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Continued observation of the natural history of low-grade ductal carcinoma in situ reaffirms proclivity for local recurrence even after more than 30 years of follow up

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Abstract

Opportunities to study the natural history of ductal carcinoma in situ are rare. A few studies of incompletely excised lesions in the premammographic era, retrospectively recognized as ductal carcinoma in situ, have demonstrated a proclivity for local recurrence in the original site. The authors report a follow-up study of 45 women with low grade ductal carcinoma in situ treated by biopsy only, recognized retrospectively during a larger review of surgical pathology diagnoses and original histologic slides for 26,539 consecutive breast biopsies performed at Vanderbilt, Baptist, and St. Thomas Hospitals in Nashville, TN from 1950–1989. Long-term follow-up was previously reported on 28 of these women. Sixteen women (36%) developed invasive breast carcinoma, all in the same breast and quadrant as their incident ductal carcinoma in situ. Eleven invasive breast carcinomas were diagnosed within 10 years of the ductal carcinoma in situ biopsy. Subsequent cases were diagnosed at 12, 23, 25, 29 and 42 years. Seven women, including one who developed invasive breast cancer 29 years after her ductal carcinoma in situ biopsy, developed distant metastasis, resulting in death 1 to 7 years post diagnosis of invasive breast carcinoma. The natural history of low-grade ductal carcinoma in situ may extend more than four decades, with invasive breast cancer developing at the same site as the index lesion. This protracted natural history differs markedly from that of patients with high grade ductal carcinoma in situ or any completely delimited ductal carcinoma in situ excised to negative margins. This study reaffirms the importance of complete margin evaluation in women treated with breast conservation for ductal

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carcinoma in situ as well as balancing recurrence risk with possible treatment-related morbidity for older women.

INTRODUCTION

For more than twenty years an overwhelming body of evidence has demonstrated ductal carcinoma in situ diagnosed by current criteria to be a surgical disease, mandating excision to negative margins. Thus opportunities to study the natural history of ductal carcinoma in situ are very rare. Before 1980, lesions diagnosed as ductal carcinoma in situ typically reached clinical attention by the presence of a palpable breast mass or nipple discharge, were usually high grade and may have even been associated with foci of invasive carcinoma. In this article, we report the follow-up on 45 women with small, low grade, ductal carcinoma in situ retrospectively diagnosed utilizing current criteria¹⁻³, who were treated by biopsy only at the time of their original evaluation. Twenty eight of these women were reported previously^{2,4-6}. These patients were recognized during a larger review of surgical pathology diagnoses and original tissue slides for 26,539 consecutive biopsies performed at Vanderbilt, Baptist, and St. Thomas Hospitals in Nashville, TN, from 1950 through 1989^{2,4-6}. In the 1950s and during most of the 1960s, when many of these biopsies were originally examined, small, lower grade ductal carcinoma in situ was not diagnosed; therefore, these women were treated by biopsy only after a benign interpretation.

MATERIALS AND METHODS

Retrospective Cohort Study

These women were recognized retrospectively during a larger review of surgical pathology diagnoses and original histologic slides for 26,539 consecutive breast biopsies performed at Vanderbilt, Baptist, and St. Thomas Hospitals from 1950 through 1989, as described previously². In brief, the initial histologic review of all available slides from the first 11,760 women was carried out by one of the authors (DLP), who reviewed all biopsies with diagnoses other than malignancy or abscess for the presence of epithelial proliferative disease, atypical hyperplasia and carcinoma in situ. All diagnoses of atypical hyperplasia and carcinoma in situ were reviewed by Dr. Lowell W. Rogers⁵ (deceased) and any discrepancies resolved over the double headed microscope. The subsequent 14,779 biopsies were reviewed by Page and colleagues⁴⁻⁶, with the all cases reviewed by at least 2 pathologists and all diagnoses of atypical hyperplasia and carcinoma in situ independently reviewed by a third pathologist (usually DLP unless he was the primary reviewer of the case). Any discrepancies were resolved at a multi-headed microscope by 3 breast pathologists (MES, JFS, DLP). For the purpose of this study, original slides and reports from all 45 women retrospectively diagnosed with ductal carcinoma in situ and all available slides and reports from subsequent carcinomas were re-reviewed by one of the current authors (MES). Approximately 50% of the index biopsies were entirely submitted where as the remainder were representatively sampled. According to the pathology reports, the representative sampling included all fibrous tissue and grossly evident masses. Since more than two thirds of the women in this study were biopsied before the advent of mammographic screening, we have not discussed the very limited mammographic data

available. Information on hormonal status at the time of the index biopsy with ductal carcinoma in situ and family history of breast cancer were self-reported by patients at the time of follow-up. A protocol to obtain informed consent and follow-up information was approved by the Vanderbilt University Institutional Review Board (VU IRB# 2548). Informed consent to participate in the Nashville Breast Cohort² was obtained from all patients and the institutional review boards of the participating hospitals in the approved study protocol. Patients eligible for follow-up were residents of Tennessee or Kentucky at the time of entry biopsy and without a previous diagnosis of breast cancer. Follow-up was obtained by contacting patients or relatives if they were deceased. Follow-up was continued until the time of death or last available information from the patient or next of kin.

Histologic definitions

In the current study ductal carcinoma in situ is defined as a monotonous, cohesive cell proliferation fulfilling at least the following criteria: 1) complete involvement of at least 2 adjacent spaces, 2) at least one of the spaces is a true duct and 3) the lesion measures at least 2.0mm in greatest dimension¹⁻³. The histologic patterns, including cribriform, micropapillary, solid or a mixture were recorded. All examples of ductal carcinoma in situ were graded⁷. Atypical ductal hyperplasia is defined as a lesion with a pure cell population, but limited in size and incompletely occupying the involved space(s). This definition has been extensively validated epidemiologically⁸⁻¹¹. Atypical ductal hyperplasia usually affects only lobular units. Invasive lobular carcinoma, classic type, was diagnosed if the tumor showed a >90% single cell infiltrative pattern and was of low cytological grade throughout^{12,13}. Invasive mammary carcinoma, no special type, was diagnosed when tumors lacked features diagnostic of special types such as pure tubular or classic invasive lobular carcinomas^{12,13}. No special type carcinomas with special type features were diagnosed when features of special type carcinomas were present in 10–90% of the invasive carcinoma¹⁴.

Statistical Methods

The cumulative incidence of invasive breast cancer and breast cancer mortality are estimated with Kaplan-Meier morbidity and mortality curves. Ninety-five percent confidence intervals for these estimates were derived using Greenwood's formula¹⁵.

RESULTS

In this article, we report a follow-up study of 45 women with low-grade ductal carcinoma in situ who were treated by biopsy only. Extended follow-up data are provided on an original cohort of 28 women plus 17 more recently identified patients. All women who reported having undergone menopause had done so starting at 50 or later. Twenty-one women (46%) were premenopausal at the time their biopsy containing the index ductal carcinoma in situ (Table 1). The remaining 53% were post menopausal. This difference was not statistically significant. Among women who developed subsequent invasive cancer, there were equal numbers of premenopausal (n = 8) and postmenopausal (n = 8) women. In comparison, 41% (12/29) of the women who did not subsequently develop invasive carcinoma were premenopausal.. Although suggesting a trend toward a greater number of premenopausal

women developing subsequent invasive carcinoma, this relationship did/not reach statistical significance. Six women had a family history of breast cancer, two of whom were among the women developing subsequent invasive carcinoma.

The morbidity graph (Fig. 1, left panel) shows the cumulative incidence of invasive breast carcinoma among the 45 women, illustrating that any woman with low grade ductal carcinoma in situ who has not received definitive treatment remains at risk for a prolonged period after this diagnosis. The risk of invasive carcinoma was greatest in the first 15 years and declined slightly as follow-up was extended. Sixteen of 45 women (36%) developed invasive breast carcinoma, all in the same quadrant and in the same breast from which the original biopsy with ductal carcinoma in situ was excised (Table 1). These carcinomas were diagnosed over a total of 47 years of follow-up. Among patients who developed invasive breast carcinoma the average time to invasive breast carcinoma diagnosis was 13 years (range 3–42 years). The median follow-up was 26 years (range 1 to 47 years) for women who did not develop carcinoma (Table 2). Eleven women were diagnosed with IBCs within 10 years of the ductal carcinoma in situ biopsy. Subsequent cases were diagnosed at 12, 23, 25, 29 and 42 years after their original ductal carcinoma in situ biopsy. The relative risk of subsequent invasive breast cancer was not significantly affected by the patient's menopausal status at the time of their index biopsy.

The year of last follow-up was 2009. The first of the five women who had invasive carcinomas identified since the previously published follow-up in 2005⁶, was diagnosed 3 years after her original ductal carcinoma in situ biopsy. She was treated by mastectomy for an intermediate grade, no special type carcinoma with negative lymph nodes. The patient died 15 years later of other causes (Table 1). The second patient developed invasive breast carcinoma 5 years after her original ductal carcinoma in situ biopsy. Her mastectomy specimen contained a pure invasive lobular carcinoma with positive lymph nodes. The patient died 2 years later of metastatic breast cancer. The third woman developed invasive breast carcinoma 8 years after her initial biopsy, and underwent mastectomy for an intermediate grade, no special type carcinoma with lobular features with positive axillary lymph nodes. The patient died 2 years later of metastatic breast cancer. The fourth patient developed invasive breast carcinoma of unknown type and grade with positive lymph nodes 12 years after her original ductal carcinoma in situ biopsy. She died of other causes 15 years later without evidence of local or distant recurrence. The last woman was diagnosed with invasive breast carcinoma of unknown type, grade and lymph node status 25 years after her ductal carcinoma in situ diagnosis. She died of other causes less than 1 year following diagnosis.

Original slides for histologic typing of ductal carcinoma in situ were available for all 45 women. Cribriform was the most common pattern and was present in 15 cases (Table 3). Other patterns observed in descending order were solid (11 cases), mixed cribriform-solid-micropapillary (10), pure micropapillary (5 cases), pure apocrine (2 cases) and encysted non-invasive papillary carcinoma. There was no relationship between the histologic pattern of the ductal carcinoma in situ and the subsequent development of invasive carcinoma.

Three additional women developed a second ductal carcinoma in situ (Table 1). One was diagnosed with recurrent ductal carcinoma in situ in the same quadrant of the same breast 3 years after her index ductal carcinoma in situ. Her index ductal carcinoma in situ was an encysted non-invasive papillary carcinoma with apocrine cytology. Her recurrence was also low-grade with pure apocrine cytology. She underwent a unilateral mastectomy and died of heart failure 5 years after her second diagnosis of ductal carcinoma in situ without evidence of recurrent carcinoma. The second woman was diagnosed with a subsequent intermediate grade ductal carcinoma in situ of unknown type in the same breast 23 years after her index ductal carcinoma in situ. She was treated by bilateral mastectomy. At the time of last follow-up 17 years later, she was alive and well. The remaining woman developed a second ductal carcinoma in situ in the same quadrant of the same breast 27 years after her initial biopsy with ductal carcinoma in situ. At the time of last follow-up she was alive and well 1 year after undergoing a unilateral mastectomy without evidence of disease.

At the time of last follow up, 30 of the 45 women were deceased. Seven died of metastatic breast cancer and 23 died of causes unrelated to their breast cancer diagnoses (Tables 1 and 2 and Figure 1, right panel). With respect to the 16 women with subsequent invasive breast carcinoma, 13 were deceased at the time of last follow-up. The women with metastatic breast cancer died an average of 3 years after their invasive breast carcinoma diagnosis (range, 1–7 years). Six died within 5 years of diagnosis, and 1 died within 7 years of diagnosis. Of the remaining 9 women, all died from other causes at an average of 13 years (range 2–19 years) after diagnosis and at an average of 24 years (range 12–39 yrs) after the original biopsy with DCIS.

DISCUSSION

This cohort of women with low grade ductal carcinoma in situ was retrospectively identified from a larger, completely characterized cohort of women with benign breast disease. When these lesions were originally examined, low grade ductal carcinoma in situ was not diagnosed, thus these women were treated by biopsy only. Sixteen of 45 women (36%) developed invasive breast carcinoma, all in the same quadrant and in the same breast from which the original biopsy with ductal carcinoma in situ was taken. These carcinomas were diagnosed over a total of 47 years of follow-up. The methodology and findings of our study are similar to those of Betsil et al.,¹⁶ who examined all available histologic slides from 8609 benign biopsies performed from 1940 through 1950 at Memorial Sloan Kettering Cancer Center in New York. Those authors identified 25 women with previously undiagnosed low-grade ductal carcinoma in situ who were treated by biopsy only. Among 10 women with long-term follow-up, which averaged 22 years, 7 women developed invasive breast carcinoma at an average of 10 years after their initial biopsy (range, 7–30 years), all in the same breast as the ductal carcinoma in situ. Using the same group of patients, Rosen et al.¹⁷ subsequently conducted a retrospective review of more than 8000 biopsies originally reported as benign and identified a total of 30 patients with micropapillary ductal carcinoma in situ. Long-term follow up was available on 15 of these women. Eight women (53%) developed invasive cancer in the same breast as the index ductal carcinoma in situ with an average follow up of 9 years.

More recently, a case-control study of 1877 originally diagnosed benign biopsies in the Nurses' Health Study¹⁸ identified 13 biopsies containing ductal carcinoma in situ which were not recognized on initial review, 6 of which developed subsequent invasive breast cancer. Among the 13 ductal carcinoma in situ, 4 were low-grade, 6 intermediate grade and 3 were high-grade lesions. Invasive breast cancer developed in 2 patients with low grade ductal carcinoma in situ, 2 patients with intermediate grade ductal carcinoma in situ and 2 patients with high-grade ductal carcinoma in situ.

These three studies likely represent the only information that ever will be available on the natural history of ductal carcinoma in situ. These results are highly relevant to current circumstances, because detection of lesser examples of ductal carcinoma in situ has increased dramatically with the practice of high quality routine mammographic screening^{19,20}, with ductal carcinoma in situ now representing approximately 20% of screen detected breast cancers. Evidence now overwhelmingly demonstrates that ductal carcinoma in situ is a spectrum of disease ranging from extensive, high-grade lesions, most likely requiring mastectomy for eradication, to small, low-grade lesions, which can be cured effectively by excision alone²¹. The existing natural history studies summarized above^{4-6,16-18} and reported herein indicate that high grade ductal carcinoma in situ left untreated will evolve to an invasive carcinoma in less than 5 years in greater than 50% of patients. Although untreated, low-grade ductal carcinoma in situ has a similar capacity to evolve into invasive carcinoma in 35-50% of patients, the time course is significantly protracted and may span more than 40 years. Given these critical differences, it is reasonable to expect that a few women with inadequately treated, lower grade lesions also would exhibit local recurrence and distant spread as their follow-up interval is extended^{22,23}. However, because of the important therapeutic implications, it will be important to document the degree to which these events actually represent a threat to life or even occur within the lifetime of the woman.

While the morbidity graph (Fig. 1, left panel) illustrates that any woman with low grade ductal carcinoma in situ who has not received definitive treatment remains at risk for a prolonged period after this diagnosis, it also suggests that these women may have stable ductal carcinoma in situ for decades. The increased detection of small, low grade ductal carcinoma in situ with widespread use of mammographic screening programs mandates constant re-evaluation of who we should be treating, how much and when? There is now good evidence that planned local excision with complete histologic examination and assurance of negative margins results in efficient and effective cure in most instances^{21,24-26}. This fact emphasizes the need for consideration of less aggressive therapy (local excision only) when these lesions are limited in size, and the recurrence interval well may be beyond a reasonable life expectancy for the patient.

Thus approach to treatment must be based on a combination of the natural history and the extent of mammary involvement. Precise case definitions are of critical importance to these considerations. The findings of Betsil et al. and of the current series^{4-6,16}, supplemented by later studies in patients with ductal carcinoma in situ who underwent planned excision^{21,24,25,27} provide a rational basis for prognostication and therapeutic recommendations for ductal carcinoma in situ. Fundamental to these studies was the careful

definition of each lesion, primarily by size, grade and histologic features. We now know that margin status is the critical delimiting element and the most important determinant of local recurrence²⁶. In fact, pathologic review of a subset of the patients that comprised the two largest cooperative trials for treatment of ductal carcinoma in situ, the National Surgical Adjuvant Breast and Bowel Project B-17 and the European Organization for Research and Treatment of Cancer (EORTC), demonstrated that most local failures were in women with high-grade ductal carcinoma in situ and with positive or unknown margin status^{22,23} and that treatment with radiation therapy appeared to reduce but did not eliminate the risk^{22,23}. In addition, patients with high-grade ductal carcinoma in situ have a high risk of developing life threatening distant metastasis after invasive local recurrence^{22,28}. Most importantly, radiation therapy had no effect on the most important outcome measure, deaths due to breast cancer in both studies^{22,23}. The long-term follow up of both studies continue to report no survival advantage from adjuvant radiotherapy²⁸⁻³⁰. A report of four randomized clinical trials of radiotherapy in ductal carcinoma in situ by the Early Breast Cancer Trialists' Collaborative Group in the UK, similarly found no significant effect on breast cancer mortality associated with use of radiation therapy³¹. Most recently, Lee et al. found no statistically significant difference in local recurrence rates between women receiving or not receiving adjuvant radiation therapy in combination with breast conservation for ductal carcinoma in situ at St. Luke's-Roosevelt Hospital Center, NY between 1990 and 2009³². In fact, in the NSABP-17 and B-24 trials, the radiated group suffered a slight increase in mortality after 15 years follow-up compared with the patients who received no radiation therapy^{29,30}. Furthermore, additional long-term follow up on the women in the Silverstein study^{26,33} has now shown a greater risk of recurrences in the radiation arm of that cohort and that these recurrences are more commonly invasive³³. Of further concern, is the fact that the median time to local recurrence for irradiated patients was more than twice as long when compared with non-irradiated patients. This strongly suggests that radiation therapy delayed rather than prevented local recurrence. These results re-emphasize the criticality of complete margin evaluation and argue strongly against the use of radiation therapy for women with low-grade ductal carcinoma in situ treated by breast conservation.

Epidemiologically speaking, small, low-grade ductal carcinoma in situ is the pivotal lesion in understanding the borderline between malignancy and non-malignancy in the female breast. Low grade ductal carcinoma in situ, is a non-obligate precursor and if left without further treatment, predicts for regional risk and will eventuate in invasive carcinoma in the same site in the same breast in 30% of patients within 15 years. Over time, any residual DCIS either regresses, remains dormant after biopsy alone, expands extensively as in situ disease, or progresses to invasive carcinoma with metastatic and death-dealing capacity. These invasive carcinomas, with few exceptions, arise in the same quadrant of the same breast as the original biopsy. The current series and the series reported by Betsil et al.¹⁶ provide important biologic validation of the diagnostic criteria currently used to delimit small low ductal carcinoma in situ lesions¹⁻³. They indicate a striking dividing point biologically between low-grade ductal carcinoma in situ lesions and the cytologically similar but lesser lesions of atypical ductal hyperplasia^{2,34}. Atypical ductal hyperplasia indicates a small, generalized, increased risk of breast carcinoma in both breasts that is approximately

one half that of low-grade ductal carcinoma in situ lesions, and these cancers may occur at any site rather than in the locality of the incident ductal carcinoma in situ⁸⁻¹¹.

However, practically speaking, an excisional biopsy of the mammographic abnormality is an appropriate initial therapy for patients with either diagnosis and may be curative. Therefore, low-grade lesions in core needle biopsies, by nature a sampling, should be conservatively diagnosed. After a diagnosis of DCIS of very limited size on core biopsy, we well recognize the phenomenon of women opting for bilateral mastectomy with the subsequent finding of no residual lesion in the index breast or receiving adjuvant radiation therapy despite a negative excisional biopsy. Knowing this, it is our current practice as well as others³⁵ to diagnose such borderline lesions as well-developed atypical ductal hyperplasia, with a comment that the lesion will be best characterized at the time of formal excision. A recent study by VandenBussche et al. provides sound evidence to justify this approach³⁵. They found among 74 patients diagnosed with well-developed “marked” atypical ductal hyperplasia at their institution on core needle biopsy followed by excisional biopsy, 27% had benign findings or atypical lobular hyperplasia, 24% had additional atypical ductal hyperplasia, 45% had ductal carcinoma in situ and 4% had invasive carcinoma associated with ductal carcinoma in situ. The patients without subsequent ductal carcinoma in situ or invasive cancer, did not undergo further surgery, post-operative radiation or experience local recurrence of carcinoma during the 54 month average follow up period. Among patients with ductal carcinoma and invasive cancer upon excision, less than 20% required mastectomy. These findings suggest no woman was harmed from this conservative approach, and they benefitted from avoidance of complications related to more extensive surgery, axillary node biopsy or dissection, and radiation therapy.

Age may also play a role in therapeutic decision making. Kong et al. report long-term follow-up on women in the Ontario Cohort Study with ductal carcinoma in situ treated by breast conservation and radiation therapy³⁶. When recurrence risk was stratified by age, the 10-year cumulative local recurrence rate for women less than 45 years of age was a striking 27%, while it was 14% for women 45 to 50 years and 11% for women greater than 50 years ($p < 0.0001$). In multivariate analyses, positive or unreported margin status and additionally high nuclear grade in the index ductal carcinoma in situ were associated with a greater risk of subsequent invasive carcinoma. The Kong paper, however, does not unfortunately permit further stratification of risk, sharing many of the issues of NSABP-17 trial design²³. Specifically, the effect of tumor size and resection margin width could not be examined due to lack of standardized reporting. Hughes et al. in their series with precise case definition²¹, also report data suggesting that women < 45 years of age are at greater risk for local recurrence than older women and that those at greatest risk have high grade ductal carcinoma in situ. Our current study is consistent with these findings showing a trend toward higher recurrence rates in younger women.

In summary, the current series and the series reported by Betsil et al.¹⁶ provide validation of the criteria currently used to delimit small, low-grade ductal carcinoma in situ lesions. In conjunction with subsequent studies of women with ductal carcinoma in situ who underwent planned excision, these findings provide strong evidence that a limited and completely delimited DCIS can be cured successfully by excision alone. Thus, approach to treatment

must be based on a combination of the natural history and the extent of mammary involvement, emphasizing the need for consideration of less aggressive therapy when these lesions are limited in size, and the recurrence interval may well be beyond a reasonable life expectancy for the patient.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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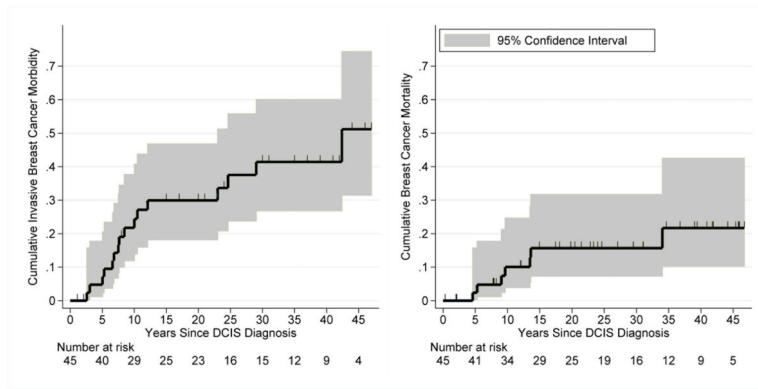


Figure 1. Cumulative breast cancer morbidity and mortality curves among the 45 women with low-grade DCIS. Any woman with non-comedo DCIS who has not received definitive treatment remains at risk for a prolonged period after this diagnosis.

Table 1

Women with DCIS who developed invasive breast cancer or a second DCIS

Patient #	Age at DX DCIS	Histotype index DCIS	Time from DCIS diagnosis to IBC diagnosis is (yrs)	Tumor type, grade, LN status	Treatment type	Status (years since IBC and last contact or death), Cause of death	Reference if previously reported
1	60	MIX	3	NST, Intermediate, negative	Mastectomy	DOC (15)	
2	33	MP	3	Unknown, unknown, unknown	Mastectomy	DOD (2), MBC	4-6
3	53	S	5	Pure ILC, Low, positive	Mastectomy	DOD (2), MBC	
4	45	S	5	NST, Intermediate, unknown	Mastectomy	DOD (4), MBC	4-6
5	38	MIX	7	NST, Low, negative	Mastectomy	DOD (7), MBC	4-6
6	47	C	7	NST, High, positive	Mastectomy	A&W (3)	4-6
7	46	C	8	NST, Low, negative	Mastectomy	A&W (12)	4-6
8	55	MIX	8	NST, Low, positive	Mastectomy	A&W (22)	4-6
9	76	MP	8	NST with lobular features, IG, positive	Mastectomy	DOD (2), MBC	
10	44	C	10	Unknown, unknown, positive	Mastectomy	DOD (3), MBC	4-6
11	74	S	10	NST, Low, positive	Mastectomy	DOC (2)	4-6
12	64	MIX	12	Unknown, unknown, positive	Mastectomy	DOC (15)	
13	57	C	23	NST with tubular features, Low, negative	Mastectomy	DOC (16)	4-6
14	62	C	25	Unknown, unknown, unknown	Mastectomy	DOC (<1)	
15	42	MIX	29	Unknown, unknown, positive	Mastectomy	DOD (5), MBC	4-6
16	37	MIX	42	NST with tubular features, Low, no lymph nodes sampled	Mastectomy	DOC (3)	4-6

Patient #	Age at DX DCIS	Histotype index DCIS	Time from original DCIS diagnosis to second DCIS diagnosis is (yrs)	Grade, Histotype second DCIS	Treatment type	Status (years since 2nd DCIS and last contact or death)	Reference if previously reported
1	75	ENIPC, A	3	Low, apocrine	Mastectomy	DOC (5)	4-6
2	69	A	23	Intermediate, unknown	Bilateral mastectomy	A&W (16)	4-6
3	61	MIX	28	High, unknown	Mastectomy	A&W (1)	

Status at last contact: A&W = alive and well, AWD = alive with disease, DOD = dead of disease, DOC = dead of other causes; MBC = metastatic breast cancer

DCIS histotype: cribriform = C; micropapillary = MP; solid = S; MIX = variable combinations of cribriform, solid and micropapillary; ENIPC = encysted non-invasive papillary carcinoma

Table 2

Women with DCIS who did not developed subsequent carcinomas

Patient #	Age at DX DCIS	Histotype index DCIS	Status (years since DCIS and last contact or death), Cause of death	Reference if previously reported
1	77	C	DOC (1)	
2	80	C	DOC (2)	
3	73	C	DOC (2)	4-6
4	78	MP	DOC (8)	
5	72	S	DOC (8)	4-6
6	85	MIX	DOC (8)	
7	60	C	DOC (12)	
8	72	C	DOC (15)	
9	44	C	DOC (17)	4-6
10	49	MP	A&W (20)	4-6
11	45	S	A&W (21)	4-6
12	59	S	A&W (23)	4-6
13	67	A	DOC (24)	4-6
14	55	MIX	DOC (30)	
15	57	C	DOC (31)	4-6
16	50	ECNIP, MP	DOC (31)	4-6
17	47	MIX	A&W (35)	4-6
18	53	C	DOC (37)	4-6
19	47	C	A&W (39)	
20	34	C	A&W (41)	4-6
21	52	S	A&W (42)	
22	43	S	DOC (42)	
23	35	MP	A&W (46)	4-6
24	46	S	A&W (46)	4-6
25	47	S	DOC (46)	4-6
26	38	S	A&W (47)	

DCIS histotype: cribriform = C; micropapillary = MP; solid = S; A = apocrine; MIX = variable combinations of cribriform, solid and micropapillary; ENIPC = encysted non-invasive papillary carcinoma

Table 3

Index DCIS histotype with respect to development of carcinoma

DCIS histotype	All patients	Patients with subsequent IBC	Patients with second DCIS
Cribriform	15	5	0
Solid	11	3	0
Mixed	10	6	1
Micropapillary	5	2	0
Pure apocrine	2	0	1
Encysted non-invasive papillary carcinoma	2	0	1

Mixed = variable combinations of cribriform, solid and micropapillary patterns

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