

EDITORIALS

Contralateral Second Breast Cancers: Prediction and Prevention

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Long-term survival after a breast cancer diagnosis has increased markedly in the last decade: 15-year relative survival in the United States is now 75% (1), up from 58% in 2001. This increase is due in part to earlier detection but also to improved treatment options (2,3). So it is highly appropriate that increasing attention is being paid to the issue of breast cancer survivorship and, in particular, the issue of second breast cancers. Several long-term studies suggest that contralateral second breast cancer rates range from 10% to 15% at 15 years after treatment and are even higher for still longer-term survivors (4,5).

The risk of a breast cancer survivor developing a second breast cancer is much higher than the risk of a comparable healthy woman developing a first breast cancer. For example, a healthy 55-year-old woman has about a 2.5% chance of developing invasive cancer in a given breast over the next 15 years, whereas a 55-year-old breast cancer survivor has a 10%–15% chance of developing invasive cancer in the contralateral breast over the next 15 years. Only a small component of this disturbingly large risk of a second breast cancer is treatment related: If anything, some chemotherapy regimens may reduce the rate of second breast cancers (6), and the comparatively low and inhomogeneous dose of scattered or leakage radiation to the contralateral breast during radiotherapy (7) results in only a small increase in the risk of contralateral breast cancer (5,8–10).

These considerations imply that women with breast cancer are prone to develop a second breast cancer. Lifestyle and reproductive factors (11), as well as genetic factors (12), are each presumably major players in the etiology of second breast cancers, as they are in the etiology of primary breast cancers. Thus, there has been much interest in trying to identify genes that are associated with second breast cancers. Not surprisingly, the same genes that have been linked to increased susceptibility to primary breast cancer have been the most studied with regard to susceptibility to second cancers. For example, Graeser et al. (13) investigated the risk of contralateral second breast cancer in *BRCA1* and *BRCA2* mutation carriers and found that women with these mutations were more likely to develop a contralateral second breast cancer compared with breast cancer survivors without these mutations. Likewise, the clinical significance of mutations in the *ATM* gene with respect to the risk of a second breast cancer has been studied by the Women's Environment, Cancer, and Radiation Epidemiology (WECARE) Study Collaborative Group (14,15) and by several other groups (16,17). In earlier studies, the WECARE group showed that several of the more common *ATM* mutations were associated with a decreased risk of a second breast cancer (15). In this issue of the Journal, the WECARE group focuses (14) on some rare *ATM* mutations, which they convincingly show are associated with an increased risk of developing contralateral second breast cancer after radiotherapy.

These new observations (14) complement the increasing evidence that some rare mutations in *ATM* confer an increased risk of primary breast cancer, whereas common *ATM* mutations generally do not (18). However, mutations in *ATM* cannot, in isolation, be major determinants of the large risks of second breast cancer faced by long-term breast cancer survivors. After all, it is estimated that, at most, 5% of primary breast cancers are due to mutations in the *ATM*, *BRCA1*, *BRCA2*, or *TP53* genes (18). For primary breast cancers, a likely picture is that large numbers of low-penetrance genes are responsible for the overall genetic risk (12,18), and the same is presumably true for the risk of a second breast cancer. Thus, as with most primary breast cancers (18), we are still far from understanding the genetics—or indeed most of the etiology—associated with the great majority of second breast cancers.

Because our understanding of the etiology of second breast cancers is so limited, prophylactic approaches to reduce risks of second breast cancer are desirable for all breast cancer survivors. For women with estrogen receptor–positive primary breast cancers, there is evidence that adjuvant tamoxifen therapy reduces the risk of a second breast cancer (6,19,20), although the magnitude and duration of the risk reduction remain uncertain (6,20); even with tamoxifen, however, the long-term risks of a second breast cancer remain disturbingly high. Beyond tamoxifen therapy for estrogen receptor–positive breast cancer survivors, regular screening and prophylactic contralateral mastectomy represent the two ends of the quite limited spectrum of prophylactic options currently available to breast cancer survivors.

Another potential option for reducing the risk of contralateral second breast cancer, independent of estrogen receptor status, is prophylactic irradiation of the contralateral breast (8). The rationale for prophylactic mammary irradiation is evidence that standard radiotherapy of the affected (ipsilateral) breast after lumpectomy substantially reduces the risk of a second cancer in the ipsilateral breast by killing the existing premalignant cells in that breast (8). This conclusion implies that there are relatively few premalignant cells in each breast (hundreds or thousands, not millions) so that even a fairly modest radiation dose to the contralateral breast—much lower than a tumoricidal dose—could kill essentially all of the premalignant cells in the contralateral breast. If this is so, then a prophylactic radiation dose delivered uniformly to the whole contralateral breast would have the potential to markedly reduce the risk of a second cancer in that breast. Because the prophylactic mammary irradiation dose would be relatively low, prophylactic mammary irradiation, potentially delivered at the same time as the higher-dose radiotherapy to the affected ipsilateral breast, would not itself be expected to produce unacceptable radiation sequelae (8).

A conceptually similar approach to prophylactic mammary irradiation that already exists in current clinical practice is prophylactic testicular irradiation of the uninvolved contralateral testicle in men with unilateral primary testicular lymphoma (21,22); the recommended radiation dose to the contralateral testicle is also quite modest (21).

In summary, the WECARE results in this issue of the Journal (14) reemphasize that we do not yet understand most of the etiology of the disturbingly high long-term risks of second breast cancers. It is important, therefore, to continue to seek prophylactic preventative options that are useful for all breast cancer survivors. Tamoxifen is a partial solution that produces some reduction in the risks of second breast cancers in estrogen receptor-positive breast cancer survivors. We should also consider more targeted approaches, prophylactic mammary irradiation being one possibility, to eliminate premalignant cells in the contralateral breast and thus to minimize a major hazard faced by long-term breast cancer survivors.

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