead to substantial side effects [18]. Particularly the effect that antiprogestins might have on the endometrium is still unclear [19]. Upregulation of OPG could be another therapeutic strategy, but OPG is not regulated throughout the menstrual cycle, and its regulation appears to involve cell-autonomous factors that are more difficult to modulate [20]. Taken together, there is now substantial evidence suggesting that the direct targeting of RANKL could overcome the low OPG levels present in mutation carriers and inhibit the RANK/RANKL axis, particularly in premenopausal women.

The pathophysiological role of the RANK/RANKL system, however, appears to be especially important in *BRCA1* mutation carriers – and this effect appears to be independent of PgR signaling. The evidence comes from two seminal papers which have recently highlighted the role of RANK/RANKL in *BRCA1*-mutated breast cancer. Sigl et al. [21] have shown that genetic inactivation of RANK in the mammary epithelium markedly delayed onset, reduced incidence, and attenuated progression of *Brca1;p53* mutation-driven mammary cancer. In their paper, the authors demonstrated that long-term pharmacological inhibition of the RANKL in mice abolished the occurrence of *Brca1* mutation-driven preneoplastic lesions. Mechanistically, genetic inactivation of *Rank* or RANKL/RANK blockade impaired proliferation and expansion of both murine *Brca1;p53* mutant mammary stem cells and mammary progenitors from human *BRCA1* mutation carriers. In addition, genome variations within the RANK locus were significantly associated with risk of

developing breast cancer in women with *BRCA1* mutations. Thus, RANKL/RANK control progenitor cell expansion and tumorigenesis in inherited breast cancer [21].

In a second publication, Nolan et al. [22] investigated a role for the RANK/RANKL pathway in the preneoplastic phase of *BRCA1*-mutation carriers and identified two subsets of luminal progenitors ($RANK^+$ and $RANK^-$) in histologically normal tissue of *BRCA1*-mutation carriers. They could demonstrate that $RANK^+$ cells are highly proliferative, have grossly aberrant DNA repair, and bear a molecular signature similar to that of basal-like breast cancer. These data provide further evidence for the hypothesis that $RANK^+$ rather than $RANK^-$ progenitor cells are a key target population in these women. Inhibition of RANKL signaling by treatment with denosumab in three-dimensional breast organoids derived from preneoplastic $BRCA1^{mut/+}$ tissue attenuated progesterone-induced proliferation. Furthermore, in female *BRCA1*-mutation carriers who underwent risk-reducing mastectomies, proliferation was markedly reduced in breast biopsies from those women treated with denosumab. Taken together, both studies have independently shown that RANKL blockade is a promising strategy in the prevention of breast cancer, particularly in *BRCA1* mutant patients [22].

While considerably less information on the role of the RANK/RANKL pathway is available for ovarian cancer, there is circumstantial evidence that PR signaling is important in endometroid and high-grade serous ovarian (HGSO) cancer, which is now believed to arise from Pax8-positive secretory cells in the distal fimbriae of the oviduct. These secretory cells, as well as the ciliated cells in the oviduct, undergo cyclical changes that are under the direct influence of estrogen and progesterone. In a recent meta-analysis of 12 studies ($n$ = 2,933) conducted in ovarian cancer patients, Sieh et al. [23] showed that ER and particularly PR were prognostic biomarkers in endometrioid and HGSO cancers. Strong PR expression was independently associated with improved disease-specific survival in high-grade serous carcinoma (HR 0.71, 95% CI 0.55–0.91; $p$ = 0.0080), but low PR expression was not (HR 1.02, 95% CI 0.98–1.18; $p$ = 0.74), suggesting that PgR-mediated signaling is also important in the development of HGSO cancer [23]. Since HGSO cancers are the predominant subtype in *BRCA*-associated ovarian cancer, it seems reasonable to assume that a disruption of the PR/RANK/RANKL system could be pertinent to tumorigenesis and therapy for mutation carriers.

*Denosumab*

Denosumab is a fully humanized IgG2 monoclonal antibody which specifically binds to the RANKL [24]. Compared to placebo, denosumab reduces the risk of new radiographic vertebral fracture and increases bone mineral density at the lumbar spine, total hip, and one-third radius more than bisphosphonates in postmenopausal women with osteoporosis at high risk for fracture. Three prospectively randomized trials in patients with breast, prostate, and other solid tumors, who suffered from one or more bone metastases, demonstrated superiority of denosumab versus zoledronic acid in reducing the risk of first skeletal-related events and first and subsequent skeletal-related events [25]. In a recently published trial in 3,425 women with endocrine-responsive breast cancer, we could also demonstrate an oncological effect of denosumab. It not only halved fractures irrespective of bone density, but also significantly improved disease-free survival compared to placebo. Importantly, we also did not observe a significant increase in any of the collected data on adverse events [26].

The collected evidence has led to the development of a clinical trial concept in which the preventive effect of denosumab is currently investigated in a prospectively randomized, international placebo-controlled trial. The BRCA-P study, which is currently recruiting, investigates the effect of 120 mg of denosumab, every 6 months, on breast cancer risk in healthy BRCA1 mutation carriers, who have not yet undergone prophylactic mastectomy. In the BRCA-P study, we will also investigate the effect of denosumab on ovarian cancer risk, on the risk of other cancers that have been implicated in *BRCA1* mutations, and on fracture risk.

## Conclusion

Until today, prophylactic removal of breast tissue is the most effective strategy to profoundly reduce breast cancer risk in *BRCA* mutation carriers. Nonsurgical chemopreventive options, such as the use tamoxifen or AI, are compromised by a lack of data from prospective trials, and by the poor side effect profile, particularly in young premenopausal women. However, the use of a RANKL-specific antibody appears to be a well-tolerated and effective option and is currently evaluated in the BRCA-P trial.

## Disclosure Statement

C.F. Singer has received research support, travel fees, and honoraria from Amgen and AstraZeneca, which is relevant to the topic reviewed in this paper. The BRCA-P Trial is funded by Amgen, Department of Defence, and by the German Ministry of Research and Education.

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