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Notes

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Comparison of Risk Factors for Ductal Carcinoma In Situ and Invasive Breast Cancer

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Background: **Ductal carcinoma in situ (DCIS) accounts for approximately 12% of newly diagnosed breast cancers. Knowledge of the factors that predict who will be diagnosed with DCIS is very limited.** ***Purpose:*** **The goal of this study was to determine risk factors associated with DCIS and whether these risk factors are similar to those associated with invasive breast cancer.** ***Methods:*** **We conducted a cross-sectional study of 39 542 women aged 30 years and older who underwent a screening mammographic examination at the University of California San Francisco Mobile Mammography Screening Program from April 1985 through September 1995. A breast cancer risk profile and clinical history were obtained for each woman. Follow-up after abnormal mammography was performed to determine the presence of DCIS or invasive breast cancer by contacting the women's physicians and by linkage to the regional Surveillance, Epidemiology, and End Results cancer registry. Multivariate analysis was performed by the use of polytomous logistic regression. Two-sided statistical tests were used to determine *P* values.** ***Results:*** **Among women aged 30-49 years, a family history of breast cancer (i.e., at least one affected first degree relative) was associated with an increased risk of DCIS (Odds ratio [OR] = 2.4; 95% confidence interval [CI] = 1.1-4.9) and body mass index greater than or equal to 25 kg/m^2 was associated with a decreased risk of DCIS (OR = 0.4, 95% CI = 0.2 to 0.9). For each of these factors, there was a trend in the same direction bordering on statistical significance for invasive cancer (ORs = 1.7 [95% CI = 0.9-3.4] and 0.6 [95% CI = 0.3-1.1], respectively). Report of a palpable mass was associated with an increased risk of invasive cancer among women aged 30-49 years (OR = 12.0; 95% CI = 7.1-20.0); there was a trend in**

the same direction for DCIS (OR = 2.0; 95% CI = 0.8-5.1), but the association was much stronger for invasive disease than for DCIS (OR = 6.0; 95% CI = 2.1-18.0; *P* = .001). Among women aged 50 years and older, family history of breast cancer and nulliparity or age at birth of first child of 30 years or older increased the risk of both DCIS (ORs = 2.2 [95% CI = 1.0-4.2] and 2.3 [95% CI = 1.3-3.8], respectively) and invasive breast cancer (ORs = 1.5 [95% CI = 1.0-2.2] and 1.6 [95% CI = 1.2-2.1], respectively). Report of a palpable mass was not associated with an increased risk of DCIS among women 50 years and older, but it was strongly associated with an increased risk of invasive cancer (OR = 9.3; 95% CI = 6.0-14.0). Increasing age was associated with an increased risk of both DCIS and invasive cancer among women aged 30-49 years, but the association was stronger for invasive disease; a trend in the same direction bordering on statistical significance was observed for women aged 50 years and older. *Conclusion:* Risk factors for DCIS are similar to those for invasive breast cancer. *Implications:* More research is needed to better understand the malignant potential of DCIS lesions and factors that predict which lesions will become invasive breast cancer if left untreated. [J Natl Cancer Inst 1997;89:77-82]

Ductal carcinoma in situ (DCIS) now accounts for about 12% of newly diagnosed breast cancers (*1*). Incidence rates of DCIS increased over 300% from 1983 to 1992 for women aged 40 years and older (*1*). The dramatic increase in the incidence of DCIS coincides with the widespread use of mammographic examinations for breast cancer screening that began in the mid-1980s (*2-4*).

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See ''Notes'' section following ''References.''

Investigators have expressed concern about the large number of cases of DCIS being detected by screening mammographic examination, since the natural history of DCIS lesions is not fully understood and there is controversy about whether all, or even most, of these lesions are precursors of invasive cancer (*5*). If DCIS is a precursor of invasive breast cancer, the risk factors for DCIS should be similar to those of invasive breast cancer. At present, knowledge of factors that predict who will be diagnosed with DCIS is very limited. Only a few studies (*6-9*) have assessed potential risk factors for carcinoma in situ of the breast (ductal or lobular) and, of these, only one assessed the relationship of standard breast cancer risk factors to invasive breast cancer and to DCIS separately (*7*). Since lobular carcinoma in situ (LCIS) is considered to be a risk factor for invasive breast cancer, whereas DCIS is considered to be a potential precursor of invasive disease, it may be important to distinguish factors associated with the development of each of these in situ lesions separately.

The purpose of this study was to determine risk factors associated with DCIS detected in a screening mammography program and whether those risk factors are the same as those for invasive breast cancer.

Subjects and Methods

Subjects

Our study sample included 39 542 (99.2%) of the 39 844 women aged 30 years and older who underwent first or subsequent screening mammographic examinations at the University of California San Francisco (UCSF) Mobile Mammography Screening Program from April 1985 through September 1995. The program offers low-cost community-based screening mammography to asymptomatic women in six counties in the San Francisco Bay Area. The 302 women with a history of breast cancer or mastectomy were excluded from all analyses reported here. Approval for these analyses was obtained from the UCSF Committee on Human Research.

Measurements at the Time of Screening

Screening procedures have been described in detail (*10,11*). In brief, mammography is performed in a mobile van staffed by three certified radiologic technologists. For each woman, a breast cancer risk profile and clinical history are obtained by interviews conducted by the technologists as well as two standard mammographic views per breast on an accredited, dedicated mammography unit (Mamex DC or Instrumentarium Alpha III). The breast cancer risk profile and clinical history include questions about: 1) personal history of breast cancer, 2) age at menarche, 3) age at birth of first child, 4) self-reported height and weight, 5) history of breast surgery, and 6) family history of breast cancer (*12*). Women are considered to have a family history of breast cancer if they have had at least one first-degree relative (mother, sister, or daughter) with breast cancer.

At the time of scheduling a screening examination, women who report breast symptoms are referred for diagnostic mammography. Screening mammographic evaluations do not include a complete breast physical examination, but women are again questioned regarding breast lumps at the time of the screening examination. Women are classified as reporting a palpable mass if they or their physicians had noted a lump or if the radiologic technologist noted a lump at the time of the screening examination. We could not discern whether a report of a palpable mass was the result of a screening clinical breast examination, in which case a woman would be considered asymptomatic, or if woman had reported a breast lump to her physician, in which case the woman would be considered symptomatic. Nor did we determine whether a report of a palpable mass in a specific breast was associated with a subsequent diagnosis of breast cancer in the same breast. Thus, a report of a palpable mass was evaluated as a potential risk factor for subsequent diagnosis with DCIS or invasive cancer in either breast.

Screening examinations are read by board-certified radiologists with additional training in reading mammographic films. Mammographic interpretations are reported as normal or abnormal, with women in the latter group requiring additional diagnostic evaluation to exclude cancer. Breast lesions were described according to which breast (i.e., right or left) and one of the following nine locations: upper, upper outer, outer, lower outer, lower, lower inner, inner, upper inner, and retroareolar.

Follow-Up of Abnormal Mammographic Examinations

Clinical outcomes for all women with abnormal screening examinations are determined by contacting the woman's personal physician and searching the UCSF pathology and radiology databases. One month after an abnormal examination, physicians are sent a standardized request for information regarding subsequent diagnostic procedures performed to evaluate abnormal mammography and the clinical outcome. If physicians do not respond to the mailed request, they are contacted by telephone. Monthly computer-generated requests for information from physicians have resulted in nearly complete follow-up (99.5%) for all abnormal screening examinations (*11,13,14*). Women were considered to have breast cancer if biopsy results showed DCIS or invasive carcinoma. For the present analyses, women with abnormal screening examinations from April 1985 through March 1992 were also linked to the Surveillance, Epidemiology, and End Results (SEER)[1] regional tumor registry to verify cancer outcomes. The linkage was limited to mammography data collected through March 1992 because reporting of cancer to the SEER program for any given year is only considered to be complete 2-3 years later. Tumor size was obtained from pathology reports for all types of breast tumors. If tumor size was not specifically stated in the pathologic report, it was estimated to be the greatest dimension

measured at mammography. Less than 5% of tumor sizes were obtained from mammography.

Data Analysis

Age-adjusted frequency distributions of various risk factors were determined for women diagnosed with DCIS, those diagnosed with invasive breast cancer, and women without disease. The two-sample *t* test was used to compare means, the chi-squared and Fisher's exact tests were used to compare proportions, and the Wilcoxon two-sample test was used to compare tumor size by type of cancer, with statistical significance reported for two-sided tests.

Since we were interested in comparing risk factors associated with two different disease outcomes (DCIS and invasive cancer), a multivariate analysis was performed with the use of polytomous logistic regression. Polytomous logistic regression is an extension of dichotomous logistic regression but incorporates more than one disease outcome. Risk factors among women with each disease outcome are compared simultaneously with factors among those women without disease to calculate odds ratios (ORs) for predictors of each outcome. All variables included in the model have been reported to be risk factors for invasive breast cancer. Age was analyzed as a continuous variable and the remaining factors as dichotomous variables. The Wald statistic was used to determine whether the ORs for various risk factors ascertained from the polytomous model differed significantly between women with invasive cancer and those with DCIS. In addition, we expressed the difference for various risk factors between women with invasive cancer and those with DCIS as an OR and a 95% confidence interval (CI). Because of several interactions with age and other risk factors reported in the literature, a separate polytomous model was performed for women aged 30-49 years old and for women aged 50 years and older. For women aged 30-49 years, the variable hysterectomy was not included in the polytomous model, since too few women with DCIS had undergone hysterectomy to perform a statistically valid comparison with those with invasive cancer. To determine whether including women who reported a palpable mass might influence the results, we analyzed the data including and excluding these women. The results were similar in the two analyses; thus, the results reported here are for all women who underwent screening.

Results

From April 1985 through September 1995, 39 844 women aged 30 years and older underwent screening mammographic examination. We excluded 302 (0.8%) women because they reported a history of breast cancer and/or had undergone mastectomy, leaving 39 542 women in the analysis. As a result of the follow-up of women with mammographic examinations interpreted as abnormal, 102 cases of DCIS and 263 cases of invasive breast cancer were detected. Ninety-four percent of breast cancers identified through the Mobile Mammography Van computerized follow-up system were reported to the SEER tumor registry; of the 15 tumors not reported to the registry, four (27%) were DCIS and 11 (73%) were invasive cancer. Similarly, 95% of the tumors identified through the SEER tumor registry were identified through the Mobile Mammography Van program; of the tumors not identified through the van program, three (25%) were DCIS and nine (75%) were invasive cancer. The distribution of breast cancer by age and various risk factors is shown in Table 1. DCIS accounted for 102 (28%) of the 365 breast tumors detected; 45 (41%) of the 110 breast cancers detected among women aged 30-49 years were DCIS compared with 57 (22%) of the 255 breast cancers among women aged 50 years and older.

Women diagnosed with DCIS were significantly younger than women diagnosed with invasive breast cancer (mean age ± standard deviation; 53.7 years ± 12.0 years versus 59.2 years ± 12.0 years; *t* test, $P < .001$). Also, a greater proportion of women with DCIS reported no palpable mass (96 [94.1%] of 102 women) compared with those diagnosed with invasive breast cancer (212 [80.6%] of 263). For women of all ages, the majority of DCIS (85 [83.3%] of 102 women) and invasive tumors (196 [74.5%] of 263) were less than 20 mm in diameter, but a greater proportion of DCIS (73 [71.6%] of 102) than invasive lesions (94 [35.7%] of 263) was 10 mm in diameter or smaller (Table 2). When the 57 women who reported having a palpable mass were excluded, those with DCIS still had smaller lesions than those with invasive cancer (woman aged 30-49 years: median 6.5 versus 12 mm, Wilcoxon test, $P = .03$; women aged 50 years and older: median 8.5 versus 12 mm, Wilcoxon test, $P = .03$). The distribution of DCIS and invasive cancer in the breast was similar, with the majority of DCIS and invasive cancer detected in the upper (11 [10.8%] of 102 women and 26 [9.9%] of 263 women, respectively), upper outer (48 [47.1%] of 102 women and 113 [43.0%] of 263 women, respectively), and retroareolar (10 [9.8%] of 102 women and 37 [14.1%] of 263 women, respectively) areas.

Polytomous Models For DCIS and Invasive Breast Cancer

Separate polytomous models were constructed for women aged 30-49 years and for women aged 50 years and older. There were no significant interactions in the polytomous models for younger or older women.

Women aged 30-49 years. Increasing age and family history of breast cancer were associated with an increased risk of both DCIS and invasive breast cancer. Elevated body mass index ($\geq$25 kg/m^2) showed a statistically significant negative association with DCIS and a trend in the same direction bordering on statistical significance for invasive cancer (Table 3). Palpable mass was the strongest independent factor associated with the risk of invasive breast cancer. Previous breast surgery, early menarche, and nulliparity or late age at birth of first child were not associated with statistically significant increases in the risk of DCIS or invasive cancer.

Women aged 50 years and older. Increasing age was associated with an increased risk of invasive cancer, and there was a trend in the same direction bordering on statistical significance for DCIS (Table 3). Family history of breast cancer and nulliparity or age at birth of first child of 30 years or older were associated with an increased risk of both DCIS and of invasive breast cancer (Table 3). Early menarche and reporting having a palpable mass were associated with an increased risk of invasive cancer but not with risk of DCIS. Previous breast surgery, elevated body mass index ($\geq$25 kg/m^2), and history of hysterectomy were not associated with an increased risk of either DCIS or invasive cancer.

Differences in risk factors for DCIS and invasive breast cancer. Three factors had a different association with invasive cancer compared with DCIS (Table 3). Increasing age, while positively associated with both outcomes, was a stronger risk factor for invasive cancer than for DCIS among women aged 30-49 years (OR = 2.6, 95% CI = 1.0-6.5; $P = .04$); a trend in the same direction bordering on statistical significance was observed for women aged 50 years and older (OR = 1.3; 95% CI = 1.0-1.8; $P = .10$). Among women aged 50 years and older, a palpable mass was associated with an increased risk of invasive cancer but not with risk of DCIS, such that women in this age category who had invasive cancer were approximately eight times more likely to have reported a palpable mass than those with DCIS (OR = 8.7; 95% CI = 1.1-66.0; $P = .04$). Similar findings were observed among women aged 30-49 years: women in

this age category who had invasive cancer were about six times more likely to have reported a palpable mass than those with DCIS (OR = 6.0; 95% CI = 2.1-18.0; P = .001). Among women aged 50 years and older, early menarche was not associated with an increased risk of DCIS but was associated with an increased risk of invasive cancer (OR = 1.9; 95% CI = 1.4-2.7); early menarche had about a twofold greater association with invasive cancer than with DCIS, but this association did not achieve statistical significance (OR = 2.2; 95% CI = 0.9-5.2; P = .08).

Discussion

We evaluated and compared risk factors for DCIS and invasive breast cancer. Among women aged 30-49 years and aged 50 years and older, we found that a family history of breast cancer, an established risk factor for invasive cancer, was associated with an increased risk of DCIS. Among younger women, a body mass index greater than or equal to 25 kg/m^2 was associated with a decreased risk of DCIS; a trend in the same direction bordering on statistical significance was also observed for invasive cancer. Report of a palpable mass was associated with an increased risk of invasive cancer among women in the younger age group and there was a trend in the same direction for DCIS, but the association with invasive cancer versus that with DCIS was much stronger. Among women aged 50 years and older, nulliparity or age at birth of first child of 30 years or older increased the risk of both DCIS and invasive breast cancer. While the presence of a palpable mass was not associated with an increased risk of DCIS among women in the older group, it was strongly associated with an increased risk of invasive cancer. Increasing age was associated with an increased risk of both DCIS and invasive cancer among women in the younger age group, but the association was significantly stronger for invasive disease; among women in the older age group, a stronger association between increasing age and invasive cancer was also observed.

Two case series (*8,15*) have reported the prevalence of a family history of breast cancer in first- and second-degree relatives to be similar among women diagnosed with DCIS and those with invasive cancer, and in two case-control studies (*6,9*), having a family history of breast cancer was positively associated with carcinoma in situ of the breast (DCIS and LCIS combined). In the one case-control study (*7*) that separately examined risk factors associated with DCIS and invasive cancer, having a first- degree relative with breast cancer was the factor most strongly associated with DCIS. We also found that a family history of breast cancer was associated with a diagnosis of DCIS. The ORs that we observed for family history and DCIS among women aged 30-49 years and among women aged 50 years and older are similar to those previously published for invasive breast cancer among younger and older women (*16-18*) and those reported for DCIS among younger women (*7*). Taken together, these data suggest that a family history of breast cancer is associated with the development of DCIS as well as invasive breast cancer.

We also observed an association between DCIS and nulliparity or late age at birth of the first child but only among women aged 50 years and older. In their case-control study involving women aged 45 years and younger, Weiss et al. (*7*) did not observe an association between age at first full-term birth and risk of in situ disease or invasive cancer. Although an interaction between nulliparity or late age at birth of first child and age at breast cancer diagnosis has been reported for invasive breast cancer (*19-21*), this interaction has not been reported previously among women with DCIS. Our observed ORs for nulliparity or late age at birth of first child and both DCIS and invasive cancer among women aged 50 years and older are consistent with previous estimates of relative risk for invasive breast cancer (range, 1.4-1.9) (*17,19-21*).

Among women aged 30-49 years, we found that an elevated body mass index was associated with reduction in risk of DCIS; a trend in the same direction bordering on statistical significance was observed for this factor and invasive cancer. Previous studies (*16,22-25*) have reported reductions in risk of invasive breast cancer ranging from 34% to 60% among young women with higher adiposity, similar to the risk reduction we observed with DCIS. The study by Weiss et al. (*7*), which was limited to women aged 45 years and younger, also showed that elevated body mass index is associated with decreased risk of DCIS. The inverse association of risk with body mass index may be due to delayed detection of breast cancer among women with high body mass index. However, analysis that have accounted for delay in detection suggest that this is unlikely (*23*). A more likely explanation is that women with elevated body mass index tend to have mammographically fatty breasts, while women with low body mass index tend to have mammographically dense breasts (*26,27*). Mammographically dense breasts have been associated with a twofold to three-fold increased

Table 1. Prevalence of risk factors among women with ductal carcinoma in situ (DCIS) and invasive breast cancer and among women without cancer*

Variable	No. of women (%)		
	DCIS (n = 102)	Invasive breast cancer (n = 263)	No cancer (n = 39 177)
Age, y			
30-39	12 (11.8)	8 (3.0)	8903 (22.7)
40-49	33 (32.4)	57 (21.7)	14 556 (37.2)
50-59	25 (24.5)	66 (25.1)	7794 (19.9)
60-69	15 (14.7)	79 (30.0)	5036 (12.9)
⩾70	17 (16.7)	53 (20.2)	2888 (7.4)
Family history of breast cancer†	20 (19.8)	39 (14.9)	3844 (9.8)
Early menarche (<12 y old)	17 (16.8)	57 (21.8)	6148 (15.6)
Nulliparous or ⩾30 y old at birth of first child	62 (62.7)	129 (49.2)	19 705 (50.4)
Previous breast surgery	13 (12.9)	48 (19.8)	4602 (11.5)
Body mass index (⩾25 kg/^{2})	29 (22.9)	91 (27.3)	12 954 (32.7)
Hysterectomy	19 (14.1)	68 (19.5)	6514 (14.0)
Palpable mass	6 (6.1)	51 (27.5)	1861 (3.4)

*Excludes women with a history of breast cancer or mastectomy. Percentages (%) for risk factors other than age are age-adjusted.

†Defined as at least one first-degree relative (mother, sister, or daughter) with breast cancer.

Table 2. Tumor size of ductal carcinomas in situ (DCIS) and invasive breast cancers, by age

Tumor size, mm	No. of women with DCIS (%)		No. of women with invasive breast cancer (%)	
	30-49 y*	⩾50 y†	30-49 y	⩾50 y
⩽10	31 (68.9)	42 (73.7)	22 (33.8)	72 (36.4)
11-19	6 (13.3)	6 (10.5)	22 (33.9)	80 (40.4)
⩾20	8 (17.8)	9 (15.8)	21 (32.3)	46 (23.2)
Total	45 (100)	57 (100)	65 (100)	198 (100)

*Chi-squared; $P<.001$, comparison group women aged 30-49 years with invasive breast cancer.
†Chi-squared; $P<.001$, comparison group women aged 50 years and older with invasive breast cancer.

risk of breast cancer (*27*), which might explain why young women with low body mass index are at increased risk of breast cancer, while young women with high body mass index are at decreased risk.

Contrary to the findings in younger women, we did not find an elevated body mass index to be associated with reduced risk of DCIS (or invasive cancer) in women aged 50 years and older. Studies of body mass index and breast cancer have shown varying results among older women. While case-control studies (*22,28,29*) suggest that elevated body mass index increases the risk of breast cancer, prospective studies (*16,22-25,30,31*) have shown no association between elevated body mass index and breast cancer risk, except possibly among women aged 65 years and older (*32*). No other studies have reported a differential effect between age and elevated body mass index on risk of DCIS.

Most evidence indicates that early menarche is a risk factor for breast cancer at all ages. Consistent with previous reports, we found that the risk of DCIS and invasive breast cancer were increased, although not significantly, in young women who experienced early menarche. However, among women aged 50 years and older, early menarche was associated with an increased risk of invasive breast cancer, but not of DCIS. The inconsistent finding among older women with DCIS may be a chance result, given that the difference in ORs is only marginally statistically significant (Table 3, $P = .08$), or it may indicate that the risk profiles for DCIS and invasive cancer are not exactly the same for older women.

Table 3. Results of multivariate polytomous models comparing associations between various factors and ductal carcinoma in situ (DCIS) versus invasive breast cancer*

Variable	OR (95% CI)		
	DCIS†	Invasive breast cancer†	Invasive breast cancer vs DCIS‡
30-49 y			
Age (per 10 y)	2.3 (1.2-4.6)	6.1 (3.3-11.0)	2.6 (1.0-6.5)
Family history of breast cancer§	2.4 (1.1-4.9)	1.7 (0.9-3.4)	0.8 (0.3-2.0)
Early menarche (<12 y old)	1.5 (0.8-3.1)	1.2 (0.6-2.2)	0.8 (0.3-1.9)
Nulliparous or ⩾30 y old at birth of first child	1.4 (0.8-2.7)	1.1 (0.7-1.8)	0.8 (0.3-1.7)
Previous breast surgery	1.0 (0.4-2.4)	1.4 (0.7-2.7)	1.5 (0.5-4.6)
Body mass index (⩾25 kg/m^2)	0.4 (0.2-0.9)	0.6 (0.3-1.1)	1.6 0.5-4.6)
Palpable mass	2.0 (0.8-5.1)	12.0 (7.1-20.0)	6.0 (2.1-18.0)
⩾50 y			
Age (per 10 y)	1.2 (0.9-1.5)	1.5 (1.3-1.8)	1.3 (1.0-1.8)
Family history of breast cancer§	2.2 (1.0-4.2)	1.5 (1.0-2.2)	0.7 (0.3-1.4)
Early menarche (<12 y old)	0.9 (0.4-2.0)	1.9 (1.4-2.7)	2.2 (0.9-5.2)
Nulliparous or ⩾30 y old at birth of first child	2.3 (1.3-3.8)	1.6 (1.2-2.1)	0.7 (0.4-1.3)
Previous breast surgery	0.9 (0.4-1.9)	1.1 (0.8-1.7)	1.3 (0.6-3.0)
Body mass index (⩾25 kg/m^2)	1.1 (0.6-1.9)	1.0 (0.7-1.3)	0.9 (0.5-1.7)
Hysterectomy	0.9 (0.5-1.5)	1.1 (0.8-1.5)	1.3 (0.7-2.5)
Palpable mass	1.1 (0.2-7.8)	9.3 (6.0-14.0)	8.7 (1.1-66.0)

*Excludes women with a history of breast cancer or mastectomy.
†Odds ratios (ORs) and 95% confidence intervals (CIs) from polytomous model.
‡Ratio of invasive cancer versus DCIS by variable.
§Defined as at least one first-degree relative (mother, sister, or daughter) with breast cancer.

Benign breast disease is a risk factor for invasive breast cancer, primarily among women with proliferative disease and atypia (*17,33,34*). Two case-control studies (*6,7*) have reported an association between previous breast biopsy and DCIS. We did not observe an association between previous breast surgery and DCIS or invasive breast cancer. As defined in our study, women who reported previous breast surgery could have had a previous excisional breast biopsy, breast reduction, or breast implants. For this reason, an association between biopsies for benign breast disease and DCIS may have been masked. The lack of an association between previous breast surgery and breast cancer risk could also occur because the vast majority of breast biopsies performed for clinical reasons show normal breast tissue or nonproliferative disease (*33*). This inference is supported by the weak, nonsignificant association we observed between previous breast surgery and invasive cancer (Table 3). Other studies (*17,33*) have shown that the risk of invasive breast cancer may be twofold to fourfold higher for women with benign breast disease exhibiting proliferative changes than for women with benign breast disease without proliferative changes.

The main differences between risk factors associated with DCIS and those associated with invasive breast cancer are that increasing age was more strongly associated with the risk of invasive cancer than of DCIS for both women aged 30-49 years and women aged 50 years and older, while palpable mass was associated with an increased risk of invasive cancer but not DCIS. That increasing age is more strongly associated with diagnosis of invasive breast cancer than DCIS is supported by our observation that the average age at diagnosis was about 5 years lower (53.7 versus 59.2 years) for women diagnosed with DCIS. These findings are consistent with the notion that at least some DCIS lesions are precursor lesions of invasive cancer. Another indication that DCIS may be a precursor of some invasive cancers is that the DCIS lesions were generally smaller than invasive cancers, and women with DCIS were much less likely to present with a palpable mass. In the event that DCIS is a precursor of some invasive cancers, the distribution of DCIS in the breast should be comparable with that for invasive cancer. Similar to an analysis of the location of DCIS cases reported to the SEER program of the National

Cancer Institute for 1992 (*2*), we found the distribution of DCIS in the breast in our series is similar to that of invasive cancer.

Our study population may not be representative of all women with DCIS and invasive breast cancer in the general population. Our case subjects were primarily asymptomatic women and were all from a program of screening mammography, which would tend to detect smaller, more indolent tumors than found in an unscreened population. Furthermore, women at increased risk for breast cancer may be more likely to undergo screening mammography, have a higher prevalence of breast cancer, and have more risk factors for breast cancer. However, one indication that our population is representative is the fact that 10% of women had a family history of breast cancer, very similar to the prevalence in a large population-based study (*16*) and a large case-control study (*35*). Another indication that the study population is representative is the observation that the age distribution of breast cancers (25% among younger women versus 75% among older women) is similar to the distribution reported by the population-based SEER program (23% versus 77%) (*1*).

A strength of our study in comparison with previous case-control studies (*6,7*) is the determination of potential risk factors before detection of DCIS or invasive breast cancer. Therefore, the associations we present and the strength of these associations may be less likely to be affected by recall bias. We also examined women of all ages, allowing evaluation of interactions previously reported between age and other risk factors for invasive breast cancer. Last, we focused on mammographically detected DCIS, making our results generalizable to the vast majority of DCIS detected today.

Our results suggest that risk factors and the magnitude of their association with DCIS and invasive breast cancer are similar, except that invasive breast cancer is more strongly associated with increasing age and the presence of a palpable mass. These results support the idea that some DCIS cases are precursors of invasive breast cancer. This idea is further supported by our findings that the average age of detection of DCIS lesions is about 5 years lower than for invasive disease, that the distribution of DCIS in the breast is similar to that of invasive cancer, and that DCIS lesions are smaller than mammographically detected invasive cancers. Despite the shared risk factors with invasive cancer, however, one cannot conclude from our data that all invasive cancers are preceded by DCIS or that all DCIS lesions will progress to invasive cancer. Further research is needed to better understand what proportion of DCIS lesions will become invasive breast cancer if left untreated beyond biopsy, whether some will remain dormant as in situ lesions, or whether some will resolve spontaneously over time.

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Notes

[1]*Editors note:* SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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