

Association between Breast Density and Subsequent Breast Cancer Following Treatment for Ductal Carcinoma *In situ*

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Abstract

Background: Risk of invasive cancer following treatment for ductal carcinoma *in situ* (DCIS) is associated with both treatment- and tumor-related factors. However, it is unknown whether stromal factors such as breast density may also influence subsequent invasive breast events. We investigated whether breast density is an independent predictor of subsequent breast events among women treated for DCIS.

Population: A prospective cohort study of 3,274 women ages 30 to 93 in the Breast Cancer Surveillance Consortium treated with lumpectomy for DCIS between 1993 and 2005. All subjects had an American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) breast density measure recorded prior to diagnosis.

Methods: Ipsilateral and contralateral breast cancer following lumpectomy for DCIS were ascertained through state tumor registries, regional Surveillance Epidemiology and End Results program or pathology

databases. A Cox proportional hazard model was used to compare adjusted risk of breast cancer among women with high (BI-RADS 3 or 4) versus low (BI-RADS 1 or 2) breast density.

Results: During a median follow-up period of 39 months (0-132 months), 133 women developed invasive breast cancer. After adjusting for age and radiation treatment, high breast density was associated with increased hazard for contralateral (hazard ratio, 3.1; 95% confidence interval, 1.6-6.1) but not ipsilateral (hazard ratio, 1.0; 95% confidence interval, 0.6-1.6) invasive breast events.

Conclusion: High breast density is associated with contralateral, but not ipsilateral, invasive breast cancer following lumpectomy for DCIS. Thus, women with DCIS and high breast density may especially benefit from antiestrogenic therapy to reduce the risk of contralateral invasive disease. (Cancer Epidemiol Biomarkers Prev 2007;16(12):2587-93)

Background

As a largely mammographically detected entity, breast ductal carcinoma *in situ* (DCIS) incidence has paralleled widespread mammographic screening practices, and DCIS currently affects >60,000 women every year in the United States (1-3). Pure DCIS is thought to bear no risk of systemic spread. However, histologic and genomic studies support a potential precursor role of DCIS for some invasive breast cancers (4-6). Accordingly, DCIS is treated aggressively in an effort to prevent subsequent invasive breast cancer. The goal of current therapy is the eradication of all histologically evident disease. This is accomplished through a combination of surgery, radio-

therapy, and hormonal therapy. With these effective treatment options, the prognosis of patients diagnosed with DCIS is excellent, and women treated for DCIS can expect a long-term breast cancer-specific mortality of <1% (7).

Substantial evidence supports the hypothesis that breast cancer development occurs through a series of genomic and epigenomic alterations (4, 8). However, even with biopsy alone, not all DCIS will be associated with a subsequent invasive breast cancer (9-11). Our understanding of the factors that can affect the occurrence of subsequent invasive breast cancer remains limited. It has been clearly shown that tumor-related factors such as grade, size, and mitotic rate, and treatment variables such as extent of surgery, width of margins, radiation, and tamoxifen can affect ipsilateral event rates after treatment for DCIS (12-15). Nevertheless, even among women selected to have the lowest risk DCIS lesions, lumpectomy alone is associated with a 0.5% to 2% annual risk of subsequent tumor events, almost half of which are invasive breast cancer (10, 12, 15, 16).

Little is known about whether modifiable risk factors for breast cancer progression from DCIS to invasive cancer exist. If such risk factors could be identified, treatment strategies focusing on altering these risk

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factors could change the goal of therapy for DCIS, effectively making DCIS an opportunity for targeted prevention rather than a disease necessitating immediate intervention. One potentially important factor in this regard is breast density. Breast cancer incidence is three to six times higher among women with increased breast density compared with age-matched controls with low breast density (17-21). In fact, breast density remains one of the strongest risk factors for invasive breast cancer, second only to deleterious germ line BRCA mutations. Mammographic breast density is a complex, multifactorial risk factor for the development of invasive breast cancer. Twin studies have confirmed a heritable component to the factors comprising breast density (22). However, some determinants of breast density are nonheritable and are affected by the hormonal milieu throughout a women's lifetime. These determinants include modifiable lifestyle factors such as body mass index, parity, and use of postmenopausal hormone therapy (21, 23-25). Research also suggests that other modifiable factors such as physical activity and dietary fat may also influence breast density (26, 27).

A link between breast density and cancer progression or invasion has been postulated, but not clearly shown. If such an association could be found, a potentially modifiable risk factor for invasive disease would be identified. We undertook this study to determine whether women with higher breast density at the time of diagnosis of DCIS are at an increased risk of subsequent invasive breast cancer compared with age- and treatment-matched controls. Furthermore, we questioned whether radiation treatment could modify this risk. A recent overview of the randomized trials of lumpectomy and radiation showed a small increase in contralateral breast cancer (RR [rate ratio], 1.09 in women treated before the age of 50 and RR, 1.25 in women treated at age 50 or later; ref. 28). We wished to see whether this effect was more pronounced in women with high breast density compared with those with low breast density. We hypothesized that increased breast density is associated with a higher risk of subsequent invasive breast cancer in women following lumpectomy for DCIS, and that this risk may be modified by radiation treatment.

Materials and Methods

Our study population was derived from the National Cancer Institute–funded Breast Cancer Surveillance Consortium (BCSC)⁷ that was established in 1994 to study breast cancer screening practices and outcomes in the United States. A detailed description of the BCSC has been previously reported (29). Briefly, the BCSC is comprised of seven mammography registries with a screened population representative of the general demographic profile of the United States (30). The centers are: the San Francisco Mammography Registry, Group Health's Breast Cancer Surveillance Project (western Washington state), Colorado Mammography Advocacy Project, Vermont Breast Cancer Surveillance System,

New Hampshire Mammography Network, Carolina Mammography Registry, and New Mexico Mammography Registry. Annually, >800,000 women are screened at a BCSC site, and ~3,000 new cancers are diagnosed. Each registry annually links women in their registry to a state tumor registry or regional Surveillance Epidemiology and End Results (SEER) program to obtain population-based cancer data. Most registries additionally link to pathology databases. Radiographic and clinical data are collected prospectively.

Using this database, we identified 5,958 women at BCSC sites who were diagnosed with unilateral DCIS between 1993 and 2005; of these, 4,431 (74%) had a breast density measurement recorded at a screening mammogram prior to diagnosis. The median interval between the breast density measurement and the diagnosis of DCIS was 1 month (range, 0-97 months). Breast density was measured by the Breast Imaging Reporting and Data System (BI-RADS) categorization, a subjective measure of mammographic breast density given by the interpreting radiologist at the time of the mammogram. The BI-RADS grouping includes the following four ordinal categories: (a) almost entirely fat (low density); (b) scattered fibroglandular densities (average density); (c) heterogeneously dense (high density); (d) extremely dense (very high density). The analysis was done by collapsing BI-RADS categories into low (BI-RADS 1 and 2) and high (BI-RADS 3 and 4) groups because of the small number of events in BI-RADS groups 1 and 4 for analysis. BI-RADS breast density, although subjective and thus potentially less reproducible than standardized techniques, has been shown to be linearly associated with adjusted rate of breast cancer. This linear relationship has been shown even between categories 2 and 3 which are thought to have the most extensive overlap (31).

Women with a diagnosis of lobular carcinoma *in situ* were excluded, as were those with previous breast cancer history. All subjects with a diagnosis of ipsilateral invasive breast cancer within 60 days of a DCIS diagnosis were also excluded ($n = 179$) because these cases were likely to represent invasive disease concurrent with the DCIS diagnosis. An additional 978 women (22% of the cohort) underwent ipsilateral or bilateral mastectomy. Mastectomy subtypes included total, simple, subcutaneous, modified radical, radical, and extended and were all excluded because these cases were uninformative for subsequent ipsilateral invasive breast events. The resulting 3,274 women who underwent lumpectomy (nipple resection, lumpectomy or excisional biopsy, reexcision, wedge resection, quadrantectomy, segmental mastectomy, or tylectomy) for DCIS comprised the study cohort. A total of 47% of women underwent lumpectomy only and 41% underwent lumpectomy and radiation therapy. An additional 12% underwent lumpectomy, but radiation status was unknown. These latter cases were included in the primary analysis, but were excluded from the analysis stratified by radiation treatment. Median follow-up time for the cohort was 39 months (range, 0-132). The Cox proportional hazard model was used to compare the risk of developing subsequent breast events between women with high versus low breast density. The outcome variables were time to any invasive locoregional breast cancer, ipsilateral invasive breast cancer, contralateral invasive breast cancer, or contralateral DCIS. Time to ipsilateral DCIS, although of

⁷ <http://breastscreening.cancer.gov>

Table 1. Characteristics of the study population

	No subsequent invasive event	Subsequent invasive event	Subsequent contralateral DCIS
<i>n</i>	3,111	133	30
Mean age at diagnosis, <i>y</i> (range)	58 (30-93)	59 (34-90)	55 (34-83)
Median months of follow-up (range)	39 (0-132)	29 (2-109)	26 (3-70)
Positive family history	21%	26%	28%
Radiation treatment	47%	43%	28%
High grade	34%	37%	33%
White race	83%	77%	90%

NOTE: Invasive events include both ipsilateral and contralateral breast cancers. Ipsilateral DCIS recurrence data was not available.

interest, was not recorded in most cancer registries and therefore could not be evaluated. The primary predictor variable of interest was breast density as determined by the BI-RADS density classification. Key covariates included in the analysis were age at diagnosis, which was treated as a continuous variable, and radiation treatment, a dichotomous variable. Follow-up times depended on the outcome being modeled. For contralateral outcomes, follow-up time was computed from the date of initial DCIS diagnosis to the earliest of the following three dates: date of subsequent outcome diagnosis, date of death or date of last contact for women who had died, or the end of the follow-up period, which was taken to be the last date with complete data from the cancer registry (December 31, 2003 to December 31, 2004, depending on the registry). The Nelson-Aalen estimator (32) was used to calculate the cumulative rate for invasive events. For ipsilateral events, follow-up time was started at 60 days in order to fulfill the proportional hazards assumption of the Cox model, as women with an ipsilateral cancer outcome within 60 days had been excluded from the analysis. All significance tests were two-sided.

A sensitivity analysis was done to determine whether new cancers could be masked by increased breast density. As part of this analysis, we started the follow-up period at different times (at 6, 12, 24, and 36 months), and thus, excluded any events occurring prior to that follow-up initiation point. All statistical analyses were done using STATA 9.0 software package (StataCorp LP).⁸

Results

Median follow-up time was 39 months (range, 0-132) for women without a subsequent breast cancer event and 29 months (range, 2-109) for women with a breast cancer event. One hundred and thirty-three women were diagnosed with an invasive event, including two women with bilateral invasive breast cancer events; 30 women were diagnosed with contralateral DCIS, and 3,112 women remained disease-free (Table 1). Median time to an invasive breast cancer event was 29 months (range, 2-109) for ipsilateral events and 31 months (6-109) for contralateral events. The 36-month cumulative incidence for invasive breast cancer was 1.8% for ipsilateral events and 1.2% for contralateral events. Most women had high breast density (BI-RADS 3: 45%) followed by average

breast density (BI-RADS 2: 41%). Only 9.8% of women were in the highest breast density category (BI-RADS 4).

A total of 83 women were diagnosed with ipsilateral invasive breast cancer, comprising 62% of all invasive breast events. More than 60% of invasive breast cancers occurred in the high-density (BI-RADS 3 and 4) group (Table 2), with 14 (16%) of these events occurring in the BI-RADS 4 group. The effect of breast density was most marked for contralateral events. A greater proportion of both contralateral invasive breast cancer (75%) and contralateral DCIS (63%) occurred among women with high breast density. Subsequent ipsilateral invasive breast events were nearly evenly distributed between the low- and high-density groups.

After adjusting for age and radiation therapy, women with high breast density had a 3-fold increased risk of contralateral invasive disease, compared with those with low density (Table 3). However, subsequent ipsilateral invasive breast cancer was not increased in the higher density group. Grouping both subsequent ipsilateral and contralateral events together abrogated the association between breast density and invasive breast cancer. The hazard ratio (HR) for contralateral DCIS was not significant; although this was a very small group, with only 11 patients recorded as having low density and 19 as high density.

Breast cancer outcomes were subdivided on the basis of radiation history to determine whether there was an interaction between breast density and radiation treatment (Table 4). No significant interaction was found after adjustment for age ($P = 0.37$ and $P = 0.68$ for ipsilateral and contralateral invasive cancer, respectively). A significantly increased risk of contralateral invasive breast cancer was again noted in women with higher breast density, with a HR of 2.7 (1.0-7.5) in women who were not treated with radiation and 3.6 (1.1-11.3) in those treated with radiation. However, subsequent ipsilateral invasive breast cancer was not increased in those with high versus low breast density.

The risk for contralateral invasive breast cancers remained stable over a wide range of follow-up time intervals from initial DCIS diagnosis (HR, ~3.0; Table 5), suggesting that masking due to high breast density does not explain the increased risk observed in this group.

Discussion

We undertook this study to determine whether women with increased breast density had a greater likelihood of developing invasive breast cancer following lumpectomy for DCIS when compared to women with lower breast density, adjusting for age and radiation treatment.

⁸ <http://www.stata.com>

Table 2. Subsequent breast events among women diagnosed with DCIS by breast density group

Breast density group	Any invasive cancer, <i>n</i> (col%)	Ipsilateral invasive cancer, <i>n</i> (col%)	Contralateral invasive cancer, <i>n</i> (col%)	Contralateral DCIS, <i>n</i> (col%)
Low (BI-RADS 1, 2)	52 (39%)	39 (47%)	13 (25%)	11 (37%)
High (BI-RADS 3, 4)	81* (61%)	44 (53%)	39 (75%)	19 (63%)
Total	133*	83	52	30

*Includes two patients with bilateral invasive breast cancer.

Our findings support the only previous report examining the association between breast density and DCIS recurrence, which suggested that the rate of second breast events following a diagnosis of DCIS may be increased in women with high breast density (33). In this previous study, breast density was measured as a continuous variable which was then categorized into four breast density groups. The number of events was comparable to the current study, with 91 ipsilateral events and 28 contralateral events. When compared with the lowest density group (<25% dense), the highest density group ($\geq 75\%$ dense) had an adjusted relative risk of 3.2 [95% confidence interval (95% CI), 1.2-8.5] for any invasive cancer. In comparison, although we found a trend for increased risk for any invasive cancer in the higher density group (BI-RADS 3 and 4; HR, 1.4; 95% CI, 0.9-2.1), the effect of breast density was significant only for contralateral invasive cancers (HR, 3.1; 95% CI, 1.6-6.1).

The current study used a different measure of breast density and thus the results are not directly comparable to the previous report. In addition, the Habel study did not distinguish between contralateral, ipsilateral, and regional invasive recurrence. Furthermore, our analysis was population-based, and thus, the results were arguably more generalizable. Nevertheless, these two studies together support an association between breast density and recurrence risk following treatment for DCIS. Importantly, the increased risk for contralateral invasive breast cancer in our cohort remained stable over time, arguing against a masking phenomenon in the detection of new cancers as a result of increased breast density.

The quality of data collection is clearly an important determinant of the results of any population-based study. Comparison of SEER treatment data to Medicare claims records shows a high degree of accuracy regarding both surgery and radiation (34, 35). Moreover, although SEER only captures surgery and radiation given as part of the initial course of treatment (defined as within the first 4 months following diagnosis), this is not a significant concern for DCIS where patients do not receive neoadjuvant therapy prior to definitive treat-

ment. Thus, neither incomplete surgery nor radiation data would be expected to affect the results of the study.

Ascertainment of incident cancers by SEER sites has been considered the gold standard among cancer registry databases in the United States. However, the definition of recurrent disease has lacked consistency over time and across sites. This is especially true for ipsilateral recurrences which are often not captured, particularly in the case of recurrent DCIS. This could clearly have underestimated the effect size seen for breast density on ipsilateral events. However, it is unlikely that ipsilateral cancers are less likely to be ascertained for one breast density group versus another, thus, our conclusions would not differ.

Because long-term follow-up studies of women undergoing radiation treatment for breast cancer have shown a significantly increased risk of contralateral cancers (28), we explored whether there existed an interaction between breast density and radiation treatment which could modify the incidence of contralateral breast cancer events. In our study, there was no statistically significant interaction between breast density and radiation for contralateral breast cancer events, although the risk ratio for contralateral invasive cancer was 2.7 (95% CI, 1.0-7.5) in women treated with lumpectomy alone versus 3.6 (95% CI, 1.1-11.3) in women who underwent both lumpectomy and radiation. Because there were only 52 women in the database who were diagnosed with contralateral invasive cancer, it is possible that this increased risk in women with high breast density treated with radiation could be significant with longer follow-up. We also found that ipsilateral subsequent invasive breast cancer was independent of breast density, not only in those who had undergone radiation as part of the primary treatment for DCIS, but also in patients undergoing lumpectomy alone.

These results suggest an important role for breast density in the initiation of breast cancer. It has been shown that the majority of subsequent ipsilateral tumor events following treatment for DCIS are identified in the index quadrant, suggesting that some of these events likely represent persistent DCIS rather than new events per se. The lack of an association between breast density

Table 3. Risk of subsequent breast events among women diagnosed with DCIS by breast density groups

Breast density	Any invasive cancer (<i>n</i> = 133)	Ipsilateral invasive cancer (<i>n</i> = 83)	Contralateral invasive cancer (<i>n</i> = 52)	Contralateral DCIS (<i>n</i> = 30)
	HR* (95% CI)	HR* (95% CI)	HR [†] (95% CI)	HR [†] (95% CI)
Low (BI-RADS 1, 2)	1.00	1.00	1.00	1.00
High (BI-RADS 3, 4)	1.4 (0.9-2.1)	1.0 (0.6-1.6)	3.1 (1.6-6.1)	1.5 (0.6-3.3)

*Adjusted for age and radiation status.

†Adjusted for age.

Table 4. Age-adjusted risk of subsequent breast events among women diagnosed with DCIS stratified by radiation status

Breast density	Any invasive cancer (n = 133)*	Ipsilateral invasive cancer (n = 83)	Contralateral invasive cancer (n = 52)	Contralateral DCIS (n = 30)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
No radiation (n = 1,536)				
Low (BI-RADS 1, 2)	1.00	1.00	1.00	1.00
High (BI-RADS 3, 4)	1.2 (0.7-2.0)	0.9 (0.5-1.7)	2.7 (1.0-7.5)	1.6 (0.5-4.7)
Radiation (n = 1,354)				
Low (BI-RADS 1, 2)	1.00	1.00	1.00	1.00
High (BI-RADS 3, 4)	1.7 (0.8-3.3)	1.1 (0.5-2.5)	3.6 (1.1-11.3)	0.8 (0.1-4.4)

*Includes two patients with bilateral invasive cancer events.

and ipsilateral invasive disease suggests that once a neoplastic process has developed, breast density may play a limited role. However, for new contralateral cancers, breast density remains an important risk factor for the development of new malignant events. Thus, women with newly diagnosed DCIS and increased breast density would benefit most from systemic treatment strategies that would reduce breast cancer risk bilaterally.

The best-studied treatment for bilateral risk reduction in the setting of DCIS is tamoxifen. NSABP B-24 showed a significant risk reduction for invasive breast cancer with the addition of tamoxifen to lumpectomy and radiation (14). However, many women forgo this treatment option due to concerns regarding side effects and the perception of small benefit. Accurate population-based data regarding prevalence of tamoxifen use for DCIS are limited, but one study suggests that only 14% of patients diagnosed with DCIS are treated with adjuvant hormonal therapy (36). A single institution study reported that of 277 women with DCIS eligible for tamoxifen treatment, only 166 (60%) were offered tamoxifen, and of those, 74 (27%) elected to pursue this therapy. Given the reluctance of many women to consider tamoxifen treatment, those women with DCIS and increased breast density should be particularly encouraged to consider global risk reduction with adjuvant hormonal therapy, as these women may derive the greatest benefit.

Previous studies have confirmed that tamoxifen use does, in fact, reduce mammographic breast density in a small proportion of women, but it is not known whether the reduction in breast density is associated with reduction in risk of breast cancer (37-39). The use of aromatase inhibitors has not yet been established in either the DCIS or prevention settings, but interestingly, one recent study did not find a reduction in breast density with the use of aromatase inhibitors (40). In the next few years, the results of several ongoing random-

ized trials will help inform the use of aromatase inhibitors for DCIS and will hopefully contribute to our current understanding of the association between breast density and antiestrogenic treatment.

Breast density has been shown to be associated with an increased risk for DCIS, as well as invasive breast cancer, supporting the role of breast density in the initiation of new cancers. The inability to confirm this association for DCIS in the present study could be related to both a small sample size (only 30 contralateral DCIS) and the smaller magnitude of this effect for DCIS than for invasive breast cancers (41, 42). A longer follow-up period for this cohort could help further clarify this association.

There were some limitations to our study. There were relatively few invasive breast cancer events during the study period. NSABP B-17, a clinical trial that randomized women to lumpectomy alone or lumpectomy with radiation, reported an annual contralateral invasive event rate of 0.46% (43). This was similar to the observed rate of 0.42% in our cohort, indicating appropriate ascertainment of contralateral events. However, the rate of ipsilateral invasive events in this study was much lower than the 1.0% per year seen in NSABP B-17. This probable underestimation of ipsilateral event rate may have reduced our ability to detect an association between breast density and breast cancer risk.

Data were limited on other variables known to affect breast density, subsequent tumor events after initial DCIS diagnosis, or both. Body mass index was recorded in less than half of the patients and was therefore not included in the analysis due to high missing data rates. Data concerning exogenous hormone use were not available and thus could also not be studied. Furthermore, in the study data set, 87 women in the study did not use tamoxifen, and 8 reported some use of tamoxifen. For the remainder, tamoxifen use was unknown. This high degree of missing tamoxifen data was observed because in most cancer registries, the source of treatment

Table 5. Risk of contralateral invasive breast cancer: effect of time to breast cancer event

Breast density	Time to breast cancer event (mo)			
	>6	>12	>24	>36
	n = 52	n = 51	n = 48	n = 43
BI-RADS 1, 2	1.00	1.00	1.00	1.00
BI-RADS 3, 4 (95% CI)	3.2 (1.7-6.2)	3.1 (1.6-5.9)	2.9 (1.5-5.7)	2.6 (1.3-5.1)

and cancer data for the BCSC, information concerning the use of adjuvant tamoxifen is under-reported because cancer registries obtain data primarily from hospital records and do not routinely review outpatient medical records where most tamoxifen use is most likely to be recorded.

Importantly, margin status, known to be an important determinant of subsequent ipsilateral DCIS events (15), was not routinely captured in cancer registry data. However, neither tamoxifen use nor margin status would be expected to be disproportionately distributed among breast density groups, and thus would not be expected to bias the relationship observed between breast density and subsequent invasive breast cancer events. In contrast, body mass index may be an important missing confounder because reports have shown that increased body mass index is particularly associated with increased postmenopausal breast cancer risk (44-46). However, the negative correlation between breast density and body mass index would be expected to underestimate the magnitude of the association observed between breast density and contralateral breast cancer risk.

An additional limitation of the study is that because ipsilateral DCIS and lobular carcinoma *in situ* recurrence as well as contralateral lobular carcinoma *in situ* disease were not well captured in the data set, women undergoing mastectomy for recurrent *in situ* disease would have remained in the study as being event-free even though it was not possible for them to have a tumor event because their breast was surgically absent. This could have resulted in an underestimation of the number of events and an overestimation of the number of follow-up years, effectively underestimating the magnitude of the effect of breast density on subsequent ipsilateral DCIS events. This effect would be most problematic in the ipsilateral breast, in which fewer DCIS and invasive events were observed because of underreporting to SEER and because of those underreported, some may have had a mastectomy for recurrent invasive cancer or DCIS. Another concern specific to regional registry data is the potential effect of relocation out of registry catchment areas because women would still be included in the analysis as being event-free. This is not expected to bias the results, as there is no obvious association between relocation patterns and breast density after adjusting for age.

In summary, we found that higher breast density was associated with a 3-fold higher risk of contralateral invasive breast cancer compared to women with low density. This effect was significant and persisted over time. We also observed that women with higher breast density were not more likely to develop invasive breast cancer in the ipsilateral breast following treatment for DCIS in the short-term. Longer follow-up is required to determine whether the observed lack of association persists with longer observation, and whether this observation is quadrant-dependent. We conclude that women with BI-RADS 3 or 4 density undergoing treatment for DCIS may be the group that benefits most from adjuvant systemic treatment to reduce contralateral as well as ipsilateral risk for invasive breast cancer.

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