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Short communication

Prophylactic breast irradiation reduces background parenchymal enhancement (BPE) on MRI: A secondary analysis[☆]

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ABSTRACT

Purpose: We recently showed that prophylactic breast irradiation (PBI) reduces the risk of contralateral breast cancer in BRCA mutation carriers undergoing treatment for early breast cancer. It has been suggested that Background Parenchymal Enhancement (BPE) may be a biomarker for increased risk of breast cancer.

Methods: For participants in the trial we reviewed the MRI prior to enrollment and following radiation treatment and scored the contralateral breast for BPE and density.

Results: Significant reduction of BPE was more commonly noted following PBI ($p = 0.011$) compared to the control group.

Conclusion: Reduction of BPE by PBI may contribute to its prophylactic effect.

1. Introduction

We recently reported that the addition of contralateral breast irradiation was associated with a significant reduction of subsequent contralateral breast cancers and a delay in their onset among *BRCA* carrier patients treated for early breast cancer, HR = 0.175, [95% confidence interval (CI) 0.038–0.8011], log-rank P = 0.011 [1]. The mechanism through which prophylactic breast irradiation (PBI) mediates risk reduction remains elusive.

Several investigators [2–4] have presented evidence to suggest that elevated "background parenchymal enhancement" (BPE) constitutes an imaging biomarker that predicts primary breast cancer risk. The BPE phenomenon arises when normal breast tissue demonstrates signal enhancement that is related to the uptake of gadolinium-based contrast material as used during MR examinations of the breast. It has been proposed [5,6] that BPE constitutes tissue at risk for neoplastic transformation since it may reflect increased tissue microvascularity or permeability [5] which is regulated by endogenous hormones. It has been reported that BPE may be decreased by cancer therapies including neoadjuvant chemotherapy [7], endocrine therapy [8] and breast radiotherapy [9].

We surmised that reduction of BPE by prophylactic breast irradiation represents a mechanism for cancer risk reduction. We obtained permission from the respective IRBs of the medical centres participating in this multi-institutional collaboration to code the MRI images in order to test the hypothesis that prophylactic breast irradiation has efficacy by virtue of reducing BPE.

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2. Methods

In our phase II, multicenter, comparative two-arm trial, the choice of prophylactic irradiation to the contralateral breast, in addition to standard loco-regional treatment including surgery and irradiation to the involved side, was offered to BRCA mutation carriers treated for early breast cancer who declined contralateral mastectomy. The control arm consisted of patients who opted for standard locoregional treatment including surgery and irradiation to the involved side. The intervention arm consisted of patients who chose additional irradiation to the contralateral breast. The main inclusion criteria were women aged 30 years or above, carriers of a deleterious mutation in BRCA1/2, with a diagnosis of stage 0–III breast cancer (AJCC 6), who were designated for breast/chest wall irradiation as part of their adjuvant therapy and declined contralateral mastectomy. Bilateral breast MRI was required within 9 months before enrollment and prior to treatment. Radiotherapy was delivered at each participating center. Standard radiation treatment was delivered to the affected breast/chest wall/reconstructed breast and associated lymphatic drainage according to the prescription of the treating physician. The contralateral breast was treated with tangent fields using 2 Gy/fraction to a total dose of 50 Gy or 42.4 Gy using 2.65 Gy/fraction [1].

For this report we searched the radiology archives at each participating center and reviewed the MRI studies prior to enrollment and following radiation treatment whenever both studies were available at the same institution. The contralateral breast BPE was graded as minimal (0), mild (1), moderate (2), or marked (3) based on consensus between the radiologist and the PI and according to prior literature [2–4]. Contralateral breast density was also scored as minimal (1) to maximal (4) by the radiologist and the PI, using conventional density scale (according to the American College of Radiology (ACR) Breast Imaging-Reporting and Data System (BI-RADS) atlas, which is a classification system commonly used for mammography and adapted for MRI [10]). Both researchers were blinded to the patients' treatment arms.

Statistics- Differences between Intervention and control groups in categorical variables were tested for significance using the Fisher Exact Test. Differences between the groups in continuous variables were tested for significance using the independent T-Test.

3. Results

Both pre and post RT MRI studies were available at the respective institutions for 43 patients in the control group and 44 patients in the intervention arm. Fig. 1 depicts the MRI studies before and after prophylactic RT of a 62-year-old woman, a carrier of a BRCA2 mutation, with right breast hormone receptor positive- DCIS. She was treated with lumpectomy followed by radiation to her right breast as well as prophylactic radiation to the contralateral left breast and then received tamoxifen. Evidently, the BPE in her left breast dropped markedly (change in BPE score 2 to 0) following prophylactic RT.

Most patients (62/87, 71.3%) had low BPE (0–1) in the pretreatment MRI that dropped by 0–1 points in the post treatment study and there was no difference between the groups in the average drop of BPE. However, there were more patients with initial high BPE (score 2 or 3) who dropped by 2 points or more following contralateral breast irradiation (11/12, 91.7%) as compared to the control arm (5/13, 38.5%) and this difference was statistically significant ($p = 0.011$) (Table 1). No equivalent drop from initial high density (score 3 or 4) was noted.

There was no significant difference between the high BPE groups in median age, number of patients that had BSO prior to entry to the trial, use of neo/adjuvant chemotherapy or patients with Hormone Receptor positive tumors who received endocrine therapy (Table 2, Supplemental Table 3). Among patients with initially high BPE, 2 in the control group developed contralateral breast cancer. One had a drop of BPE by 2 points (3–1) and the other had no change in BPE (2–2). In the intervention group, one patient developed contralateral breast cancer in spite of a 2 points drop in her BPE (2–0, Supplemental Table 3).

4. Discussion

Potential reduction of breast cancer by prophylactic mammary irradiation was previously proposed [11] and subsequently supported by an experimental mouse model [12]. In mammary-cancer-prone mice, irradiation of the mammary glands on one side decreased the tumor incidence rate compared with the mammary glands on the contralateral shielded side [12]. We recently showed, in a multicenter nonrandomized trial, that prophylactic contralateral breast irradiation in BRCA mutation carriers significantly reduced the risk of subsequent cancer in that breast and also delayed its appearance [1]. Although the trial was not randomized and the patients could choose their treatment arm [13], the groups were balanced with regard to age, clinical parameters and systemic therapies. Further follow-up is needed to determine whether the prophylactic irradiation works via mechanisms that truly prevent the development of cancer cells or rather by active treatment of preclinical disease [14].

Possible explanations for the preventative effect of breast irradiation in BRCA mutation carriers [15] include eradication of cells that already transformed, RT-related reduction of epithelial cell proliferation and cell division thereby decreasing the accumulation of genetic aberrations, and depletion of the luminal epithelial compartment which is the origin of BRCA associated breast cancers [16,17]. In their recent study, Chiang et al. analyzed tumor-free breast tissues from risk reducing mastectomies of BRCA mutation carriers who were previously treated by breast RT for unilateral breast cancer. They found marked reduction of the luminal cell population in the irradiated breast as compared to the non-irradiated breast in 2 of 3 BRCA1 and in 1 BRCA2 carriers [17]. In addition, there was RT-associated reduction in the colony-forming ability of the breast epithelial cells. As it has been shown that BRCA associated cancers originate from luminal progenitors [18–20], the authors concluded that breast irradiation may reduce the incidence of BRCA1/2 associated breast cancers through depletion of their cellular source [17].

In this report we show that in BRCA mutation carriers, prophylactic breast RT reduces background parenchymal enhancement. It is possible that this phenomenon reflects the effect of RT on tissue vasculature.

For most patients in the trial BPE was low prior to irradiation and dropped by 0–1 points in the post treatment study. Likely, this drop is attributable to the systemic treatment (chemotherapy, endocrine therapy, BSO) that they received. For these patients other mechanisms must explain cancer risk reduction by prophylactic RT. However, among the 25 patients who had initial moderate or high BPE (scores 2 or 3), significant reduction of BPE by 2 or 3 points was seen in 11 of 12 irradiated contralateral breasts as compared to 5 of 13 control non-irradiated breasts ($p = 0.011$). There was no significant difference between the groups in other relevant parameters such as age, BSO, use of adjuvant chemotherapy or endocrine therapy. These findings suggest that reduction of BPE may be an additional mechanism by which breast irradiation contributes to cancer risk reduction in BRCA mutation carriers. Within our dataset there were a limited number of patients who presented with BPE scores that were high at the outset. Accordingly, firm conclusions cannot be drawn although a thought-provoking hypothesis has

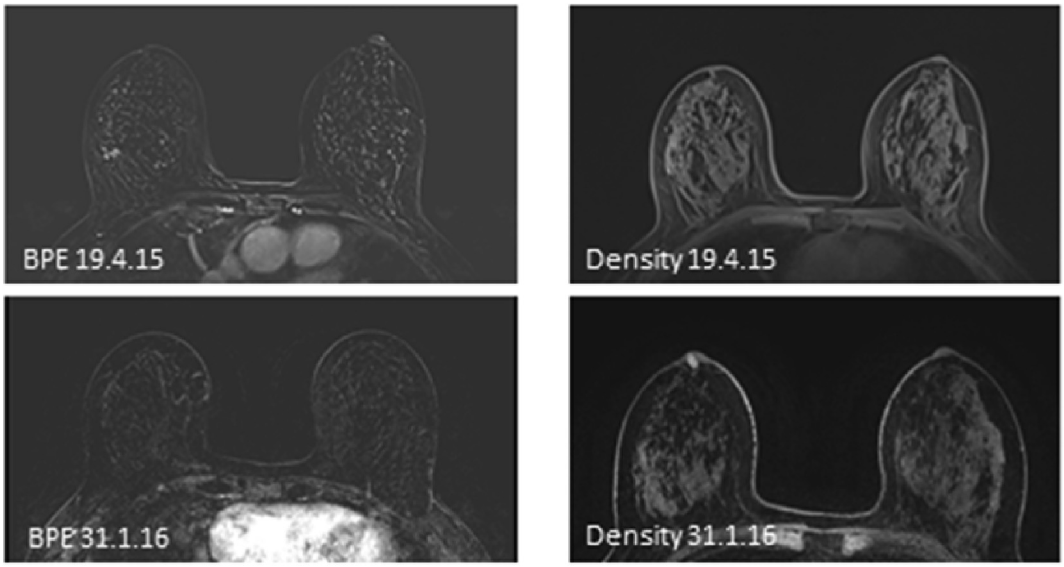

Fig. 1. MRI studies before and after prophylactic RT.

Table 1
Pre and post prophylactic RT: BPE and Density on MRI.

	Control n = 43	Intervention n = 44	P value
BPE difference – Any Difference:	23 (53.49%)	23 (52.27)	1[a]
– Mean (SD)	−0.698 (0.803)	−0.773 (0.831)	0.6695[b]
Pre-BPE score 2 or 3	13 (30.23%)	12 (27.27%)	0.816[a]
Drop by 2 points or more (out of subjects with Pre-BPE score of 2 or 3)	5 (38.46%)	11 (91.67%)	0.011[a]
Density difference – Any Difference:	13 (30.23%)	19 (43.18%)	0.268[a]
– Mean (SD)	−0.349 (0.573)	−0.500 (0.629)	0.2441[b]
Pre-Density score 3 or 4	26 (60.47%)	28 (63.64%)	0.827[a]
Drop by 2 points or more (out of subjects with Pre-Density score of 3 or 4)	2 (7.69%)	3 (10.71%)	1[a]

[a] Fisher's exact test.
[b] T-Test.

Table 2
Patients with high BPE on Pre-RT MRI: Comparison between the groups.

	Control	Intervention	P value
Pre-BPE score 2 or 3	13	12	
Drop by 2 points or more	5	11	0.011[a]
Median Age (range)	41 (34–64)	47 (33–74)	0.286[b]
BSO prior to accrual	4	4	1[a]
Hormone Receptor Positive	6	7	0.695[a]
Chemotherapy	11	9	0.645[a]
CLT breast ca	2	1	

[a] Fisher's exact test.
[b] T-Test.

been generated. Longer follow-up and larger trials will be needed to establish the association between reduction of BPE and reduced risk of subsequent malignancy among patients carrying the BRCA mutation.

5. Conclusion

Breast RT is a powerful means for reducing BPE in BRCA mutation carriers. This may contribute to the prophylactic activity of breast irradiation.

Declaration of competing interest

The authors state no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2019.10.011.

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