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Risk factors for non-invasive and invasive local recurrence in patients with ductal carcinoma in situ

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Abstract

We aimed to identify clinicopathologic factors associated with local recurrence (LR) in a large population of DCIS patients treated with breast-conserving therapy between 1990–2001 in three health plans. Regression methods were used to estimate relative risks (RR) of LR. Among 2,995 patients, 325 had a LR [10.9 %; median follow-up 4.8 years (range 0.5–15.7)]. After adjusting for health plan and treatment, risk of LR was increased among women <45 years (RR = 2.1, 95 % CI 1.5–2.8), African-Americans (RR = 1.6; 95 % CI 1.1–2.1) and those with DCIS detected because of signs/symptoms (RR = 1.6; 95 % CI 1.2–2.0). After also adjusting for age and diagnosis year,

pathologic features associated with increased LR were larger lesion size (RR = 2.9 for 20 low power fields of DCIS; 95 % CI 1.6–5.6) and involved (RR = 2.9; 95 % CI 1.6–5.2), or close margins (RR = 2.4; 95 % CI 1.6–3.8). Presentation with symptoms/signs was associated with increased risk of invasive recurrence; while African-American race, larger tumor size, and involved/close tumor margins were more strongly associated with increased risk of DCIS recurrence. Our findings suggest some risk factors differ for non-invasive and invasive LRs and that most factors are only moderately associated with increased LR risk. Future research efforts should focus on non-clinicopathologic factors to identify more powerful risk factors for LR.

Keywords

Ductal carcinoma in situ; Local recurrence; Risk factors invasive recurrence

Introduction

The term ductal carcinoma in situ (DCIS) encompasses a heterogeneous group of lesions that differ in their clinical presentation, histopathologic features, biologic, molecular and genetic markers, and clinical course. The widespread use of mammographic screening has resulted in a striking increase in the detection of DCIS [1]; yet, how best to manage patients with DCIS, particularly those with small, mammographically-detected lesions, is a matter of ongoing controversy [2–4].

The results of four randomized clinical trials demonstrated that the addition of radiation therapy following breast-conserving surgery is associated with about a 50 % reduction in the risk of recurrence in the ipsilateral breast (local recurrence) when compared with breast-conserving surgery alone [5–9]. The addition of tamoxifen further reduces the risk of local recurrence (LR) [8, 10]. However, the majority of DCIS patients do not recur after treatment with breast-conserving surgery alone, and therefore, only a minority requires additional therapy to obtain satisfactory levels of local control.

Attempts to determine which patients with DCIS can be adequately treated with breast-conserving surgery alone, which patients benefit from the addition of radiation therapy, and which patients are best served by mastectomy have focused on the identification of risk factors for LR following breast-conserving treatment [4, 11]. Various patient, treatment and pathologic factors have been found to be associated with an increased risk of LR [7, 9, 10, 12–20]. However, study results have varied with regard to the degree to which these factors are associated with LR. In addition, the relative importance of these factors and the interactions among them in determining LR risk has not been well-defined. Furthermore, many studies are limited by small numbers of patients precluding the ability to analyze separately, the risk factors for in situ and invasive LRs [7, 10, 12, 14–20]. This is of particular importance since it is only invasive LRs that pose a potential threat to the patient's survival.

The purpose of this study, was to identify clinical and pathologic risk factors for LR after breast-conserving therapy in a large cohort of women with DCIS receiving their care in a

community setting. Further, our goal was to determine if risk factors associated specifically with in situ and invasive LRs were similar or different.

Methods

This study was conducted through the Cancer Research Network (CRN), which is a National Cancer Institute-funded consortium of 14 integrated health care delivery sites whose goal is to foster collaborative research in cancer among diverse populations and health care systems.

Study population

The study population and methods have been described in detail in prior publications from this group (see [21]). In brief, we identified all patients diagnosed with a first primary unilateral DCIS between 1990 and 2001 and treated with breast-conserving therapy at Kaiser Permanente Northern California (KPNC), Kaiser Permanente Southern California (KPSC), and Harvard Pilgrim Health Care (HPHC) [21]. Patients <85 years at diagnosis with no prior invasive cancer (breast or other site) were eligible for inclusion in the study [21]. Patients who received a mastectomy <6 months of their index DCIS and those with breast cancer in the contralateral breast, at the time of diagnosis with the index DCIS were excluded [21]. Local recurrences were defined as DCIS or invasive cancer in the involved breast at least 6 months after the index diagnosis [21]. In selected analyses, we also included any regional or distant breast metastasis [21].

Of the 3,668 patients identified as potentially eligible by our cancer registries or electronic medical records, 673 patients were determined to be ineligible by chart review leaving 2,995 patients available for this study [21].

Central pathology review

For efficiency of resources, we conducted a case-control study with pathology review nested within the full DCIS cohort. Cases included all patients who developed LRs ($n = 325$). At the time of each case's recurrence, up to two controls ($n = 614$) were selected from cohort members under follow-up and without a recurrence (i.e., risk set sampling) [21, 22]. Controls were individually matched to their case on health plan, age at diagnosis (<45, 45–54, 55–64, 65–84 years), and calendar year of diagnosis (1990–1991, 1992–1993, 1994–1995, 1996–1997, 1998–1999, and 2000–2001) [21].

Hematoxylin and eosin-stained sections for all biopsies and open surgical procedures pertaining to the index DCIS were reviewed by two breast pathologists (LCC, SJS) blinded to the case/control status of the patient [21]. The original slides or tissue blocks for 84 % of patients were retrieved for the case-control study.

Information abstracted from pathology reports included specimen size, proportion of the specimen submitted for microscopic evaluation and macroscopic tumor size (if present). Pathologic features, such as nuclear grade, extent of DCIS and margin status were evaluated during central pathology review [23].

Of those patients included in the central pathology review, 131 patients (52 cases and 79 controls) were excluded because the index tumor was re-classified as other than a DCIS lesion. Of these 131, 53 were invasive cancers (24 cases, 29 controls), 43 were papillary carcinomas, which could not be definitively categorized as being either in situ or invasive on original sections alone or had foci suspicious for microinvasion (21 cases, 22 controls), 24 were ADH (3 cases, 21 controls), and 11 were other benign conditions (4 cases, 7 controls). There were 239 cases and 412 controls considered to be DCIS after review, (225 cases and 394 matched controls).

Statistical analyses

Patient and clinical factors (full cohort)—Cox regression methods were used to estimate relative risks of recurrence associated with patient and clinical factors on the full cohort, while controlling for health care site and adjuvant treatment. The follow-up period for recurrences began 6 months after diagnosis of the index DCIS and ended at recurrence (ipsilateral DCIS, ipsilateral invasive breast cancer or regional/distant disease), prophylactic mastectomy of the ipsilateral breast (if it occurred >6 months after the index diagnosis), contralateral breast cancer, non-breast invasive cancer, termination of membership from the health plan, last chart note, or death, whichever came first. Time since diagnosis was the time scale used in the Cox models. We also estimated 5- and 10-year absolute risks for patients treated with BCS alone and for patients treated with BCS plus adjuvant radiotherapy [24].

Pathologic factors (cases and controls)—Given, the nested-case-control sampling design for the examination of pathology factors, conditional logistic regression, which accounts for matching variables (age, diagnosis year, health care site), was used to calculate odds ratios as estimates of the relative risks of recurrence associated with each pathology factor. Minimally adjusted conditional logistic regression models, with matching factors (health care site, age, calendar year, time since diagnosis) and treatment as the only covariate, were fitted first. In multivariable models, those variables that were statistically and significantly associated with LR (overall recurrence, DCIS or invasive recurrence), or with RR estimates of 1.5 (from minimally adjusted analyses) were included [25].

In models with interaction terms between variables of interest (e.g., race, age) and treatment (breast-conserving surgery alone vs. adjuvant radiation and/or tamoxifen), we saw little evidence that associations between patient, clinical and pathology factors, and risk of recurrence differed materially for those treated with surgery alone versus those also treated with adjuvant therapy. We, therefore, present results for both treatment groups combined.

Institutional Review Board approval

Approval for this study was given by the Inter-regional IRB of Kaiser Permanente and by the IRBs at Beth Israel Deaconess Medical Center and HPHC.

Results

Characteristics of the full study cohort

Within the full study cohort of 2,995 DCIS patients with known treatment, 325 women (10.9 %) developed a LR as a first cancer event (median follow-up 4.8 years (range 0.5–15.7); Data for the full study cohort is previously reported, see [21]). Of these recurrences, 294 were confined to the ipsilateral breast only, and 31 also had regional/distant disease [21]. Another 127 (4.2 %) DCIS patients had a subsequent contralateral breast cancer as a first event during follow-up [21]. The majority of DCIS patients were white, but approximately one-third were minorities; 41 % were <55 years, and 32 % were aged ≥ 65 years at the index DCIS diagnosis [21]. Approximately 55 % of patients were treated with one or more adjuvant therapies (radiation therapy and/or tamoxifen).

Relative risks associated with patient and clinical factors for the full cohort (Table 1)

After adjusting for health care site and treatment, the relative risk of any LR was modestly increased among African-American patients (RR = 1.6; 95 % CI 1.1–2.1), and for those whose disease was detected because of clinical signs or symptoms (and/or a diagnostic mammogram) (RR = 1.6; 95 % CI 1.2–2.0). Increased risks of LR were also seen for patients who were <45 years of age (RR = 2.1; 95 % CI 1.5–2.8) and pre- or peri-menopausal (RR = 1.5; 95 % CI 1.2–1.9) at diagnosis. Compared to those diagnosed in 1990–1991, a decreased risk was observed for those diagnosed in 2000–2001 (RR = 0.4, 95 % CI 0.2–0.7).

Relative risks associated with histopathologic factors (nested-case–control study) (Table 2)

While several factors were associated with increased risk of LR, the only pathologic features that were significantly associated with LR were larger lesion size as determined by the number of low power fields (LPF) of DCIS (RR = 3.9 for 15–19 LPF of DCIS; 95 % CI 1.8–8.4; RR = 2.9 for ≥ 20 LPF; 95 % CI 1.6–5.6) and final margins of excision that were involved (RR = 2.9; 95 % CI 1.6–5.2), or close (<1 mm) (RR = 2.4; 95 % CI 1.6–3.8). Of note, nuclear grade was not associated with risk of LR. Both comedo and punctate necrosis, and comedo and papillary architectural patterns were associated with increased risk of LR, although elevated RRs could have occurred by chance alone.

Relative risks associated with type of recurrence (invasive vs. DCIS) (Tables 1, 2)

We stratified the analysis by type of LR to distinguish factors associated with invasive LR from those associated with recurrent DCIS. Within the whole cohort, African-American race was associated with DCIS recurrence (RR = 1.8, 95 % CI 1.2–2.7), but not with invasive LR. In contrast, presentation with signs or symptoms was associated with invasive LR (RR = 2.0, 95 % CI 1.4–2.8), but not recurrence of DCIS. Young age (<45 years) was associated with both DCIS and invasive LR (RR = 2.0, 95 % CI 1.3–3.2 and RR = 2.1, 95 % CI 1.3–3.4, respectively).

Within the nested-case–control study, pathologic features such as larger lesion size, the presence of positive or close final margins, and the presence of adjacent lobular neoplasia

were all associated with a statistically significant increased risk of recurrent DCIS. Although RRs associated with papillary and comedo architectural subtypes, punctuate and comedo necrosis, and intermediate and high nuclear grade were modestly elevated for risk of subsequent invasive disease they were not statistically significant. DCIS extent, margin status, and presence of lobular neoplasia remained statistically significantly associated with recurrent DCIS in multivariable analyses after adjustment for multiple factors (model accounted for matching factors and included treatment, size, margin status). In multivariable models, the RRs associated with subsequent invasive disease remained elevated for several pathology factors (involved or close surgical margins, papillary and comedo architecture, necrosis), with the RR for presence of flat epithelial atypia and uncertain or 1–2.9 mm margins being statistically significant.

Absolute risk of recurrence at 5 and 10 years

The cumulative incidence of any recurrence was 16.0 % (95 % CI 13.8–18.2 %) at 5 years and 22.9 % (95 % CI 20.0–25.9 %) at 10 years for those treated with breast-conserving surgery alone. Among those who also received adjuvant radiation therapy, the cumulative incidence of any recurrence was 5.8 % (95 % CI 4.4–7.2 %) at 5 years and 10.8 % (95 % CI 8.5–13.1 %) at 10 years. Note, treatment changed over the study period; adjuvant radiotherapy approximately doubled and by 2001 virtually all patients had clear margins on final surgery [21].

Discussion

Numerous prior studies have attempted to identify risk factors for LR in women with DCIS treated with breast-conserving therapy [7, 9, 10, 12–20]. However, many of these studies have been limited by small numbers of patients and few LRs which affected their power to identify such risk factors, and in particular, to distinguish risk factors for in situ versus invasive LRs [7, 10, 12, 15–20]. In contrast to these prior studies, our patient population is large (almost 3,000 patients), and there was a relatively large number of events: 325 LRs in the cohort (172 in situ and 153 invasive) and 225 LRs in the case–control study. Notably, in our nested-case–control study the number of women with recurrences was larger than in any of the prospective randomized trials of breast-conserving therapy for DCIS [5–7, 10], except for the most recent update of the NSABP B-17 and B24 trials [8]. However, even with our large cohort, we still had marginal power to examine many risk factors.

We identified several clinical and pathologic factors associated with an increase in the risk of LR. African-American race and presentation with symptomatic disease were each associated with about 60 % increase in LR risk. Young age (<45 years) was associated with a two-fold increase in the LR risk. Among the pathologic factors studied, only larger lesion size and positive or close final margins of excision were associated with an increased risk of LR. Further, the relationship between these factors and the LR varied with the type of LR. African-American race, larger lesion size, the presence of positive or close final margins and lobular neoplasia, stromal desmoplasia and inflammation were more strongly associated with the risk of recurrent DCIS than of subsequent invasive disease. In contrast, presentation

with clinical signs/symptoms was strongly associated with invasive LR. For unclear reasons, the presence of flat epithelial atypia was also associated with invasive recurrence.

Several prior studies have examined the association between patient and clinical factors and risk of LR after breast-conserving therapy for DCIS. Consistent with previous reports [7, 8, 10, 12, 14–20], we found that younger women were at an increased risk for LR. Why younger women are at increased risk for LR has not been adequately explained. The possibility that there is a higher prevalence of unfavorable characteristics associated with the DCIS seen in younger women has been raised [7, 10, 12, 13, 15–20, 26–28]. In this regard, in a prior publication from our group, we showed that among women <45 years, DCIS more often presents as symptomatic disease, is more extensive, and more often shows cancerization of lobules than DCIS in older women [26].

We also found a slight increased risk of LR among African-American women which is unlikely to be due to differences in healthcare utilization given that all women were medically insured during the observation period [29]. In a prior small study ($n = 399$), Nassar et al. [30] evaluated DCIS in African-American and Caucasian women. In contrast to our study, the authors found no difference in LR rate or in the proportion of invasive versus non-invasive recurrences among African-American and Caucasian women. However, the time to development of invasive recurrences was significantly shorter in the study conducted by Nassar et al. (32.8 months in African-American vs. 58 months in Whites; $p < 0.02$) and overall survival at 10 years was poorer among African-American women (71 vs. 92 %; $p < 0.003$). Additionally, there were no differences among the pathologic features examined, though African-American women were significantly more likely to have larger lesion size (1.83 vs. 1.15 cm; $p < 0.001$) at the time of diagnosis. Given the small population sizes in these subsets, it is difficult to separate out whether recurrence rates, time to recurrence, type of recurrence, and overall survival are confounded by other factors, such as patient age, lesion size, and margin status among African-American women. Our findings that women who presented with symptomatic disease were significantly more likely to experience a LR than those whose DCIS presented as a mammographic abnormality or as an incidental finding are similar to those observed by others [13, 31].

A key aspect of our analysis that has not been addressed in detail in many prior studies, is an attempt to determine if factors associated with recurrent DCIS are similar to those that predict for invasive LR. We found that larger lesion size and positive or close margins of excision appeared to be more strongly associated with in situ rather than an invasive LR. Kerlikowske et al. also evaluated the characteristics associated with type of recurrence in 431 women with DCIS treated by breast-conserving therapy alone. In that study, women whose initial lesion was detected by palpation were at increased risk for invasive recurrence [13]. In contrast, positive or uncertain resection margins and age 40–49 years at diagnosis were associated with recurrent DCIS. High nuclear grade was associated with both in situ and invasive LR.

A few prior studies have assessed the presence of concomitant precursor lesions (such as atypical hyperplasia or lobular neoplasia) and LR risk [32, 33]. Rudloff et al. [32] demonstrated that lobular neoplasia in the presence of DCIS was associated with an almost

three-fold increase in the risk of LR. We also found that women in whom lobular neoplasia co-existed with DCIS had a two-fold increase in their risk of LR compared to those without concurrent lobular neoplasia. Moreover, the presence of lobular neoplasia was more strongly associated with the development of recurrent DCIS than invasive LR. The explanation for the stronger association with recurrent DCIS is unclear. One possible explanation is that the presence of lobular neoplasia identifies patients in whom there is a more widespread field effect that results in the development of additional foci of in situ carcinoma which are detected before their progression to invasive disease.

As with any study, certain limitations should be considered when interpreting our findings. The number of events in this series was large; however, our ability to analyze the data stratified on both treatment and type of recurrence was limited by small numbers in the various subsets. Further, our median follow-up time of 5 years is relatively short and does not permit us to identify risk factors for LRs that occur at longer intervals following a diagnosis of DCIS. Moreover, factors that were found to be associated with LR risk in the full cohort, such as African-American race and detection by signs/symptoms were no longer associated with LR in the case-control study. It is not clear why these factors were no longer significant in the case-control study, but it may be a reflection of bias in the subjects for whom we were unable to obtain slides (e.g., an institution that served a particular ethnic population). While not an objective of our study, our data confirms the substantial additive effect of radiation therapy following breast-conserving surgery in reducing the rate of LR [34].

Strengths of our study include the fact that, the study population was drawn from three large, diverse health plans making the likelihood of applicability to the general US population greater. Also, central pathology review was provided by pathologists with expertise in breast pathology thereby creating one of the larger DCIS study populations for which this has been conducted.

Based on the results of this study and in conjunction with those of prior studies, it appears that the ability of clinical and pathologic features to identify patients at substantially increased risk of LR after breast-conserving treatment for DCIS in the current era is limited. In our large study as well as in most prior smaller studies, clinical and pathologic risk factors that have been identified are associated with only modest increases in risk of LR. However, our findings, taken together with those of Kerlikowske et al., do suggest that risk factors for recurrent DCIS may differ from those for the subsequent development of invasive breast cancer in patients with DCIS treated with breast-conserving therapy. Thus, attempts to identify risk factors for “LR” as a single group could obscure potentially important differences in the biology and mechanism of LR of DCIS and the progression to invasive cancer in patients with DCIS.

Future research efforts should focus on factors other than clinical and pathologic prognostic factors to identify strong risk factors for LR. To that end, the identification of biological markers of progression is an area of active investigation. Evaluation of biomarkers such as estrogen receptor, HER2, Ki-67 and others, however, is problematic because many of these biomarkers are highly correlated with each other, as well DCIS grade. A new quantitative

multigene RT-PCR assay for predicting recurrence risk after breast-conserving surgery alone has recently become available. This new assay provides a “DCIS score” associated with the risk of subsequent ipsilateral events. The test was validated on the ECOG E5194 trial population and reports ipsilateral recurrence rates of 12, 24.5, and 27.3 % for low intermediate and high risk groups and ipsilateral invasive recurrence rates of 5.1, 8.9, and 19.1 % for these three groups, respectively (HR 3.73 95 % CI = 1.3–9.8; $p = 0.01$). In multivariable analyses, both menopausal status (HR 0.49 95 % CI = 0.3–0.9; $p = 0.02$) and DCIS size (HR 1.52 per 5 mm 95 % CI = 1.1–2.0; $p = 0.01$) were also predictive of tumor recurrence [35]. In addition to assessment of gene expression signatures, studies of the DCIS microenvironment could provide important new insights into factors associated with LR and progression to invasive breast cancer.

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Abbreviations

LR	Local recurrence
RR	Relative risk
CI	Confidence interval

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Table 1

Relative risks for local recurrence associated with patient and clinical factors

Patient/clinical factors	Total (n = 2,995)	All recurrences (cases = 325)		DCIS recurrence (cases = 172)		Invasive recurrence (cases = 153)	
		RR	95 % CI	RR	95 % CI	RR	95 % CI
Race							
White	2,045	1	Ref	1	Ref	1	Ref
Asian	360	0.9	0.6–1.3	1.1	0.7–1.8	0.7	0.4–1.2
African-American	289	1.6	1.1–2.1	1.8	1.2–2.7	1.3	0.8–2.2
Hispanic	257	1.1	0.8–1.7	1.1	0.6–2.0	1.2	0.7–2.0
Age (years)							
<45	356	2.1	1.5–2.8	2.0	1.3–3.2	2.1	1.3–3.4
45–54	873	1.3	1.0–1.7	1.1	0.7–1.7	1.5	1.0–2.2
55–64	813	1.3	1.0–1.7	1.3	0.9–2.0	1.2	0.8–1.9
65+	953	1	Ref	1	Ref	1	Ref
Menopausal status							
Postmenopausal	2,065	1	Ref	1	Ref	1	Ref
Pre/perimenopausal	864	1.5	1.2–1.9	1.5	1.1–2.1	1.5	1.1–2.1
Detection method							
Mammography	2,463	1	Ref	1	Ref	1	Ref
Signs/symptoms	525	1.6	1.2–2.0	1.2	0.8–1.8	2.0	1.4–2.8

Adjusted for health care site, treatment, time since diagnosis

The figures in bold are to allow for ready recognition of statistically significant variables

Table 2
Relative risk for local recurrence associated with significant histopathologic features in nested-case-control study

Histopathologic features		All recurrences (cases = 225, controls = 394)		DCIS recurrence (cases = 125, controls = 225)		Invasive recurrence (cases = 100, controls = 169)	
		RR	95 % CI	RR	95 % CI	RR	95 % CI
Size (#LPF with DCIS)							
1		1.0	Ref	1.0	Ref	1.0	Ref
2-5		1.6	0.8-2.9	2.0	0.8-4.6	1.0	0.4-2.7
6-9		2.0	1.0-3.8	2.5	1.0-6.4	1.4	0.5-3.8
10-14		2.5	1.3-4.9	5.1	2.0-12.7	0.8	0.3-2.4
15-19		3.9	1.8-8.4	6.5	2.4-18.0	1.8	0.5-6.4
20+		2.9	1.6-5.6	4.1	1.7-9.7	1.9	0.7-5.0
Margins by review							
Negative, 3 mm		1.0	Ref	1.0	Ref	1.0	Ref
Negative, 1-2.9 mm		2.4	1.2-4.5	2.1	0.8-5.4	2.5	1.0-6.5
Close, <1 mm		2.4	1.6-3.8	3.0	1.7-5.4	1.9	1.0-3.7
Positive		2.9	1.6-5.2	4.7	2.1-10.5	1.5	0.6-3.9
Uncertain		3.1	1.5-6.4	3.1	1.2-8.3	3.4	1.1-10.4

Adjusted for matching factors (health care site, age, calendar year, time since diagnosis), plus treatment

The figures in bold are to allow for ready recognition of statistically significant variables