

# Reducing Second Breast Cancers: A Potential Role for Prophylactic Mammary Irradiation

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Breast-conserving surgery followed by radiotherapy is the standard of care for most women with early-stage breast cancer,<sup>1</sup> resulting in excellent long-term survival.<sup>2</sup> Post-treatment, however, the rate of second breast cancers is significant; for example, the average ipsilateral second-cancer rate from four long-term studies<sup>3-6</sup> is 13% after 15 years, and increases with still longer follow-up times. Rates in the contralateral breast are typically only slightly lower.<sup>5-7</sup>

We focus here on the rate of second cancers, which are genetically independent of the primary (ie, not recurrences); this rate is much higher than could be explained from the natural background rate of breast cancer in the general population, for both breasts.<sup>7,8</sup>

After conservative surgery, the ipsilateral breast is typically administered a fractionated whole-breast radiotherapeutic dose of at least 45 Gy, followed by a local boost to the tumor site. There is now considerable evidence that such large radiation doses to the breast result in significantly increased breast cancer risks. For example, recent long-term studies of Hodgkin's disease patients<sup>9-11</sup> who underwent radiotherapy show large radiation-induced breast cancer risks at sites exposed to doses ~40 Gy, with excess relative risks in the range of 10 to 30.

That tissues exposed to fractionated radiation doses as high as 40 to 50 Gy are at significant risk for radiation-induced cancer has only recently become apparent. Early models of radiation-induced cancer had predicted that virtually all radiation-mutated cells would be killed by such large doses, and thus the risk of radiation-induced cancer would be minimal. However, the epidemiologic data showing high risks of radiation-induced cancer at high radiation doses<sup>9-12</sup> have made it apparent that simple models of radiation carcinogenesis involving radiation-induction of premalignant cells, modulated solely by cell killing, are not adequate at high radiation doses. Consequently, more recent models take into account repopulation of normal and of premalignant cells by proliferation, occurring during and after fractionated radiotherapy,<sup>13-15</sup> whereby some repopulating cells carry and pass on radiation-induced premalignant damage. Including repopulation in models of radiation-induced cancer results in predictions of substantial cancer risks at high radiation doses, consistent with epidemiologic data.<sup>13</sup>

Thus, recent epidemiologic data and theory both lead to the expectation that women who receive a whole breast dose of 45 to 50

Gy will be at significant long-term risk for radiation-induced breast cancer, for all relevant ages. Here we estimate the cancer risks associated with adjuvant whole-breast irradiation after lumpectomy, both in the ipsilateral and contralateral breasts, and compare the predictions with the measured long-term risks of genetically independent second cancers in each breast. This allows an assessment for each breast of the relative importance of tumor recurrence, background risk, and radiation risk. The resulting insights in turn suggest potential strategies for reducing these risks.

## ESTIMATING THE MAIN CAUSES OF SECOND CANCERS IN EACH BREAST

### Data Set Used

There are many reports assessing second cancers in the ipsilateral breast after radiation therapy.<sup>3-6,8,16-18</sup> Because of our emphasis on genetically independent cancers versus recurrences, we have analyzed a data set in which second ipsilateral cancers were classified as either in the same or a different quadrant from that of the initial tumor. The data were from the Fox Chase Cancer Center (Philadelphia, PA) reported by Freedman et al<sup>6</sup> on 1,990 women with stage 0-II breast cancers who were treated between 1970 and 1998 with lumpectomy and ipsilateral whole-breast irradiation, at a median age of 57 years. There were 345 ipsilateral and 246 contralateral second breast cancers reported in this study, with a median follow-up of 80 months, and Kaplan-Meier–based recurrence rates reported up to 20 years after treatment. We chose to analyze this study on the basis of the long follow-up, the quadrant-based classification, and the fact that corresponding contralateral breast cancer rates were also reported, but similar results have been described in other reports,<sup>3,18-20</sup> generally with somewhat shorter follow-up times.

Freedman et al<sup>6</sup> essentially classified second ipsilateral tumors located in the same quadrant as the primary as true local (T) tumors, and those in the remaining three quadrants as genetically independent elsewhere (E) tumors. Presumably, it is proportionately likely that genetically independent tumors can occur in the same quadrant as the primary, so we have estimated the true frequency of genetically independent second tumors as  $E + E/3$ . Freedman et al<sup>6</sup> also report on the long-term frequency of contralateral second breast cancers; these

results are similar to those reported in the large Surveillance, Epidemiology, and End Results tumor registries database.<sup>7</sup>

### Estimating Radiation Risks in Each Breast

Predictions of radiogenic cancer risks as a function of dose were obtained for each breast, using a quantitative mechanistic cell initiation/inactivation/proliferation model<sup>13</sup>; this approach has been validated previously using data on radiation-induced breast and lung cancers in Hodgkin's disease patients treated with extended-field radiotherapy.<sup>9,10</sup>

The approach provides a practical methodology for predicting organ-specific cancer risks at high and low doses based on cancer risk data from atomic bomb survivors (who were exposed to lower doses), the demographic variables (age, time since exposure, sex, ethnicity) of interest, and organ-specific parameters describing radiation-induced cellular repopulation (which have been estimated previously for breast and for lung).<sup>13</sup> In this approach, excess relative risks (ERRs) are first directly estimated for single radiation exposures at moderate doses, based on cancer incidence data among atomic bomb survivors.<sup>21</sup> A well-established methodology described by Land et al<sup>22</sup> (and almost identically in the recent Biological Effects of Ionizing Radiation [BEIR] VII report<sup>23</sup>) is used to adjust dose-dependent ERRs from atomic bomb survivors to apply to the demographics of the individuals being studied. These two steps are implemented through publicly available on-line software (Interactive Radio-Epidemiological Program).<sup>24</sup> Finally, the ERR estimates for single moderate-dose radiation exposures are adjusted to fractionated radiotherapeutic exposures, using the initiation/inactivation/proliferation model.<sup>13</sup>

Once ERRs are calculated as a function of dose, age, and time after exposure, excess absolute risks (EAR) can be estimated for each year post exposure, and then summed to give the cumulative excess absolute risk for each breast:

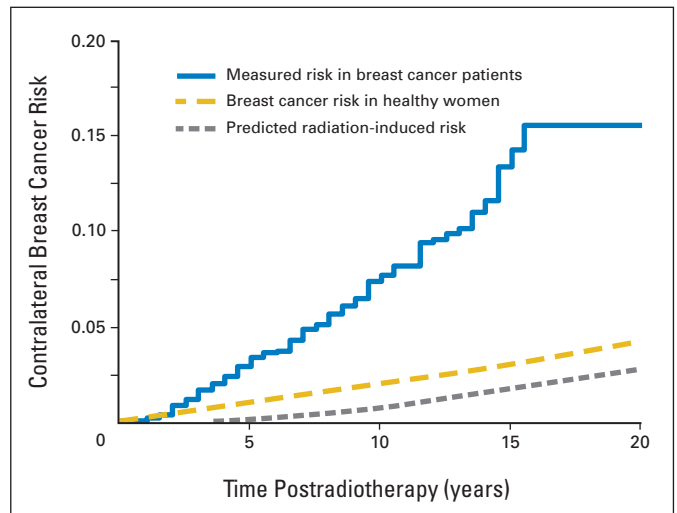
$$EAR(D, A, Y) = \frac{1}{2} ERR(D, A, Y) B(A + Y) P(A, Y) R(Y)$$

where *D* is the radiation dose, *A* is the age at radiotherapy treatment (in years), and *Y* is the number of years after radiotherapy. *ERR(D, A, Y)* is the estimated excess relative risk (see above); *B(A + Y)* is the background yearly risk of developing breast cancer, taken from the Surveillance, Epidemiology, and End Results 17 database<sup>25</sup>; *P(A, Y)* is the average probability for a woman age *A* surviving to year *Y*, taken from US population-wide life-tables<sup>26</sup>; and *R(Y)* is the relative breast cancer survival (probability of a breast cancer patient surviving to year *Y* after treatment, adjusted for expected mortality).<sup>27</sup> The factor of one half is because we are separately estimating cancer risks in each breast, given that the two breasts receive very different doses.

## MAIN CAUSES OF SECOND CANCERS IN EACH BREAST

### Contralateral Breast

The contralateral breast typically receives a comparatively small average dose that is less than 10% of that to the ipsilateral breast. Figure 1 shows the predicted radiation-associated risk in the contralateral breast from a fractionated uniform dose of 4.6 Gy, again for women age 57 years at the time of radiotherapy. As expected, the predicted radiation-associated risk is small; it is also much smaller than the observed contralateral second cancer risk, as pointed out by several investigators.<sup>7,28-30</sup> In the contralateral breast, therefore, most of



**Fig 1.** Cumulative second breast cancer risks in the contralateral breast of women with a primary breast cancer who underwent lumpectomy and radiotherapy (age 57 years at first cancer). The predicted radiation-induced risk (see text), and also the corresponding breast cancer risk in women who do not have breast cancer,<sup>25</sup> are both much smaller than the measured<sup>6</sup> risk.

the second cancer risk must be from background genetically independent cancers.

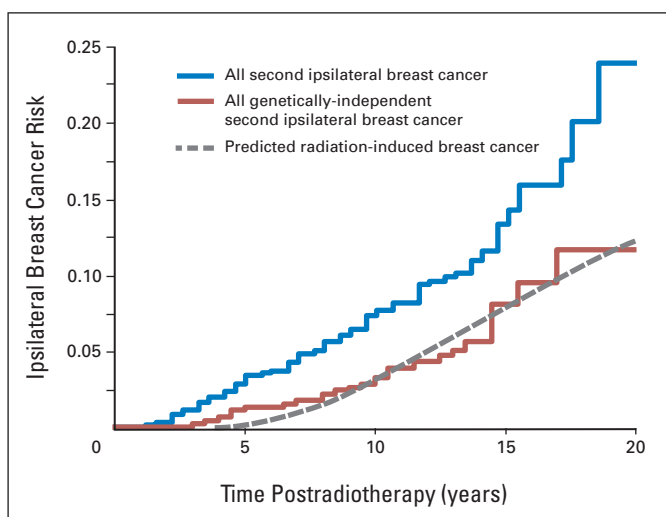
From Figure 1, the estimated background cumulative risk of a genetically independent second breast cancer in an unirradiated breast is approximately 14% at 20 years after treatment (observed value of 16%, minus predicted risk of 2% from the scattered radiotherapy dose). This background rate in breast cancer survivors is about three times larger than the overall general population background rate<sup>25</sup> (Fig 1), as has been pointed out in several studies,<sup>8,31</sup> and is probably attributable to genetically based enhanced breast cancer susceptibility in some or all breast cancer patients.

### Ipsilateral Breast

Figure 2 shows the predicted cumulative radiation risk of a second cancer in the ipsilateral breast of women who receive a uniform fractionated dose to the ipsilateral breast of 46 Gy at an average age of 57 years. The dose-risk relationship for radiation-induced breast cancers is predicted to be quite flat in the dose range from 45 to 60 Gy, so the effect on second cancer risk of an extra boost dose of 10 to 15 Gy to the tumor bed is likely to be minimal. The results in Figure 2 suggest that virtually all of the risk of a genetically independent second cancer in the ipsilateral breast can be attributed to the radiation exposure—thus, surprisingly, there appears to be essentially no contribution to second cancer risks in the ipsilateral breast from background genetically independent cancers.

## AN ADDITIONAL BENEFICIAL EFFECT OF RADIOTHERAPY ON THE IPSILATERAL BREAST?

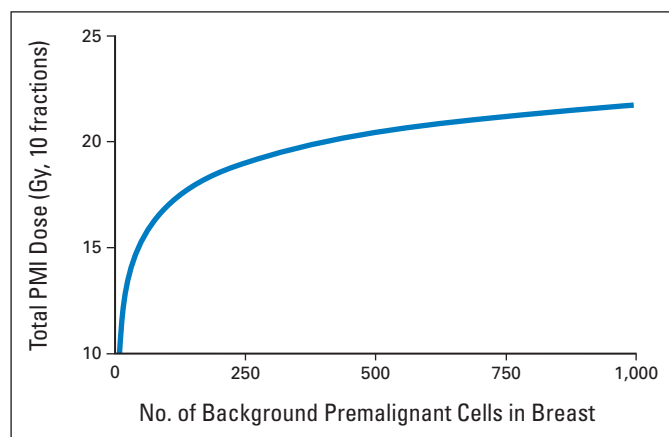
Why might there be essentially no risk from genetically independent second cancers in the ipsilateral breast, whereas there is a high probability in the contralateral breast, when presumably both breasts contain genetically identical cells? The likely explanation is that the approximately 46-Gy fractionated dose administered to the ipsilateral breast has killed essentially all of the genetically independent



**Fig 2.** Second breast cancer risks in the ipsilateral breast of women with breast cancer after lumpectomy + whole-breast radiotherapy (age 57 years at first cancer). The predicted radiation risk is essentially the same as the measured risk<sup>6</sup> for all genetically independent second cancers, suggesting that the risk of background genetically independent second cancers has been reduced essentially to zero by the radiation treatment.

pre-malignant cells in that breast that were present before the radiotherapy, and thus effectively eliminated the background cancer risk in the ipsilateral breast. This is not a surprising conclusion in that only about one in  $10^6$  cells would be expected to retain their clonogenic capacity after a prolonged (eg, 5 week) fractionated dose of approximately 46 Gy, even taking into account repopulation during the fractionated regimen, assuming a cell doubling time of 14 days (refer to cell survival parameters in Fig 3 legend).

It is not suggested that these background pre-malignant cells are killed differentially by radiation, compared with normal cells, but rather that because there are far fewer of them compared with normal cells, even a fairly modest kill level to all of the cells in the breast would be expected to result in the extinction of all the independent back-



**Fig 3.** Estimated prophylactic mammary irradiation (PMI) dose (here, in 10 fractions during 5 days) to kill given numbers of pre-malignant mammary cells. Cell survival ( $S$ ) is estimated by the standard linear-quadratic formula ( $S = \exp[-\alpha D - \beta D^2/N]$ , where  $D$  is the total dose and  $N$  is the number of fractions), with parameters ( $\alpha = 0.23 \text{ Gy}^{-1}$ ,  $\alpha/\beta = 4 \text{ Gy}$ ) appropriate for radioresistant pre-malignant cells.<sup>43</sup>

ground pre-malignant cells—a suggestion supported by the clinical data analysis described earlier.

In summary, in addition to improving control of the primary tumor, ipsilateral whole-breast radiotherapy appears to largely eliminate the significant background genetically independent ipsilateral second cancer risk to which breast cancer patients are subject. This phenomenon of radiation-induced reduction of background cancer risk has the potential to be exploited with new therapeutic strategies to reduce second breast cancer risks.

## POTENTIAL THERAPEUTIC IMPLICATIONS

### Potential Therapeutic Implications for the Ipsilateral Breast

We have argued that a whole-breast fractionated dose of 45 to 50 Gy serves the additional function of preventing genetically independent second cancers in the ipsilateral breast. There is much recent interest in the notion of accelerated partial-breast radiotherapy, in which only the tumor bed plus a margin in the ipsilateral breast is targeted.<sup>32-36</sup> The potential benefits of partial-breast irradiation in terms of cardiac and pulmonary sequelae, as well as breast cosmesis, are clearly attractive; however, according to the analysis described here, such a strategy may well be associated with an increased long-term risk of genetically independent cancers in the nontargeted parts of the ipsilateral breast, which would not have been cleared of pre-malignant cells by the radiation exposure. If such an analysis were correct, a more efficacious approach to partial-breast irradiation would be to administer the full dose to the tumor bed and margin, as is now done, but also to administer a uniform prophylactic lower dose to the remainder of the ipsilateral breast to clear it of pre-malignant cells. By analogy with prophylactic cranial irradiation (PCI), designed to reduce brain metastases from small-cell lung cancer,<sup>37</sup> we term this potential procedure prophylactic mammary irradiation (PMI). Such an approach should maintain much of the advantage of partial-breast radiotherapy, while minimizing the genetically independent cancer risk in the ipsilateral breast.

The key question here is to estimate the uniform subclinical PMI dose to the rest of the ipsilateral breast that would be sufficient to kill all of the pre-malignant cells. An estimate of this dose requires the number of pre-malignant cells present, a number that is not well established, although it is presumably very much less than the total number of stem cells in the breast, for which an approximate estimate is  $10^7$ .<sup>38-41</sup> Whatever the number, however, it is clear that treating the breast with radiation in as short a total time as possible would facilitate radiation-induced extinction of the pre-malignant cells by minimizing their repopulation during the treatment; an example of such an accelerated protocol is the 5-day/10-fraction 38.5-Gy partial-breast irradiation scheme used in Radiation Therapy Oncology Group studies 0319 and 0413.<sup>35,36</sup> In addition, the use of tamoxifen before and during the treatment would also be a potentially useful strategy for minimizing repopulation during the course of the radiotherapy.<sup>42</sup>

Assuming that a very short treatment time, perhaps with the addition of neoadjuvant/concomitant tamoxifen, essentially prevents repopulation during the course of partial-breast radiotherapy, Figure 3 shows estimates of the PMI doses that would be required to kill the pre-malignant cells in the remainder of the ipsilateral breast (ie, outside the irradiated tumor bed), as a function of the total number of such

cells in the breast. Thus, for example, if 100 (or 1,000) cells in the breast were premalignant, for the 10-fraction partial-breast protocol described,<sup>35,36</sup> a uniform 10-fraction dose totaling 17 Gy (or 22 Gy) to the rest of the ipsilateral breast might be appropriate (Fig 3), which is about half of the prescribed tumor-bed dose. Of course, this PMI dose would itself produce some breast cancer risk, in this case an estimated cumulative breast cancer risk of approximately 4% (17 Gy) and 5.5% (22 Gy) at 20 years. Other late effects (such as telangiectasia at 3 years<sup>44</sup>) and serious late cardiac or pulmonary sequelae<sup>45</sup> have estimated risks of  $\leq 0.5\%$  at 22 Gy, and significantly less at 17 Gy. However, these risks are all significantly smaller than either the radiation-induced cancer risk associated with conventional whole-breast radiotherapy using the prescribed dose (Fig 2), or the background cancer risk that PMI is designed to eliminate (Fig 1).

This potential overall gain from PMI would be expected to increase with increasing age at treatment. This is because, even though the number of background premalignant cells is likely to increase slowly with age, the corresponding radiation-induced cancer risk decreases sharply. However, an overall gain might be expected even at ages as young as 45 years.

### Potential Therapeutic Implications for the Contralateral Breast

Women with breast cancer have a much higher than average risk of developing an genetically independent cancer in the contralateral breast.<sup>8,31,46</sup> Based on the analysis described earlier, adjuvant radiotherapy to the ipsilateral breast might logically be accompanied by a concomitant uniform low-dose PMI to the contralateral breast; the appropriate dose would be expected to be in the range from 17 to 22 Gy in 10 fractions, the same as discussed and illustrated in Figure 3. The point is that, because there are only a comparatively small number of background premalignant cells in the breast, we suggest that it is possible to kill essentially all of them with a comparatively low radiation dose, therefore causing only a low level of complications (quantified in the previous section) resulting from killing/mutagenesis of the far more numerous normal cells. In this sense, the situation is different from PCI, in which far more cancer cells need to be eliminated to control metastases.<sup>47</sup>

In fact, a conceptually similar approach has been used successfully<sup>48</sup> to treat carcinoma in situ in the contralateral testicle of men with unilateral testicular germ cell cancer; the dose to the contralateral testicle is in the range from 16 to 20 Gy in 2-Gy fractions, similar to that estimated here.

One might also speculate whether whole-breast low-dose PMI could be an alternative to prophylactic mastectomy for women with breast cancer susceptibility genes, such as *BRCA1* and *BRCA2*. However, whether these mutation carriers have a significantly increased susceptibility to radiation-induced cancer has not yet been established.<sup>49,50</sup>

### Application of Potential New Therapeutic Strategies

It is axiomatic that prophylactic radiation treatment of the contralateral breast should be approached with considerable caution. Although the arguments presented here suggest that second cancer risks in the contralateral breast, which are high in long-term survivors, may be reduced significantly with this PMI approach, such treatments would represent a departure from current clinical practice (although PCI and irradiation of the contralateral testicle are both conceptually similar). In contrast, the proposed PMI strategies for modifying ipsi-

lateral partial-breast techniques fall about midway between current partial-breast and current whole-breast irradiation techniques.

Although use of animal models to test the concepts described here seems quite feasible, of course any clinical testing should be done in the context of an institutional review board–approved, peer-reviewed trial.

### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

### AUTHOR CONTRIBUTIONS

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**Final approval of manuscript:** David J. Brenner, Igor Shuryak, Sandra Russo, Rainer K. Sachs

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