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Relationship Between Clinical and Pathologic Features of Ductal Carcinoma in Situ and Patient Age: An Analysis of 657 Patients

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Abstract

Prior studies have shown that young patient age at diagnosis is associated with an increased risk of local recurrence (LR) among women with DCIS treated with breast-conserving therapy. Whether this can be explained by differences in clinical or pathologic features of DCIS according to age is an unresolved issue. We compared clinical and pathologic features of DCIS among 657 women in four age groups: <45 years (n=111), 45–54 years (n=191), 55–64 years (n=160), and 65+ years (n=195). DCIS presented as a mammographic abnormality less often in younger than in older women (68%, 82%, 81% and 86% for women <45, 45–54, 55–64 and 65+ years, respectively; p=0.003). Among the pathologic features analyzed, DCIS extent as determined by the number of low power fields (LPF) was greater in younger than in older women (mean #LPF 18.6, 14.2, 10.8 and 11.3 in women <45, 45–54, 55–64 and 65+ years; p<0.001). In addition, cancerization of lobules was present more often in younger than in older women (77%, 73%, 66%, and 50% for women <45, 45–54, 55–64 and 65+ years, respectively; p<0.0001). Of note, we found no statistically significant relationship between age and DCIS architectural pattern, nuclear grade, comedo necrosis or expression of ER, PR or HER2. We conclude that DCIS in younger women is more often symptomatic, is more extensive, and more often shows cancerization of lobules than DCIS in older women. Whether these features contribute to the higher LR risk in young women with DCIS treated with breast-conserving therapy requires further study.

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Keywords

Young age; ductal carcinoma in situ; breast cancer

Introduction

Breast-conserving therapy is the local treatment of choice for many women with ductal carcinoma in situ (DCIS) of the breast and is associated with high levels of local tumor control in most patients (2,7,9,13). However, some patients treated with the breast-conserving approach will develop a recurrence in the ipsilateral breast. The elucidation of risk factors for such local recurrences has been an area of active investigation for the past two decades.

A variety of treatment factors and tumor factors have been reported to be associated with an increased risk of local recurrence or progression to invasive cancer in the ipsilateral breast following breast-conserving treatment for DCIS. For example, the use of radiation therapy following breast-conserving surgery is associated with at least a 50% reduction in the local recurrence risk. In addition, tumor factors such as high nuclear grade, the presence of comedo necrosis, and margin involvement have been reported to be associated with an increased risk of local recurrence (2,6,15–16,29–30). Of the clinical factors analyzed in this regard, young patient age at diagnosis has been shown in some, but not all, studies to be associated with an increased risk of local recurrence or progression to invasive breast carcinoma (2,3,6,8–10,16, 22–23,26,28–30).

The basis for the apparent association between young patient age, which is variably defined in the literature, and an increased risk of local recurrence has not been elucidated. A better understanding of the association between clinical and pathologic features of DCIS and patient age could provide new insights into this relationship. The purpose of this study, therefore, was to assess the relationship between clinical and pathologic features of DCIS and patient age among the patients in a large case-control study of women with DCIS treated with breast-conserving therapy. Whether or not local recurrence differs according to patient age will be the focus of a separate analysis.

Materials and Methods

Study population

The population for this study consists of patients derived from a case-control study nested within a cohort of women diagnosed with a first primary unilateral DCIS and treated with breast-conserving therapy between 1990 and 2001 and for whom pathology has been reviewed. The cohort was identified using cancer registries or electronic medical records at three integrated health care delivery systems which are members of the NCI-funded Health Maintenance Organization (HMO) Cancer Research Network, a network of research programs, enrollee populations and databases of 14 HMO members whose overall goal is to conduct collaborative research to determine the effectiveness of preventive, curative and supportive interventions for major cancers (17). The three health plans participating in this study were Kaiser Permanente of Northern California, Kaiser Permanente of Southern California, and Harvard Pilgrim Health Care.

Patients were eligible if they were less than 85 years at diagnosis and had no prior breast cancer or invasive cancer at another site. Patients were excluded if breast cancer (DCIS or invasive disease) had been diagnosed in the contralateral breast at the time of the index DCIS diagnosis or if they had a mastectomy within 6 months of their DCIS diagnosis. Patients were also

excluded from this analysis if the pathology review determined that the initial diagnosis was not DCIS (see below).

At each of the three sites, medical records of potentially eligible patients were reviewed to confirm the initial diagnosis, treatment and laterality of the index DCIS and to obtain information on subsequent breast cancer events. Information was also collected on surveillance mammography and on all subsequent breast biopsies. In addition, data were abstracted on several patient and clinical factors at the time of their index DCIS (e.g., use of exogenous hormones (including tamoxifen), demographics, reproductive history, as well as on several patient and clinical factors after their index DCIS).

The cohort was followed from the initial DCIS diagnosis until the earliest of the following events: subsequent DCIS or invasive breast cancer, other invasive cancer, mastectomy of the ipsilateral breast, death, termination of health plan membership, or end of study period (last chart note at time of medical record review).

Design of Nested Case-Control Study

Cases were patients whose first event during follow-up was a breast cancer recurrence. A recurrence was defined as any ipsilateral breast cancer event (DCIS or invasive) or any regional or distant metastasis. At the time of each case's recurrence, up to two controls were randomly selected from all surviving patients with no evidence of a breast cancer recurrence as of that date (i.e., incidence density sampling). Controls were individually matched to their case on age (<45, 45–54, 55–64, 65+ years), calendar year of diagnosis (1990–1991, 1992–1993, 1994–1995, 1996–1997, 1998–1999, and 2000–2001), and site.

A total of 3,668 potentially eligible DCIS patients were identified. Of these, 520 were ineligible for one or more of the following reasons: miscoding of DCIS in the tumor registry (n=97), prior breast or other cancer (n=216), bilateral breast cancer at diagnosis (n=29), 85 years of age or older at diagnosis (n=15), or had less than 6 months of follow-up (mastectomy within 6 months (n=96), death within 6 months (n=6), or not a member at diagnosis or left the health plan within 6 months (n=92)). In addition, medical records were unavailable on 82 patients and 29 did not have complete information on adjuvant therapy. Of the 3037 women determined to be eligible by chart review, 42 had no pathology report confirming breast-conserving therapy, leaving 2,995 patients. Of the 2,995 remaining patients, we identified 334 with a recurrence (cases; 325 if restricted to local recurrences) and selected 628 controls. Diagnostic slides were unavailable on 34 cases and 124 controls. Pathology was reviewed on 804 patients. Of these, 147 patients (55 cases and 92 controls) were found not to be DCIS at pathology review or found to have insufficient tumor to fully evaluate the pathologic features, leaving 657 patients for the present analysis.

Pathology Review

Available histologic slides and pathology reports from all biopsy and surgical procedures (core needle biopsy, initial excision and all re-excisions) pertaining to the index DCIS diagnosis were obtained and reviewed simultaneously by two breast pathologists (LCC, SJS) blinded to the case/control status of the patient. Information regarding specimen size, presence of a macroscopically evident tumor, macroscopic tumor size (if present), status of the surgical margins, and the proportion of the specimen submitted was abstracted from pathology reports. Histologic features of DCIS evaluated included architectural patterns (comedo, solid, cribriform, micropapillary, papillary or clinging), nuclear grade (low, intermediate, or high) (25), comedo necrosis, involvement of lobules (defined as the presence of ductal carcinoma cells within identifiable, pre-existing lobular units), stromal desmoplasia, stromal inflammation, and status of surgical margins. For architectural pattern, the primary (or

predominant), secondary, and tertiary patterns were recorded; for the purposes of this analysis, only the predominant architectural pattern was used. Similarly, for nuclear grade, the predominant as well as the highest nuclear grade was recorded. The presence in breast tissue adjacent to DCIS of atypical ductal hyperplasia (either immediately adjacent or as separate foci), lobular carcinoma in situ, atypical lobular hyperplasia, flat epithelial atypia and non-atypical columnar cell lesions (columnar cell change and columnar cell hyperplasia) as well as other benign non-proliferative and proliferative changes were also recorded. In this analysis, we compared clinical and pathologic features of DCIS in women across four age groups: <45 years (n=111), 45–54 years (n=191), 55–64 years (n=160), and 65+ years (n=195).

In a subset of this population, immunohistochemical assays for estrogen receptor (ER), progesterone receptor (PR), and HER2 were performed at PhenoPath Laboratories (Seattle, WA). These biomarkers were selected for analysis because they are commonly used in clinical practice as prognostic and predictive factors. More recently, these three biomarkers represent the minimal panel that can be used as a surrogate to classify invasive breast cancers and DCIS according to their molecular phenotypes (4,18,21,24). Sources and dilutions of the primary antibodies used in this study are listed in Table 1. Immunostaining was conducted according to established protocols which have been previously described in detail (5,12,27) (Table 1). ER and PR were scored as negative if <1% of tumor cell nuclei stained and positive if $\geq 1\%$ of nuclei demonstrated staining. HER2 was scored as negative if there was no staining (0) or if there was weak staining (1+) of the tumor cell membranes, indeterminate if there was weak-moderate membrane staining (2+) and positive if there was moderate-strong membrane staining (3+). In this subset, we investigated whether the inferred molecular phenotypes of DCIS differed by age among women with DCIS.

Statistical Analysis

For the current study, we conducted an analysis of all eligible patients for whom pathology had been reviewed. We examined the clinical and pathologic features of DCIS associated with patient age regardless of the patient's case-control status. The chi-squared test was used to examine whether patient age was statistically significantly associated with other variables of interest without stratification by case-control status. Variables of interest included: method of detection of DCIS, history of breast cancer in first degree blood relative, nuclear grade, architectural pattern, presence of necrosis and other associated pathologic changes (i.e. atypical ductal hyperplasia, lobular neoplasia and columnar cell lesions) as well as extent of DCIS (as measured by number of low power fields (LPFs) of DCIS) and margin status.

Institutional Review Board approval

The study was approved by the Kaiser Permanente Inter-regional Institutional Review Board and by the Institutional Review Boards at Harvard Pilgrim Health Care and Beth Israel Deaconess Medical Center, Boston, MA.

Results

Among the 657 women in this analysis, the median patient age was 56 years (range 26–84 years). The median number of slides reviewed per patient was 17 (range, 1–117 slides). Overall, DCIS was diagnosed on a screening mammogram in 530 women (81%) and because of a palpable mass or other clinical sign or symptom in 124 (19%). In the remaining 3 patients, the mode of presentation was unknown. DCIS presented as a mammographic abnormality significantly less often in younger than in older women (68% for women <45 years; 82% for those 45–54 years; 81% for those 55–64 years; 86% for those 65+ years; $p=0.003$) (Table 2).

Among the pathologic features analyzed, the extent of DCIS as determined by the number of LPFs of DCIS was greater in younger than in older women (mean #LPF 18.6, 14.2, 10.8, and 11.3 for women <45, 45–54, 55–64 and 65+ years, respectively; $p<0.0006$). In addition, cancerization of lobules was present more often in younger than in older women (77% for women <45 years; 73% for those 45–54 years; 66% for those 55–64 years; 50% for those 65+ years, $p<0.0001$) (Table 2).

Neither architectural pattern, nuclear grade (evaluated either as predominant or highest nuclear grade), nor comedo necrosis varied significantly according to age. The presence of stromal inflammation did not vary according to patient age, though the presence of stromal desmoplasia was significantly more frequent in younger than in older women (36% in women <45 years vs. 30% in women 65+ years, $p=0.02$) (Table 2). The presence or absence of atypical ductal hyperplasia, lobular neoplasia, or a family history of breast cancer did not vary according to patient age. The prevalence of the pathologic features studied was similar in cases and controls (data not shown).

There were no significant differences in the frequency of expression of ER, PR, or HER2 by age. Using the combination of ER, PR, and HER2 status as surrogates to approximate the molecular phenotype of DCIS lesions as luminal (ER and/or PR positive, HER2 positive or negative), HER2 (ER and PR negative, HER2 positive) and triple negative/basal-like types (ER, PR and HER2 negative), there was no significant association between age and molecular subtype of DCIS (Table 3).

Discussion

Clinical follow-up studies have suggested that young patient age is a risk factor for recurrence in the ipsilateral breast among women with DCIS treated with breast-conserving therapy (2, 3,6,8–10,16,22–23,26,28–30). Although the nature of this association has not been established, it is possible that this association is related, at least in part, to a higher prevalence of unfavorable characteristics of the DCIS in younger women (2,3,6,8–10,15–16,20,22–23,26,28–30).

Several studies have attempted to address this issue, but interpretation of the available data is limited by the fact that various studies have used different definitions for “young age”. Of the studies that have evaluated pathologic features according to age, age cutoffs for “young” have varied between <39 to <49 years, and the number of patients in each category have been small, ranging from only 9 patients to 65 patients (2,11,15–16,20,30) (Table 4).

The current study is the largest to date to evaluate the relationship between clinical and pathologic features of DCIS and patient age. We found that DCIS in younger women more often presented with symptomatic disease, was more extensive, and more often showed cancerization of lobules and stromal desmoplasia than DCIS in older women. However, we did not find a difference according to patient age with regard to other histopathologic characteristics of DCIS, such as nuclear grade, comedo necrosis, or architectural pattern. Further, we found no relationship between expression of ER, PR, or HER2 in relation to age.

Several prior studies have similarly reported a greater likelihood of younger women with DCIS presenting as symptomatic disease (3,6,8–10,16,22–23,26,28–30). This may well be related to the fact that younger women are less likely to undergo mammographic screening. Further, it would follow that when DCIS is identified as a mass or other symptomatic lesion, it would more likely be greater in extent and would exhibit stromal desmoplasia, a histopathologic feature that could account for DCIS being palpable. Furthermore, young women have greater numbers of lobules and more expanded lobules than older postmenopausal women, hence the likelihood of identifying lobular involvement by DCIS is greater among this age group (1, 17).

Of note, we did not find a difference across the different age groups among several histopathologic characteristics of DCIS that have previously been reported to be associated with an increased risk of local recurrence following breast-conserving therapy, such as high nuclear grade, comedo necrosis or architectural pattern (2,11,30). Several prior studies have also reported a similar lack of correlation between young age and histologic features of DCIS (2,16,28,30). In contrast, Goldstein, et al found that DCIS in women younger than 45 years of age was more likely to exhibit high nuclear grade compared to DCIS in women 45–59 years of age or >60 years of age (38%, 32% and 24%, $p=0.08$), though this difference only reached statistical significance when the highest rather than when the predominant nuclear grade was evaluated (69%, 60% and 39% respectively; $p<0.003$). In addition, in that study, DCIS in younger women was more likely than that in older women to show any comedo necrosis (72%, 62% and 44% respectively; $p<0.01$). There were no differences according to patient age among any of the other 11 pathologic features evaluated in that study. It is possible that the differences between our study and that of Goldstein, et al with regard to these features may be related to differences in the numbers of patients in these two studies. For example, the population of the current study consisted of 657 women whereas in the study of Goldstein, et al, there were 177 patients. Moreover, in the Goldstein, et al study, there were only 32 women <45 years of age whereas in the current study there were 111 women in the <45 year age group.

Both our study and the study of Goldstein et al found that the extent of DCIS was significantly greater in younger than in older women. Goldstein and colleagues recorded extent of DCIS in several different ways and found that the mean maximum tumor dimension (measured on a subset of 106 DCIS cases with “tumorous growth” only) was significantly greater in younger compared with older women (9.1 mm for women <45 years, 6.8 mm for women 45–59 years, and 6.5 mm for women >60 years, $p=0.03$). In our study, we also attempted to record size in a number of different ways. However, given that the tissue had been processed in at least three different institutions over an 11-year period and that in most instances was not totally and sequentially embedded, it was not possible to determine the exact size of the DCIS in most cases. However, we could determine the extent of the lesion for all cases by assessing the number of low power fields (LPFs) of DCIS in each case. Thus, in our study, younger women had significantly greater numbers of LPFs of DCIS than older women (mean #LPF 18.6, 14.2, 10.8 and 11.3 for women <45, 45–54, 55–64 and 65+ years, respectively; $p<0.0006$). While other studies have suggested that DCIS in younger women is more extensive than in older women each of these studies has determined the extent of DCIS in a different manner (14,19, 30).

We found no differences in the frequency of expression of ER, PR or HER2 according to patient age. Of interest, in a study evaluating pathologic and molecular features of DCIS, Rodrigues, et al found no differences in expression of molecular markers including ER, PR, bcl2, p53, Ki67 and cyclin D1 between younger (<42 years) and older (>60 years) with DCIS. In that study, HER2 was overexpressed (2+ and 3+) more frequently in younger women (65% positive) compared to older women (38.2%) though this difference did not reach statistical significance ($p=0.06$) and is perhaps influenced by the fact that there was a greater number of patients in the older age group with low grade DCIS (20). When we analyzed our data using the criteria of Rodrigues (i.e. combining HER2 2+ and 3+ cases into the “positive” category), there was no significant difference between the proportion of young women and older women overexpressing HER2 (39% for both groups).

We also used combinations of ER, PR and HER2 expression to approximate the major breast molecular phenotypes (i.e., luminal, HER2 and triple negative/basal-like) we found no difference in frequency of luminal, HER2 and triple negative/basal-like types of DCIS among the different age categories. To our knowledge, this is the first study to assess the inferred

molecular phenotype of DCIS (using immunophenotype as a surrogate) according to patient age.

There are a number of strengths to our study worth emphasizing. First, in at least 82% of subjects all of the tissue submitted for pathologic examination was available for review (in some subjects the number of blocks submitted for pathologic examination was not recorded in the original pathology report). Second, all histologic sections were subject to central review by two pathologists with expertise in breast pathology. Finally, this analysis consists of the largest population of women with DCIS in which a systematic evaluation of clinical and pathological variables were related to patient age. Moreover, this is a population based study and thus not subject to the inherent biases found in studies using populations derived from referral centers.

In conclusion, we have demonstrated that in women <45 years of age, DCIS more often presents with symptomatic disease, is more extensive, and more often shows cancerization of lobules than DCIS in older women. Whether these features explain in part the higher LR rate observed in young women with DCIS treated with breast-conserving therapy will be the subject of a subsequent analysis.

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Table 1

Sources and dilutions of primary antibodies used in this study.

Antigen	Antibody Source	Type	Dilution	Detection System (Dako)
ER	LabVision	Rabbit monoclonal (clone SP1)	1:250	EnVision+, rabbit
PR	Dako	Mouse monoclonal (clone PgR 636)	1:500	EnVision+, rabbit
HER2	Dako	Rabbit polyclonal (A085)	1:400	EnVision+, rabbit

Table 2

Clinical and pathologic characteristics of DCIS according to patient age.

Factor	Age						p-value
	Total (N=657)	<45 (N=111)	45-54 (N=191)	55-64 (N=160)	65+ (N=195)		
Presentation⁺							
Mammogram abnormality	530 (81)	75 (68)	157 (82)	130 (81)	168 (86)		.003
Palpable mass	122 (19)	34 (31)	32 (17)	30 (19)	26 (13)		
Other	2 (<1)	1 (1)	1 (<1)	0 (0)	0 (0)		
Unknown	3 (<1)	1 (1)	1 (<1)	0 (0)	1 (<1)		
Family history⁺⁺							
No	526 (80)	93 (84)	157 (82)	126 (79)	150 (77)		.65
Yes	113 (17)	17 (15)	31 (16)	26 (16)	39 (20)		
Unknown	18 (3)	1 (1)	3 (2)	8 (5)	6 (3)		
DCIS nuclear grade[#]							
Low	68 (10)	8 (7)	21 (11)	21 (13)	18 (9)		.48
Intermediate	349 (53)	65 (59)	95 (50)	78 (49)	111 (57)		
High	238 (36)	38 (34)	74 (39)	60 (38)	66 (34)		
Unknown	2 (<1)	0 (0)	1 (<1)	1 (<1)	0 (0)		
DCIS highest nuclear grade							
Low	53 (8)	5 (5)	14 (7)	19 (12)	15 (7)		.17
Intermediate	333 (51)	62 (56)	90 (47)	73 (46)	108 (55)		
High	269 (41)	44 (40)	86 (45)	67 (42)	72 (37)		
Unknown	2 (<1)	0 (0)	1 (<1)	1 (<1)	0 (0)		
DCIS pattern[#]							
Solid	248 (38)	44 (40)	69 (36)	60 (38)	75 (38)		.74
Cribiform	228 (35)	40 (36)	71 (37)	56 (35)	61 (31)		
Micropapillary	43 (7)	10 (9)	10 (5)	9 (6)	14 (7)		
Conedo	73 (11)	6 (5)	25 (13)	18 (12)	24 (12)		
Papillary	53 (8)	10 (9)	12 (6)	13 (8)	18 (9)		
Other: Clinging	10 (15)	1 (1)	3 (2)	3 (2)	3 (2)		
Unknown	2 (<1)	0 (0)	1 (<1)	1 (<1)	0 (0)		
Conedo necrosis							
Absent	272 (41)	40 (36)	85 (45)	60 (38)	87 (45)		.27
Present	383 (58)	71 (64)	105 (55)	99 (62)	108 (55)		
Unknown	2 (<1)	0 (0)	1 (<1)	1 (<1)	0 (0)		
% of Ducts with Conedo necrosis							
< 50%	241 (37)	49 (44)	62 (32)	62 (39)	68 (35)		.67
> 50%	136 (21)	21 (19)	40 (21)	36 (23)	39 (20)		
Unknown	6 (1)	1 (1)	3 (2)	1 (<1)	1 (1)		
Cancerization of lobules							
Absent	226 (34)	26 (23)	49 (26)	54 (34)	97 (50)		< .0001
Present	428 (65)	85 (77)	140 (73)	105 (66)	98 (50)		
Unknown	3 (<1)	0 (0)	2 (1)	1 (<1)	0 (0)		
Stromal desmoplasia							
Absent	406 (62)	71 (64)	108 (57)	90 (56)	137 (70)		.02
Present	249 (38)	40 (36)	82 (43)	69 (43)	58 (30)		
Unknown	2 (<1)	0 (0)	1 (<1)	1 (<1)	0 (0)		
Stromal inflammation[#]							
Absent	438 (67)	77 (69)	122 (64)	104 (65)	135 (69)		.67
Present	217 (33)	34 (31)	68 (36)	55 (34)	60 (31)		
Unknown	2 (<1)	0 (0)	1 (<1)	1 (<1)	0 (0)		
ADH							

Factor	Age							p-value
	Total (N=657)	≤45 (N=111)	45-54 (N=191)	55-64 (N=160)	65+ (N=195)			
Absent	406 (62)	72 (65)	124 (65)	92 (58)	118 (61)			.49
Present	250 (38)	39 (35)	67 (35)	67 (42)	77 (39)			
Unknown	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)			
ALH/LCIS								
Absent	488 (74)	91 (82)	137 (72)	120 (75)	140 (72)			.18
Present	169 (26)	20 (18)	54 (28)	40 (25)	55 (28)			
Columnar cell change								
Absent	451 (69)	74 (67)	112 (59)	113 (71)	152 (78)			.0006
Present	206 (31)	37 (33)	79 (41)	47 (29)	43 (22)			
Extent of DCIS								
Mean No. of LPF	13.2	18.6	14.2	10.8	11.3			.0006
Median (range)	7 (1-138)	8.5 (1-138)	8 (1-87)	7 (1-89)	7 (1-109)			
Mean No. of slides reviewed	18.7	19.1	20.1	18.0	17.8			.21
Median (range)	17 (1-117)	17 (3-54)	18 (3-85)	16.5 (2-117)	15 (1-69)			

Numbers in parentheses are percentages unless otherwise indicated

⁺ Mammographic abnormality (screening, no symptoms); mass (or other symptoms); other (breast reduction, etc.).

⁺⁺ History of breast cancer in 1st degree blood relative noted at or within 6 months of DCIS diagnosis.

[#] Predominant or prominent

Values adjusted for matching factors (health plan, age at diagnosis, year of diagnosis and follow-up time).

Table 3

Biomarker profile and inferred molecular phenotype of DCIS according to patient age.

Factor *	Age						p-value
	Total (N=554)	<45 (N=93)	45-54 (N=157)	55-64 (N=140)	65+ (N=164)		
ER							
Positive	474 (86)	87 (94)	129 (82)	118 (84)	140 (85)		.07
Negative	80 (14)	6 (6)	28 (18)	22 (16)	24 (15)		
PR							
Positive	413 (75)	79 (85)	118 (75)	99 (71)	117 (71)		.08
Negative	136 (25)	14 (15)	38 (24)	39 (28)	45 (27)		
Unknown	5 (1)	0 (0)	1 (1)	2 (1)	2 (1)		
HER2							
0 to 1+	340 (61)	57 (61)	97 (62)	87 (62)	99 (60)		.17
2+	120 (22)	28 (30)	28 (18)	27 (19)	37 (23)		
3+	92 (17)	8 (8)	30 (19)	26 (19)	28 (17)		
Unknown	2 (<1)	0 (0)	2 (1)	0 (0)	0 (0)		
Tumor Subtypes **							
Luminal (ER/PR+, HER2+ or -)	472 (85)	87 (94)	127 (81)	118 (84)	140 (85)		.30
Triple negative/Basal like (ER-, PR-, HER2-)	38 (7)	4 (4)	14 (9)	9 (6)	11 (7)		
HER2 type (ER-, PR-, HER2+)	41 (7)	2 (2)	14 (9)	12 (9)	13 (8)		
Unknown	3 (<1)	0 (0)	2 (1)	1 (1)	0 (0)		

* Restricted to those with known ER.

** HER2 negative are 0 to 1+ and 2+; HER2 positive are 3+.

Values adjusted for matching factors (health plan, age at diagnosis, year of diagnosis and follow-up time).

Table 4

Prior studies that have evaluated pathologic features of DCIS according to patient age.

	Definition of young age, years (n)	Other age groups evaluated, years (n)	Pathologic features significantly more frequent in younger women
Vicini, 2000 (30)	<45 (31)	≥45 (117)	<ul style="list-style-type: none"> • Larger lesion size • Presence of central necrosis • Cancerization of lobules (COL) ≤5mm from the margin
Goldstein, 2000 (11)	<45 (32)	45–59 (60) >60 (85)	<ul style="list-style-type: none"> • Larger lesion size • High grade • Presence of central necrosis • COL ≤5mm from the margin
Kerlikowske, 2003 (15)	40s (51)	50s (49) 60s (43) 70s (57)	None
Rodrigues, 2003 (20)	≤42 (20)	>60 (34)	None
Bijker, 2006 (2)	≤40 (65)	>40 (945)	<ul style="list-style-type: none"> • Clinical symptoms as method of detection • Intermediate grade • Cribriform and solid/comedo architecture • Involved margins
Meijen, 2008 (16)	≤39 (9)	>40 (201)	None
Current study, 2009	<45 (111)	45–54 (191) 55–64 (160) 65+ (195)	<ul style="list-style-type: none"> • Non-mammographic method of detection • Larger lesion size • Presence of cancerization of lobules • Presence of stromal desmoplasia