Breast Carcinoma In Situ: Risk Factors and Screening Patterns

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**Background:** Risk factors associated with invasive breast cancer are well documented, but those associated with breast carcinoma in situ are not well defined. **Methods:** We conducted a population-based, case–control study among female residents of Connecticut to identify risk factors for breast carcinoma in situ. Case patients, diagnosed with ductal carcinoma in situ (DCIS) (n = 875) or lobular carcinoma in situ (LCIS) (n = 123), were matched by 5-year age groups with control subjects (n = 999). Case patients were diagnosed between September 15, 1994, through March 14, 1998, and all subjects were between the ages of 20 and 79 years. Information on risk factors and cancer-screening history was collected by telephone interviews. Conditional logistic regression was used to determine odds ratios (ORs) for the association of these factors with the risk of DCIS and LCIS. **Results:** Case patients with DCIS were more likely than control subjects to report a family history of breast cancer (OR = 1.48; 95% confidence interval [CI] = 1.19 to 1.85) or previous breast biopsy (OR = 3.56; 95% CI = 2.86 to 4.43). They also had fewer full-term pregnancies (OR = 0.86; 95% CI = 0.80 to 0.93) and were older at first full-term pregnancy (OR for being 20–29 years old relative to being <20 years old = 1.68; 95% CI = 1.17 to 2.43) and at menopause (OR for being ≥55 years old relative to being <45 years old = 1.71; 95% CI = 1.05 to 2.77). DCIS case patients were more likely than control subjects to have had a mammographic examination (OR = 2.46; 95% CI = 1.78 to 3.40) or an annual clinical breast examination (OR = 1.83; 95% CI = 1.48 to 2.26). DCIS patients and control subjects did not differ with respect to oral contraceptive use, hormone replacement therapy, alcohol consumption or smoking history, or breast self-examination. Associations for LCIS were similar. **Conclusions:** The risk factors associated with DCIS and LCIS are similar to those associated with invasive breast cancer. Diagnosis of DCIS is associated with increased mammography screening. [J Natl Cancer Inst 2001;93:1811–7]

Mammography-screening efforts have increased; consequently, the number of breast tumors classified as noninvasive has also increased. In particular, up to 20% of breast cancer patients are diagnosed with ductal carcinoma in situ (DCIS) (1). However, few studies have examined the epidemiology of DCIS or lobular carcinoma in situ (LCIS) (2–15), and those that have attempted to define risk factors for DCIS or LCIS have focused on small subsets of case patients with breast carcinoma in situ nested within larger invasive breast cancer case–control studies (3,4,13) or screened cohorts (6,9,14). A population-based study (3) of 1616 breast cancer case patients aged less than 45 years, including 228 case patients with breast carcinoma in situ, reported that DCIS and LCIS were positively associated with many risk factors for invasive breast cancer, including a family history of breast cancer, previous breast biopsy, and nulliparity. A second population-based, case–control study (4) that included 233 case patients with breast carcinoma in situ who were 40 years old and younger or who were between 55 and 64 years old also reported an increased risk of in situ carcinoma with family history of breast cancer and benign breast disease. In premenopausal women, the risk of breast carcinoma in situ decreased with increasing body mass index; in contrast, in postmenopausal women, the risk of breast carcinoma in situ increased with the use of unopposed estrogen replacement therapy. Neither of these factors was associated with an increased risk of invasive disease (4). Additional case–control analyses of cohorts of screened women reported an increased risk of breast carcinoma in situ associated with age (9,14), a

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positive family history of breast cancer (6,9), ethnicity (14), nulliparity (9), a previous breast biopsy (6), and increased age at first live birth (6,9).

Although many risk factors associated with invasive breast cancer may also play a role in the development of breast carcinoma in situ, the results are not consistent, in part because small sample sizes do not allow for precise estimates of risk. Information on screening variables is often not available (4,6,8,9) or is available only on specific populations. The one study to collect information on screening (3) included only case patients under age 45 years.

Here, we undertook a large, population-based study specifically designed to examine the association between breast cancer risk factor history and a diagnosis of breast carcinoma in situ across a spectrum of ages and histologies and incorporating cancer-screening data.

PATIENTS AND METHODS

Case Patients and Control Subjects

All case patients with breast carcinoma in situ diagnosed among female residents of Connecticut from September 15, 1994, through March 14, 1998, were included in this study. Case patients, aged 20–79 years at the time of diagnosis, were identified through the rapid-case-ascertainment shared resource of the Yale Cancer Center (Yale University, New Haven, CT). Control subjects were female Connecticut residents selected by random-digit-dialing methods by an outside consulting firm (Northeast Research, Oremo, ME). Control subjects were frequency matched by 5-year age groups to the case patients. The study, consent forms, and questionnaire were approved by the Human Investigation Committee of Yale University School of Medicine. All subjects provided verbal consent to be interviewed over the telephone. Medical records and pathology slides were reviewed only after the participants had provided written, informed consent.

We contacted the physician of each eligible case patient to request permission to approach the case patient. After receiving consent from the physicians, we sent case patients and control subjects, identified by Northeast Research, a letter of introduction describing the study and inviting them to participate. Before the interview, potential study subjects were sent an oral contraceptive picture booklet developed for the Harvard University Nurses’ Health Study (16) to allow them to review products used in the past. Approximately 1–2 weeks after the letter of introduction and the booklet were sent, a trained interviewer contacted the potential study subject by telephone to conduct the interview. For this study, the majority of case patients were interviewed within 6 months of the date of diagnosis. Subjects were interviewed for an average of 43 minutes. The questionnaire included detailed questions on family history of cancer, pregnancy and menstrual histories, exogenous hormone history, demographics, medical and screening histories, and smoking and alcohol consumption.

Eligible case patients and control subjects were 20–79 years old, were residents of Connecticut, were English speaking, and did not have a history of breast cancer or breast biopsy of unknown outcome. Two hundred forty-one potential case patients were ineligible because they were out-of-state residents (eight patients), were non-English speaking (21 patients), had a history of breast cancer/biopsy of unknown outcome (181 patients), or were older than age 79 years (31 patients). We received consent from the physicians of 91% of the eligible case patients to contact the case patients. Of those whom we contacted, 83% participated in the study. Seventy-four control subjects were ineligible because they were out-of-state residents (three subjects), were non-English speaking (18 subjects), had a history of breast cancer/biopsy of unknown outcome (51 subjects), or were older than age 79 years (two subjects). Among control subjects, the initial household-screening response rate when approached by Northeast Research was 85.7%. Of those whom we contacted, 81% agreed to be interviewed. The final study population included 1668 case patients and 999 control subjects, with overall estimated response rates of 76% and 70% for case patients and control subjects, respectively.

The pathology reports of all case patients were reviewed by the study pathologist (D. Carter). Case patients were grouped according their pathologic diagnosis as either DCIS (n = 875) or LCIS (n = 123) patients. Case patients with mixed or other pathologic conditions (i.e., both DCIS and LCIS, invasive cancer, or no identifiable disease) (n = 70) were excluded from these analyses. Information on breast cancer risk factors and screening was truncated at the date of diagnosis for case patients and the date of interview for control subjects (hereafter referred to as the “reference date”). Data on screening variables included information on routine checkups, clinical breast examinations, breast self-examinations, Pap smears, and mammograms. For each of the screening methods, respondents were asked to provide their age at first screening. For the determination of the usual screening behavior of study subjects, respondents were asked to provide the date of their most recent screening and the frequency of each screening in the 5-year time period 1 year before the reference date. This information was used to construct two mammography-screening variables: 1) the existence of at least one mammographic examination in the 5-year period 1 year before the reference date and 2) the number of mammographic examinations in the 5-year period 1 year before the reference date (coded as 0, 1, or 2). Study subjects were also asked how many breast lesions were found (i.e., by mammography or other means).

Statistical Analysis

The initial portion of the statistical analysis included descriptive statistics. Student’s t tests and chi-square tests were used to examine the association between the risk of breast carcinoma in situ and independent covariates. To assess the relative risk of breast carcinoma in situ associated with risk factors, we used conditional logistic regression to provide maximum likelihood estimates of the odds ratios (ORs) (adjusted and unadjusted) with 95% confidence intervals (CIs). All statistical analyses were performed with PC-SAS version 6.11 (17). Relative risk estimates were adjusted for age, college education (yes/no), history of at least one screening mammogram in the 5-year period 1 year before the reference date, body mass index (i.e., weight in kilograms divided by height in meters, squared), and ethnicity (white/other) and were mutually adjusted for other statistically significant risk factors in the logistic model. All reported P values were two-sided.

RESULTS

To determine the risk factors associated with breast carcinoma in situ, we conducted a population-based, case-control study. Approximately 92% of the case patients and control subjects were white, 6.5% were African-American, and the remaining 1.5% were of other ethnicities (Table 1). The mean age ± standard error of the case patients and control subjects was similar (56.6 ± 11.4 years for DCIS case patients, 54.7 ± 9.5 years for LCIS case patients, and 55.7 ± 12.1 years for control subjects). There was a difference, however, in the level of education, with 33% of case patients being college educated versus 29% of control subjects. Among DCIS case patients, 65% reported discovery of their lesion by mammogram, 8% reported discovery by breast self-examination, and 10% reported discovery by a clinical breast examination. Among LCIS case patients, 60% reported discovery of their lesion by mammogram, 11% reported discovery by breast self-examination, and 10% reported discovery by a clinical breast examination. The remaining DCIS and LCIS lesions were discovered by a variety of means, including accidentally by one-self or by a partner.

We examined cancer-screening history to determine the extent to which the identification of risk factors for carcinoma in situ might be confounded by screening practices. The proportions of women who participated in various breast cancer-screening procedures is presented in Table 2. DCIS case patients were more likely than control subjects to report having had at least one mammographic examination 1 year before the reference date (OR = 2.46; 95% CI = 1.78 to 3.40) and annual clinical breast examinations (OR = 1.83; 95% CI = 1.48 to 2.26) but were as likely as control subjects to have performed breast self-examinations (OR = 1.01; 95% CI = 0.84 to 1.21). The percentage of women under 45 years of age who reported ever having had a mammographic examination was greater for DCIS case patients (78%) than for control patients.
LCIS case patients were more likely than control subjects to report having an annual clinical breast examination (OR = 2.37; 95% CI = 1.44 to 3.90) but not statistically significantly more likely to report having a mammographic examination (OR = 1.81; 95% CI = 0.92 to 3.55) or to having performed breast self-examinations (OR = 0.89; 95% CI = 0.61 to 1.31).

We next determined the association between known breast cancer risk factors and screening procedures (Table 3). Women with a family history of breast cancer among first-degree relatives were more likely to report having had a mammographic examination (OR = 2.4; 95% CI = 1.4 to 3.9) or an annual clinical breast examination (OR = 1.4; 95% CI = 1.0 to 1.8) than were women with no family history of breast cancer. Furthermore, among women with a positive family history of breast cancer, those with an affected mother (OR = 3.20; 95% CI = 1.55 to 6.60) were more than twice as likely to report having had at least one mammographic examination compared with those with an affected sister (OR = 1.47; 95% CI = 0.76 to 2.86). White women were more likely than nonwhite women to report having had a mammographic examination, equally likely to report having had an annual clinical breast examination, and less likely to report having performed a breast self-examination (Table 3). Women who reported having had at least one breast biopsy also reported a higher incidence of all three screening modalities than women without breast biopsy.

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such a history. Women who received hormone replacement therapy (HRT) were approximately four times more likely to report having had a mammographic examination (OR = 4.1; 95% CI = 2.8 to 5.9) and approximately two times more likely to report having had an annual clinical breast examination (OR = 2.2; 95% CI = 1.8 to 2.8) compared with women who did not receive HRT. College-educated women were more likely than non-college-educated women to report having had an annual clinical breast examination, but they were equally likely to report having had a mammographic examination or having performed a breast self-examination.

Multivariate-adjusted ORs for various risk factors among women with breast cancer are presented in Table 4. Among women with LCIS, case patients were more likely than control subjects to report older age at menopause, to report having had at least one breast biopsy, and to report having had an annual clinical breast examination. Although the data were too sparse to examine the relationship between family history of breast cancer and the age at onset of LCIS, an association between family history of breast cancer and a diagnosis of LCIS was suggested that did not reach statistical significance (P = .07). Table 4 shows that the magnitude and direction of the associations of many risk factors for carcinoma in situ were the same for the two histologic subtypes. However, several risk factors showed a statistically significant association with DCIS but not with LCIS, likely due in part to the smaller number of LCIS patients.

Because of the association between case-control status and mammography, all ORs were adjusted for mammogram history (categorized as having had at least one mammographic examination in the 5-year period 1 year before the reference date). Additional adjustment for other breast cancer-screening procedures did not statistically significantly alter the ORs and were not included in the final model.

The logistic regression analyses were also performed retaining the original frequency-matched study design (5-year age strata); the results obtained were essentially unchanged from those presented in Table 4.

### DISCUSSION

The epidemiology of invasive breast cancer has been studied extensively (18–26). After controlling for age, among those variables that have a relationship with invasive breast cancer, the greatest risk (twofold to threefold) is associated with a positive family history of breast cancer (18–26). Individuals with multiple first-degree family members diagnosed with breast or ovarian cancer, particularly at younger ages, are at even greater risk, and examination of such families has led to the identification of the BRCA1 and BRCA2 breast–ovarian cancer susceptibility alleles (27,28). However, little work has specifically examined the effect of a family history of breast cancer on the risk of breast carcinoma in situ, with existing data hampered by the limitations of small sample size, age at onset, or pathology. Despite these caveats, several studies (3,4,6,9,10) have reported an increased risk of breast carcinoma in situ associated with a family history of breast cancer, with ORs ranging from 1.6 to 2.7, and similar to risks observed for invasive breast cancer. In the current study, which uses a large sample, we calculated ORs of 1.48 and 1.68 for women diagnosed with DCIS and LCIS, respectively, confirming the previous findings (3,4,6,9,10). These values match well to those reported in studies that include similarly aged women (6) but are somewhat lower than those that include younger women (3,4,9). However, when risk was dichotomized by age, we observed an inverse relationship between the age at onset and risk of DCIS associated with a family history of breast cancer and similar to that documented for
invasive breast cancer. Case patients diagnosed before age 50 years had a risk of 2.4, similar to other reports that include younger case patients (3,4,9), versus a risk of 1.4 for case patients diagnosed at age 50 years or older. At present, no study has examined the prevalence of mutations in breast cancer susceptibility alleles, such as BRCA1 and BRCA2, in women with breast carcinoma in situ (29), so the role of these alleles in breast carcinoma in situ is as yet unclear. Although we noted a positive association between family history of breast cancer and the risk of LCIS, similar to that reported elsewhere (3,13), limitations of sample size may have reduced the power to obtain a statistically significant result.

Other variables associated with invasive breast cancer risk include those with endogenous or exogenous hormonal components. The risk of DCIS was also associated with several hormone-related factors. Similar to previous reports, DCIS case patients were more likely than control subjects to be older at first full-term pregnancy (4,6,9–11) and at menopause (4) and to have fewer full-term pregnancies (4,30,31) but not all (32) of
the previous studies reporting an increased risk. It is possible that some of this effect may be the result of increased breast cancer screening among HRT users compared with nonusers because all of the studies mentioned made some attempt to adjust for screening history. To further explore the relationship between exogenous hormones and the development of breast carcinoma in situ, detailed analyses will be presented elsewhere to define the role of age, duration, frequency, composition, and potency of hormone use on this relationship.

Previous studies have associated alcohol consumption (33–35), but not active smoking (36–38), with an increased risk of invasive breast cancer. We found no association between either alcohol consumption or cigarette smoking and the risk of breast carcinoma in situ. To our knowledge, this is the first examination of the effect of these two variables on the risk of breast carcinoma in situ. Further analyses will study whether subsets of these variables are associated with any change in breast carcinoma in situ risk.

A history of breast biopsy is strongly associated with a diagnosis of DCIS or LCIS in our study and in other studies (3,4,6,9,10). The association between benign breast disease and risk of invasive breast cancer is well known. The association reported here between a diagnosis of breast carcinoma in situ and a benign breast disease biopsy is likely due to a combination of factors, including the likelihood that some benign breast disease is associated with the eventual development of breast carcinoma in situ. However, this observed association is also likely a function of increased surveillance and thus early detection. It is not possible at present to quantify the extent to which each of these possibilities plays a role in this association.

There were a number of statistically significant associations between screening patterns and risk factors for breast cancer in situ. At least within the state of Connecticut, women with either a family history of breast cancer or a previous breast biopsy appear to be participating in more intensive screening programs than those without such a family history. Ethnicity was also statistically significantly associated with screening frequency, with white women twice as likely as nonwhite women to report having had a screening mammogram but less likely to report having practiced breast self-examination.

This is of note, given the increased rates of diagnoses of breast carcinoma in situ associated with mammography use but not with breast self-examinations. The risk factor most strongly associated (four-fold) with screening in our data was the use of HRT. Women with this risk factor were almost twice as likely as women with a family history of breast cancer among a first-degree relative to receive a mammographic examination. This finding suggests that, unless screening history is controlled for, results of studies reporting a relationship between HRT use and the risk of DCIS may be confounded by screening variables.

Although the strong association between mammography use and the diagnosis of breast carcinoma in situ makes collection of these data important in any study of the topic, it is necessary to consider a number of potential biases in reporting mammographic history. In particular, women with breast carcinoma in situ may be more likely to report increased numbers and/or a greater frequency of screening because of guilt related to their diagnosis. Researchers should be careful to attempt to collect information on usual screening behavior for both case patients and control subjects and to avoid the collection of information only on the screening mammogram that led to the diagnosis of breast carcinoma in situ for case patients because, once diagnosed, all case patients will have a recent mammographic examination as part of their work-up. Furthermore, to minimize any differences in the recall of screening data, researchers should interview case patients relatively soon after diagnosis.

This study provides evidence that many of the risk factors for DCIS are similar in nature and magnitude to those for invasive breast cancer, suggesting the possibility that some in situ lesions may be a part of the pathway leading to invasive disease. These data represent the largest examination to date of the epidemiology of breast carcinoma in situ across all categories of age and histology. Furthermore, because information on screening was included in all analyses, the estimates of risk presented here should be relatively free of any screening bias, which is particularly important in the analysis of noninvasive tumors that are more likely to be diagnosed at an early stage during screening procedures, such as mammographic examinations.

References

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NOTES

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