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Pathologic Characteristics of Second Breast Cancers After Breast Conservation for Ductal Carcinoma in Situ

Nils D. Arvold, MD,

Harvard Radiation Oncology Program, Harvard Medical School, Boston, MA

Rinaa S. Punglia, MD, MPH,

Department of Radiation Oncology, Dana-Farber Cancer Institute, Boston, MA

Melissa E. Hughes, MSc,

Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Wei Jiang, MS,

Department of Surgery, Brigham & Women's Hospital, Boston, MA

Stephen B. Edge, MD,

Department of Surgical Oncology, Roswell Park Cancer Institute, and Department of Surgery, University at Buffalo, Buffalo, NY

Sara H. Javid, MD,

Department of Surgery, University of Washington Medical Center, University of Washington School of Medicine, Seattle, WA

Christine Laronga, MD,

Comprehensive Breast Program, Department of Women's Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Joyce C. Niland, PhD,

Department of Information Sciences, City of Hope National Medical Center, Duarte, CA

Richard L. Theriault, DO, MBA,

Department of Breast Medical Oncology, The University of Texas, M. D. Anderson Cancer Center, Houston, TX

Jane C. Weeks, MD, MSc,

Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Yu-Ning Wong, MD, MSCE,

Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA

Sandra J. Lee, ScD, and

Department of Biostatistics, Harvard School of Public Health, and Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA

Michael J. Hassett, MD, MPH

Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Corresponding Author: Nils D. Arvold, MD, Harvard Radiation Oncology Program, Brigham & Women's Hospital, Department of Radiation Oncology, L-2 Level, 75 Francis St., Boston, MA 02115, Phone: 617-278-0330, Fax: 617-732-7347, narvold@partners.org.

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Abstract

Background—The number of women diagnosed with ductal carcinoma in situ (DCIS) is increasing. While many eventually develop second breast cancers (SBC), little is known about the characteristics of SBC. We describe the characteristics of SBC and examine associations between the pathologic features of SBC and index DCIS cases.

Methods—We identified women in the National Comprehensive Cancer Network Outcomes Database diagnosed with DCIS from 1997–2008 and treated with lumpectomy who subsequently developed SBC (including DCIS or invasive disease occurring in the ipsilateral or contralateral breast). Fisher exact and Spearman tests were used to examine associations between the pathologic characteristics of SBC and index DCIS cases.

Results—Among 2,636 women who received lumpectomy for DCIS, 150 (5.7%) experienced an SBC after a median of 55.5 months of follow-up. Of these 150 women, 105 (70.0%) received adjuvant radiotherapy and 50 (33.3%) received tamoxifen for their index DCIS. SBCs were ipsilateral in 54.7% of cases and invasive in 50.7% of cases. Among index DCIS cases, 60.6% were estrogen receptor (ER) positive and 54.0% were high grade, while 77.5% of SBCs were ER-positive and 48.2% were high grade. Grade ($P = .003$) and ER status ($P = .02$) were significantly associated between index DCIS and SBC; tumor size was not ($P = .87$).

Conclusions—After breast conservation for DCIS, SBC in either breast exhibits pathologic characteristics similar to the index DCIS, suggesting that women with DCIS may be at risk for developing subsequent breast cancers of a similar phenotype.

Keywords

DCIS; Breast conserving therapy; Lumpectomy; Radiation; Tamoxifen; Second breast cancer; Contralateral breast cancer; Grade; Estrogen receptor

INTRODUCTION

With the growing adoption of screening mammography, the incidence of ductal carcinoma in situ (DCIS) has increased markedly over the past 25 years.^{1–4} Currently, DCIS accounts for approximately one-quarter of all newly diagnosed breast cancers in the United States^{1–5} and one-half of the malignancies identified by mammography.^{6–9} It is estimated that over 1 million women will be living with a diagnosis of DCIS in the U.S. by the year 2020. The majority of women with DCIS in the U.S. now receive breast-conserving surgery.¹

Women with a history of DCIS are at risk for developing second breast cancer (SBC), including DCIS or invasive disease occurring in the ipsilateral or contralateral breast. SBC may represent re-growth of the initial lesion (i.e., recurrence) or development of a new primary tumor in either breast. Clinical trials and retrospective series have demonstrated that, after lumpectomy for DCIS, the risk of an ipsilateral breast tumor recurrence ranges from 2–20% at 5 years.^{10–14} This risk is higher than that observed in the general population. One study has suggested a clonal relationship may exist between index DCIS and second ipsilateral DCIS events.¹⁵ Women with DCIS also have a 3–6% risk of contralateral breast cancer 5 to 10 years after their initial DCIS diagnosis.^{10,11,16–18} Previous studies suggest that, among women with a history of DCIS, approximately 50% of ipsilateral^{10–12,19–22} and more than half of contralateral breast cancers are invasive.

While several studies have examined risk factors for SBC after lumpectomy for DCIS, there are minimal data on the pathologic characteristics of SBC events, such as size, grade, and hormone receptor status. One prior study examined the pathologic characteristics of SBCs compared with index DCIS,²³ but included only ipsilateral SBC events and was in the

context of a clinical trial, thereby limiting the ability to generalize results.²⁴ Despite the large number of patients at risk, little is known about the pathologic characteristics of SBC events among women who received lumpectomy for DCIS as part of routine care.

Our goals were to characterize the pathologic features of SBC events among women who received lumpectomy for DCIS, and to compare these features to those of the index DCIS. Examination of SBC events in both ipsilateral and contralateral breasts might inform our understanding of the behavior or biology of DCIS.

PATIENTS AND METHODS

Data Source

The National Comprehensive Cancer Network (NCCN) Breast Cancer Outcomes Database was the source of data for this analysis; the Outcomes Database project is a prospective registry of all patients treated at participating NCCN member institutions, and includes chart abstraction and patient survey data. The institutional review boards at each center approved the protocol as well as data collection, transmission, and repository procedures. Chart reviews were conducted to identify SBC events; charts were analyzed by trained abstractors at 4 months, 9 months, and 18 months after index DCIS presentation, and annually thereafter. Rigorous quality-assurance processes were in place to ensure the accuracy of data in the registry, including initial and follow-up data management training; online edit checking during web-based data entry; programmed logic checks against the pooled data repository; routine quality assurance reports to the NCCN centers for rectification by data managers; and annual on-site audits.

Patient Characteristics

The study cohort consisted of women with DCIS who received some or all of their care at one of seven institutions participating in the NCCN Breast Cancer Outcomes Database Project: The Ohio State University Comprehensive Cancer Center; City of Hope Cancer Center; Dana-Farber/Brigham and Women's Cancer Center, Massachusetts General Hospital Cancer Center; Fox Chase Cancer Center; The University of Texas M.D. Anderson Cancer Center; Roswell Park Cancer Institute; and University of Michigan Comprehensive Cancer Center. Patients were eligible for this analysis if they were diagnosed with DCIS between July 1, 1997 and December 31, 2008, had breast conserving surgery, not mastectomy, for their index DCIS, and had no prior history of breast cancer. SBC was defined as subsequent DCIS or invasive cancer in the ipsilateral or contralateral breast. For patients with more than one breast cancer episode after the index DCIS event ($n = 4$), only the first episode was considered in the analysis. No patients experienced simultaneous bilateral SBC. Data collected from patients' medical records for this analysis included socio-demographic characteristics, index DCIS characteristics, therapies administered, and SBC characteristics. Follow-up was based on the date the patient was last seen at an NCCN institution.

Variable Definitions

Comorbidities at presentation to the NCCN institution were classified and scored using either the Charlson Index²⁵ (based on chart review) or the modified version of this index developed by Katz et al²⁶ (based on a patient survey). Patients were considered to have received adjuvant tamoxifen if the drug was started on or after the index DCIS diagnosis, before any SBC, and within 365 days after first presentation to an NCCN center. No patient received an aromatase inhibitor. The same rules were applied when considering receipt of adjuvant radiation therapy.

Estrogen receptor (ER) and progesterone receptor (PR) status were analyzed separately, and were considered to be either positive or negative based on immunohistochemical staining. Grade 1 or well-differentiated tumors were defined as low grade, grade 2 or moderately differentiated tumors were defined as intermediate grade, and grade 3 or poorly differentiated tumors were defined as high grade. If a patient with invasive cancer had both histologic and nuclear grade recorded and they were not the same, the higher value was used. Tumor size was based on the pathologic specimen, measured in centimeters. Surgical margins were considered negative if there was no tumor within 2 mm of ink, and defined as close if between 0 and 2 mm; in patients with more than one excision, margin status was based on the final excision. Type of SBC was categorized as DCIS or invasive; tumors with invasive disease plus DCIS in the same specimen were recorded as invasive. Time to SBC was dichotomized at the median follow-up in months since index DCIS diagnosis in the analytic cohort. Tumor size and margin status for DCIS patients were not collected before July 1, 1999; and collection of hormone receptor status data for DCIS was not collected before April 2003. Variables were coded as 'unknown' when there was not sufficient information about the data element in the medical record.

Statistical Methods

For categorical variables, the Fisher exact test was used to examine associations between pathologic characteristics of index DCIS compared to SBC, as well as associations between adjuvant treatments received and SBC characteristics. For tumor size, the one continuous variable, the Spearman ranked correlation was used to assess associations. All p-values were two-sided. Additionally, we performed analyses according to breast laterality to test if associations between index DCIS and SBC characteristics would be affected.

Patients with ER status information available for both the index DCIS and the SBC (n = 51) contributed to the analyses regarding ER status. Patients with PR status information available for both the index DCIS and the SBC (n = 47) contributed to the analyses regarding PR status. Patients with grade information available for both the index DCIS and the SBC (n = 42) contributed to the analyses regarding grade.

RESULTS

We identified 150 women who were diagnosed with DCIS between July 1, 1997 and December 31, 2008, had breast conserving surgery as definitive local therapy for their DCIS, and eventually developed an SBC. This represented 5.7% of the cohort who had breast conserving surgery for DCIS during this time. Among those who experienced an SBC event, the median follow-up after the index DCIS diagnosis was 55.5 months (range, 11.2 to 139.1 months), and the median age at diagnosis of the index DCIS was 53.5 years (range, 36.0 to 83.5 years). Eighty-two percent of the patients were white, 57% were postmenopausal, and 72% had a comorbidity score of 0 (Table 1).

Histopathologic characteristics of the index DCIS are summarized in Table 2. Median tumor size was 1.0 cm (range, 0.1 to 6.0 cm), and 95% of patients had negative surgical margins. Fifty-four percent of tumors were high grade, 61% were ER positive, and 58% were PR positive. For the index DCIS, 24% of the patients had no adjuvant RT or tamoxifen treatment, 43% had RT without endocrine therapy, 27% had RT and tamoxifen, and 6% had tamoxifen without RT. The median duration of tamoxifen use was 26.9 months (range, 0.2 to 66.8 months); at analysis, 11 patients were still taking tamoxifen, and the reason for stopping tamoxifen among the 39 other patients was not available.

The median time to SBC was 33.2 months (range, 3.8 to 120.3 months; Table 3). SBCs were similarly likely to be invasive (51%; 95% CI, 42–59%) vs. non-invasive (49%; 95% CI, 41–

58%), and were similarly likely to occur in the ipsilateral (55%; 95% CI, 46–63%) vs. contralateral (45%; 95% CI, 37–54%) breast. Of the invasive SBCs, tumor size was under 2 cm in 82% of cases, and 78% were node negative.

Median time to SBC was 36.3 months for ipsilateral cases vs. 28.5 months for contralateral cases. A majority of ipsilateral SBC events were non-invasive (59%), whereas a majority of contralateral SBC events were invasive (62%). SBC were high grade in 48% of cases, ER positive in 77% of cases, and PR positive in 59% of cases (Table 4).

Comparisons between index DCIS and SBC pathologic features are demonstrated in Table 5. Among patients with ER positive index DCIS, 82% had ER positive SBC; among patients with ER negative index DCIS, 53% had ER negative SBC. Seventy-one percent of patients with high grade index DCIS had high grade SBC, 50% of patients with intermediate grade index DCIS had intermediate grade SBC, and no patients with low grade index DCIS had high grade SBC.

ER status of index DCIS was associated with ER status of SBC ($P = .02$; Table 5). This association for ER status was present even after stratification at the median age of diagnosis (53.5 years). Prior studies have shown that approximately 70% of all breast cancers are ER positive. Despite the baseline expectation that most SBCs would be ER positive, we still observed a significantly higher number of hormone-receptor concordant cases than would have been expected if the index DCIS and SBC events were independent ($P = .001$). In addition, tumor grade of the index DCIS was associated with grade of SBC ($P = .003$). There was no significant association between index DCIS and SBC with regard to PR status ($P = .23$) or tumor size (Spearman correlation = 0.02; $P = .87$), and among the non-invasive SBC no significant association with regard to DCIS subtype (comedo vs. non-comedo; $P = .07$).

We performed analyses according to breast laterality to assess whether the pathologic associations varied by side of the SBC (ipsilateral vs. contralateral). Comparing ER status of the index DCIS and SBC, there was a significant association among the 22 ipsilateral events ($P = .002$), but not the 29 contralateral events ($P = .99$). Comparing grade, there was a significant association among the 19 contralateral events ($P = .01$), but not the 23 ipsilateral events ($P = .17$). We considered analyzing effects of RT and tamoxifen on pathologic associations, but elected not to do so due to the small sample sizes in these subgroups.

DISCUSSION

Among women who had lumpectomy for DCIS and subsequently developed SBC, we observed significant associations for tumor grade and ER status between the index DCIS and SBC events. Further, we found that development of ipsilateral SBC was not significantly more likely than contralateral SBC (55% vs. 45%), and that development of invasive SBC was not significantly more likely than non-invasive SBC (49% vs. 51%).

A prior report examining associations between the pathologic characteristics of index DCIS and SBC observed concordant grade in 62% of cases and concordant hormone receptor expression in 63% of cases,²³ but only focused on the correlation between index DCIS and *ipsilateral* SBC events. In addition, a previous study utilizing comparative genomic hybridization (CGH) data has suggested a clonal relationship between index DCIS and second ipsilateral DCIS events.¹⁵ Our data, which included events in both breasts, found similar overall concordance rates for grade and ER status. That pathologic associations between index DCIS and SBC events exist, and that ipsilateral SBC events are more alike than different from contralateral SBC events, raise the intriguing possibility that DCIS characteristics and patient traits both influence the type of breast cancer patients develop.

Specifically, women with DCIS may be more likely to experience SBC with similar pathologic features, in either breast.

Given that the features of SBC are clinically relevant, our data may provide useful information about the potential type of SBC that could develop if a woman were to experience recurrence after lumpectomy for DCIS. Moreover, this information could influence her/his physician's decision-making regarding adjuvant therapy for her index DCIS. For example, if a woman who is treated for an ER positive DCIS were to develop a second breast cancer, it is most likely to be ER positive again. Knowing that a second breast cancer event would be likely to have favorable prognostic features could make some feel more comfortable with a decision to forgo adjuvant tamoxifen or RT for an index DCIS. Since patterns of care data indicate substantial heterogeneity in the management of DCIS, with many patients not receiving adjuvant tamoxifen or RT after lumpectomy,^{27–33} our data could help clinicians and patients predict features of a potential SBC and thus better inform their decisions regarding index DCIS, as they weigh the risks of possible 'overtreatment' of index DCIS with the risks of SBC.

Several prior studies have evaluated risk factors for the development of SBC. Some have suggested that selected women with DCIS treated with lumpectomy without RT have low rates of ipsilateral SBC^{34–37}, particularly those who are older and have small, low grade primary cancers, and negative surgical margins.^{19,38–41} Others have revealed high rates of SBC even among highly-selected patients who received lumpectomy without RT.⁴² Regardless, these and other studies have raised questions about who should vs. should not receive adjuvant therapy (RT or tamoxifen) after lumpectomy for DCIS. Additional research is warranted, and our findings suggest that future clinical trials investigating when to omit adjuvant therapy after lumpectomy for DCIS should include ER status as a stratification factor in addition to grade; this has not been the case in prior trials.^{37,42}

Among women from the NCCN Breast Cancer Outcomes Database who underwent lumpectomy for DCIS, 2.6% developed a contralateral SBC, whereas 3.1% developed an ipsilateral SBC at a median of 4.6 years. Previous studies evaluating recurrence after DCIS have yielded conflicting results. After 8 years of follow-up in the NSABP trial,¹⁶ there was a substantially higher proportion of ipsilateral vs. contralateral SBC as a first event after initial treatment for DCIS (19% ipsilateral vs. 4% contralateral). Another study showed a similar risk of ipsilateral vs. contralateral SBC after initial DCIS, but only assessed invasive SBC events.¹⁸ Lower rates of ipsilateral SBC in our data may reflect improvements in breast imaging that have made it possible to detect smaller foci of DCIS upfront and to better delineate the lumpectomy cavity for RT planning, use of an RT boost which was not utilized in the randomized trials from the 1980s and 1990s evaluating BCT for DCIS,^{10–12,16} or possibly higher rates of guideline-concordant care delivered at NCCN centers. Other modern series have also demonstrated very low rates of ipsilateral SBC after BCT for DCIS with similar follow-up.⁴³ Clearly, the ratio of ipsilateral to contralateral SBC will be influenced by the use of lumpectomy, RT, tamoxifen, and contralateral prophylactic mastectomy at time of index DCIS.

A proportion of patients had missing pathologic characteristics. Causes of missing data include that tumor size and margin status were not collected prior to July 1999, and hormone receptor status was not collected prior to April 2003. If the pattern of missing data is not random, this could lead to over- or underestimates of the strength of association between index DCIS and SBC pathologic features. However we do not have evidence that missing pathologic data was related to characteristics of the patients, and thus the observed associations should be unaffected. In addition, overall associations we observed for grade and ER status between index DCIS and SBC were modified when analyzed by breast

laterality, but given the small sample sizes of the subgroups, we have refrained from drawing general conclusions from those results. Also, with our median follow-up being 55.5 months, it is possible that the SBC events we observed may have different characteristics compared with potential later SBC events, and thus longer follow-up is required to confirm our findings. Finally, patients receiving management at an NCCN institution for index DCIS may not have returned to the same NCCN institution for diagnosis or management of their SBC, which could lead to under-reporting of SBC event rates. Nonetheless, we have no reason to believe that DCIS characteristics would lead to differential patient follow-up at these institutions, so the pathologic associations we observed should remain valid even if there exists under-reporting of the true incidence of SBC.

In conclusion, we have described the clinical and pathologic characteristics of SBC after breast conservation for DCIS. SBC occurred with almost equal frequency in the ipsilateral and contralateral breast, and the grade and ER status of the index DCIS and SBC events were significantly associated. These results suggest that women with DCIS may be at risk to develop second breast cancers of a similar phenotype, and could have the potential to inform clinical decision-making at the time of index DCIS. Further work is required to confirm our findings and define additional characteristics that may help guide optimal treatment recommendations for DCIS.

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Table 1

Baseline clinical characteristics of women who experienced an eventual second breast cancer (N = 150).

Clinical Characteristic	No. (%)
Age at diagnosis, years	7 (4.7)
< 40	50 (33.3)
40 to < 50	45 (30.0)
50 to < 60	28 (18.7)
60 to < 70	20 (13.3)
70	53.5 (36.0–83.5)
Median age (range)	
Race / ethnicity	123 (82.0)
White/non-Hispanic	13 (8.7)
African American/non-Hispanic	7 (4.7)
Asian/non-Hispanic	6 (4.0)
Hispanic	1 (0.7)
Other	
Menopausal status	65 (43.3)
Premenopausal	85 (56.7)
Postmenopausal	
Body mass index	9 (6.0)
< 20	44 (29.3)
20 to < 25	34 (22.7)
25 to < 30	38 (25.3)
30	25 (16.7)
Unknown	
Presentation	127 (84.7)
Screening mammography	20 (13.3)
Symptomatic	3 (2.0)
Unknown	
Year of diagnosis	45 (30.0)
1997 – 2000	77 (51.3)
2001 – 2005	28 (18.7)
2005 – 2008	
Comorbidity score	108 (72.0)
Comorbidity 0	42 (28.0)
Comorbidity 1	

Table 2

Histopathologic characteristics of index DCIS among women who experienced an eventual second breast cancer (N = 150).

Histopathologic Factor	No. (%)
Tumor size, ^a centimeters	
< 1	42 (28.0)
1 to < 2	24 (16.0)
2 to < 3	13 (8.7)
3	12 (8.0)
Unknown	59 (39.3)
Median size in centimeters (range)	1.0 (0.1–6.0)
Margin distance ^a from tumor	
Involved	6 (4.0)
Close (< 2 mm)	1 (0.7)
Negative (≥ 2 mm)	132 (88.0)
Unknown	11 (7.3)
Grade	
High	27 (18.0)
Intermediate	16 (10.7)
Low	7 (4.7)
Unknown	100 (66.7)
ER ^b	
Positive	40 (26.7)
Negative	26 (17.3)
Unknown	84 (56.0)
PR ^b	
Positive	36 (24.0)
Negative	26 (17.3)
Unknown	88 (58.7)
Subtype	
Comedo	56 (37.3)
Non-comedo	93 (62.0)
Unknown	1 (0.7)
Multicentric	
Yes	4 (2.7)
No	144 (96.0)
Unknown	2 (1.3)

Abbreviations: DCIS, ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor; NCCN, National Comprehensive Cancer Network.

^aTumor size and margin status were not collected in the NCCN database before July 1, 1999.

^bHormone receptor status was not collected in the NCCN database before April 1, 2003.

Table 3Clinical characteristics of second breast cancers (N = 150).^a

Characteristic	No. (%)		
Median patient follow-up in months since index DCIS diagnosis (range)	55.5 (11.2 – 139.1)		
Median time to SBC, months	33.2 (3.8 – 120.3)		
Ipsilateral (range)	36.3 (7.9 – 120.3)		
Contralateral (range)	28.5 (3.8 – 101.5)		
Presentation of SBC			
Screening mammography	93 (62.0)		
Symptomatic	22 (14.7)		
Unknown	35 (23.3)		
Laterality of SBC			
Ipsilateral	82 (54.7)		
Contralateral	68 (45.3)		
Type of SBC			
Ipsilateral			
DCIS	48 (58.5)		
Invasive	34 (41.5)		
Contralateral			
DCIS	26 (38.2)		
Invasive	42 (61.8)		
SBC according to index DCIS management		<u>No. Ipsilateral</u>	<u>No. Contralateral</u>
Lumpectomy alone	36 (24.0)	26	10
Lumpectomy + RT	64 (42.7)	36	28
Lumpectomy + RT + tamoxifen	41 (27.3)	17	24
Lumpectomy + tamoxifen	9 (6.0)	3	6

Abbreviations: DCIS, ductal carcinoma in situ; SBC, second breast cancer; RT, radiotherapy.

^a All values are No. (%) except where indicated otherwise.

Table 4

Histopathologic characteristics of second breast cancers (N = 150).

Histopathologic factor	DCIS-only (n = 74)	Invasive (n = 76)
	No. (%)	No. (%)
Tumor size, ^a centimeters		
< 1	25 (33.8)	25 (32.9)
1 to < 2	6 (8.1)	31 (40.8)
2 to < 3	2 (2.7)	8 (10.5)
3	4 (5.4)	4 (5.3)
Unknown	37 (50.0)	8 (10.5)
Median size in centimeters (range)	0.7 (0.1–6.5)	1.1 (0.1–14.0)
Grade		
High	15 (20.3)	26 (34.2)
Intermediate	3 (4.1)	29 (38.1)
Low	2 (2.7)	10 (13.2)
Unknown	54 (73.0)	11 (14.5)
ER ^b		
Positive	33 (44.6)	53 (69.7)
Negative	7 (9.5)	18 (23.7)
Unknown	34 (45.9)	5 (6.6)
PR ^b		
Positive	26 (35.1)	39 (51.3)
Negative	14 (18.9)	32 (42.1)
Unknown	34 (45.9)	5 (6.6)
HER2/neu ^c		
Over-expressed	–	15 (19.7)
Not over-expressed	–	55 (72.4)
Unknown	–	6 (7.9)
Subtype		
Comedo	25 (33.8)	–
Non-comedo	38 (51.4)	–
Unknown	11 (14.9)	–
Histologic type		
Ductal	–	61 (80.3)
Lobular	–	9 (11.8)
Ductal and lobular	–	3 (3.9)
Tubular/colloid/papillary	–	3 (3.9)

Histopathologic factor	DCIS-only (n = 74)	Invasive (n = 76)
	No. (%)	No. (%)
EIC		
Positive	–	15 (19.7)
Negative	–	61 (80.3)
LVI		
Positive	–	15 (19.7)
Negative	–	53 (69.7)
Unknown	–	8 (10.5)
Lymph nodes involved (no.)		
cN0	–	7 (9.2)
0	–	49 (64.5)
1–3	–	9 (11.8)
4	–	7 (9.2)
Unknown	–	4 (5.3)

Abbreviations: DCIS, ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; EIC, extensive intraductal component; LVI, lymphovascular invasion; cN0, clinically node-negative; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; NCCN, National Comprehensive Cancer Network.

^aTumor size and margin status were not collected in the NCCN database before July 1, 1999.

^bHormone receptor status was not collected in the NCCN database before April 1, 2003.

^cResults according to IHC or FISH; for cases with discrepant findings between IHC and FISH, status was determined by FISH results.

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Table 5
Comparison between index DCIS and second breast cancer marker expression and tumor grade.

Index DCIS	Second Breast Cancer (No. of Cases)		No. Identical Cases ^a / No. Eligible	<i>p</i> ^b
	ER Positive	ER Negative		
ER				
Positive	28	6	37 / 51	.02
Negative	8	9	(72.5%)	
PR				
Positive	20	10	29 / 47	.23
Negative	8	9	(61.7%)	
Grade				
High	17	6	27 / 42	.003
Intermediate	6	7	(64.3%)	
Low	0	1	3	

Abbreviations: DCIS, ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor.

^aIndicates number of cases with the same hormone receptor status or grade between index DCIS and second breast cancer.

^bAssociation between histopathologic factor of the index DCIS and that of the second breast cancer assessed by Fisher exact test.