EDITORIAL

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Breast cancer prevention for *BRCA1* and *BRCA2* mutation carriers: is there a role for tamoxifen?

Kelly-Anne Phillips^{*1,2,3,4} & Geoffrey J Lindeman^{5,6,7}

“...the option of tamoxifen for breast cancer prevention should be discussed along with the evidence of benefits and potential side effects, thereby enabling an informed choice for women who wish to consider prevention therapy.”

For women who carry a mutation in the *BRCA1* or *BRCA2* genes, the risk of breast cancer by age 70 years is approximately 65 and 45%, respectively [1]. Breast cancer prevention for these women has predominantly focused on surgical strategies, such as bilateral mastectomy and endocrine ablation by premenopausal bilateral salpingo-oophorectomy (BSO). These procedures are associated with a substantially reduced risk of breast cancer [2]. However, in many countries the uptake of these highly effective prevention strategies is low [3]. This highlights the need for additional, nonsurgical alternatives for breast cancer prevention for *BRCA1* and *BRCA2* mutation carriers.

The oral selective estrogen receptor (ER) modulator, tamoxifen, taken 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* [4]. Moreover, this benefit is sustained for at least 5 years after ceasing tamoxifen. Mounting evidence, albeit observational, suggests that tamoxifen may also be efficacious for the prevention of breast cancer for *BRCA1* and *BRCA2* mutation carriers.

For primary prevention, the only published data on the efficacy of tamoxifen for *BRCA1* and *BRCA2* mutation carriers come from a subgroup analysis of the NSABP-P1 breast cancer prevention trial. That trial randomized 13,388 women at increased risk of breast cancer to receive either tamoxifen 20 mg daily or placebo for 5 years. The risk ratio for breast cancer 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 [5]. However, few mutation carriers were enrolled: only eight *BRCA1* and 11 *BRCA2* mutation carriers were identified among 288 study participants who developed breast cancer, so the confidence

KEYWORDS

- *BRCA1* • *BRCA2* • breast cancer
- chemoprevention • denosumab
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“Breast cancer prevention for [women who carry a mutation in the *BRCA1* or *BRCA2* genes] has predominantly focused on surgical strategies...”

¹Division of Cancer Medicine, Peter MacCallum Cancer Centre, Locked Bag 1, A'Beckett St, Victoria, 8006, Australia

²Sir Peter MacCallum Department of Oncology, The University of Melbourne, Australia

³Centre for Molecular, Environmental, Genetic & Analytic Epidemiology, School of Population & Global Health, The University of Melbourne, Australia

⁴Department of Medicine, St Vincent's Hospital, The University of Melbourne, Australia

⁵ACRF Stem Cells & Cancer Division, The Walter & Eliza Hall Institute of Medical Research, Australia

⁶Familial Cancer Centre, Royal Melbourne Hospital, Australia

⁷Department of Medicine, Royal Melbourne Hospital, The University of Melbourne, Australia

*Author for correspondence: Tel.: +61 3 9656 1697; Fax: +61 3 9656 1408; kelly.phillips@petermac.org

intervals were quite wide. Nevertheless, this study raised the possibility that tamoxifen could modulate breast cancer risk, at least for *BRCA2* mutation carriers.

More data are available in the secondary prevention setting, although all of these studies were observational rather than randomized. The largest, comprising data from 2464 mutation carriers, showed that tamoxifen use after a first breast cancer was associated with a reduced risk of contralateral breast cancer [6]. 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. Several earlier studies also examined the association between tamoxifen use and contralateral breast cancer in *BRCA1* and *BRCA2* mutation carriers [7–10]. Although their power was limited due to study size, 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, consistent with tamoxifen being efficacious for contralateral breast cancer prevention for both *BRCA1* and *BRCA2* mutation carriers.

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 negative at the time of diagnosis [11]. Data from the randomized primary prevention studies suggested that the benefit of tamoxifen was confined to the prevention of ER-positive breast cancer [4]. 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 BSO.

In fact, there is strong evidence that female hormones play a critical role in the early ontogeny of *BRCA1*-associated breast cancer. As noted above, BSO in premenopausal *BRCA1* mutation carriers is associated with reduced breast cancer risk [2]. Importantly, *BRCA1* has been shown to repress ER α -mediated transcription and may therefore alter estrogenic response [12]. Moreover, in mouse models activation of estrogen signaling has been shown to collaborate with *Brca1* loss to promote tumor development [13]. A

link between estrogen and breast cancer development in *BRCA1* mutation carriers is also suggested by the finding that two single nucleotide polymorphisms located close to *ESR1* (which encodes ER α) are associated with breast cancer risk for *BRCA1* mutation carriers [14]. Finally, progesterone receptor (PR) expression may be altered in *BRCA1* and *BRCA2* mutation carriers. In one study, the estrogen-responsive PR-B isoform was reduced in breast tissue from mutation carriers [15]. On the other hand, total PR expression was reported to be elevated in *Brca1/p53*-deficient mice where the progesterone antagonist mifepristone (RU486) appeared to ameliorate mammary tumorigenesis [16].

It is noteworthy that female steroid hormones profoundly affect mammary epithelial cell function by both direct and indirect means [17,18]. Indeed, mammary stem cells (which lack ER α and PR) appear to be indirectly activated by steroid hormones [19,20] via paracrine signaling mediated by RANK ligand (RANKL), a PR target. These findings raise the possibility that BSO 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, where breast tumors are believed to arise from aberrant luminal progenitor cells [21].

The limited evidence for the efficacy of tamoxifen in *BRCA1* and *BRCA2* mutation carriers has been an important factor restricting its use [22]. It is unlikely that a randomized study of tamoxifen for either primary or secondary breast cancer prevention for mutation carriers will ever be conducted. For women without a history of cancer, who are prepared to undergo bilateral mastectomy, that option is clearly preferable owing to its proven and substantial benefit. However, for those who decline bilateral mastectomy, or choose to delay it until they are older, tamoxifen should be considered, particularly for premenopausal women for whom the absolute risk of serious side effects is small and the benefit is potentially large, given that mutation carriers often develop breast cancer at an early age. For mutation carriers who have been diagnosed with hormone receptor-positive breast cancer, tamoxifen (or other endocrine therapy) is considered a standard of care. The combined secondary prevention data on mutation carriers described in this article suggest that tamoxifen might also be considered in the context of prevention for mutation carriers with

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hormone receptor-negative breast cancer who do not undergo bilateral mastectomy.

For premenopausal women, the main serious side effect of tamoxifen is deep venous thrombosis. The absolute risk, however, is small and similar to the risk associated with the combined oral contraceptive pill [23]. Due to its agonist activity in endometrial tissue, tamoxifen is also associated with endometrial hyperplasia and increased endometrial cancer risk, although the latter appears to be largely confined to women above the age of 50 years [23]. Two small retrospective observational studies have suggested that tamoxifen is associated with increased endometrial cancer risk in *BRCA* carriers [6]. A recent prospective study had similar findings, with all nine cases arising in postmenopausal women [24].

Although tamoxifen can cause vasomotor and sexual symptoms for some premenopausal women, it is generally well tolerated and does not alter overall physical and emotional well-being [25]. For women who are concerned about whether they will be able to tolerate the reversible side effects of tamoxifen, a short trial of therapy may be useful to inform their choice regarding a 5-year course of prevention therapy.

In the future there may be other efficacious chemoprevention options for women with a mutation in *BRCA1* or *BRCA2*. Aromatase inhibitors and selective ER modulators other than tamoxifen have been shown to be effective for breast cancer prevention in women at increased risk who do not carry a *BRCA1* or *BRCA2* mutation [2]. There are no data on their efficacy for mutation carriers. 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 emerging importance of progesterone/RANKL

signaling as a key mediator of normal breast epithelial function raises the possibility that RANKL inhibition, using agents such as denosumab, could offer a novel approach for breast cancer prevention [19], although this has not been evaluated in the clinic. Interestingly, the cognate receptor for RANKL, RANK, is expressed in both mouse [26] and human luminal progenitors in mammary epithelium, including in *BRCA1* mutation carriers [27].

In conclusion, until better targeted therapies are available for *BRCA1* and *BRCA2* mutation carriers, particularly those who have not undergone premenopausal BSO, the option of tamoxifen for breast cancer prevention should be discussed along with the evidence of benefits and potential side effects, thereby enabling an informed choice for women who wish to consider prevention therapy.

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