Characteristics Associated With Recurrence Among Women With Ductal Carcinoma *In Situ* Treated by Lumpectomy

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Background: **Clinical and histopathologic characteristics that may predict risks of recurrence in women with ductal carcinoma *in situ* (DCIS) have not been consistently identified. We identified factors associated with recurrence as DCIS versus invasive breast cancer and determined the 5-year absolute risks of recurrence as a function of these factors.** ***Methods:*** **We conducted a population-based cohort study among 1036 women in the San Francisco Bay Area who were aged 40 years or older when diagnosed with DCIS and treated by lumpectomy alone from January 1983 through December 1994. Standardized pathology reviews were conducted to determine disease recurrence, defined as DCIS or invasive breast cancer diagnosed in the ipsilateral breast containing the initial DCIS lesion or at a distant site more than 6 months after the initial diagnosis and treatment of DCIS. Conditional logistic regression models were used to determine factors associated with recurrence. All statistical significance tests were two-sided.** ***Results:*** **During a median follow-up of 77.9 months, 209 women (20.2%) experienced a recurrence. Overall, the 5-year risks of recurrence as invasive cancer and as DCIS were 8.2% (95% confidence interval [CI] = 6.6% to 9.8%) and 11.7% (95% CI = 9.9% to 13.3%), respectively. The 5-year risks of recurrence as invasive cancer and as DCIS were 4.8% (95% CI = 3.7% to 6.8%) and 4.8% (95% CI = 3.8% to 5.8%), respectively, for women with low-nuclear-grade DCIS; 11.8% (95% CI = 9.9% to 14.1%) and 17.1% (95% CI = 15.5% to 18.7%), respectively, for women with high-nuclear-grade DCIS; 11.6% (95% CI = 11.3% to 12.0%) and 8.6% (95% CI = 7.1% to 10.2%), respectively, for women whose initial DCIS lesion was detected by palpation; and 6.6% (95% CI = 6.2% to 7.1%) and 14.1% (95% CI = 11.4% to 17.8%), respectively, for women with DCIS detected by mammography alone. High- (versus low-) nuclear-grade DCIS lesions and detection of the initial DCIS lesion by palpation (versus mammography) were associated with recurrence as invasive cancer. High- (versus low-) nuclear-grade lesions; resection margins that were positive, uncertain, or less than 10 mm disease-free (versus ≥10 mm disease-free); and age 40–49 years at diagnosis (versus ≥50 years) were associated with recurrence as DCIS.** ***Conclusions:*** **Nuclear grade is strongly associated with recurrence but not with the type of recurrence. Women with high-nuclear-grade DCIS or DCIS detected by palpation who are treated by lumpectomy alone are at relatively high risk of having an invasive breast cancer recurrence, compared with women with low-nuclear-grade or mammographically detected DCIS, and may be appropriate candidates for additional treatment. [J Natl Cancer Inst 2003;95:1692–1702]**

Ductal carcinoma *in situ* (DCIS) accounts for 20% of all newly diagnosed cases of breast cancer in the United States and for 17%–34% of all mammographically detected cases *(1–7)*. DCIS has a 10-year mortality of 1%–2%, whereas stage I invasive cancer has a 10-year mortality of 7%–10% *(8–10)*. In 1997, similar proportions of women in the United States with stage I breast cancer and DCIS were treated with mastectomy (36% and 32%, respectively), but a higher proportion of women with stage I disease than women with DCIS received radiation in addition to lumpectomy (50% and 30%, respectively) *(10)*. Although randomized trials that have evaluated various treatments for DCIS were not designed to assess mortality, it is notable that none has demonstrated a difference in breast cancer mortality between DCIS patients treated with lumpectomy and radiation (with or without tamoxifen) and those treated with lumpectomy alone *(11–13)*.

The consensus among DCIS experts is that the goal of treatment for women with DCIS should be breast conservation, with optimal cosmesis and with a minimum risk of a subsequent invasive cancer or DCIS recurrence *(14)*. Our knowledge of clinical and histopathologic characteristics that may predict disease recurrence among women with DCIS is based primarily on non–population-based case series of women with DCIS. Most of those studies included a small number of women with recurrent disease, represented the experience of single institutions, or relied on nonstandard definitions of DCIS with regard to classifying margin status, histologic subtype, nuclear grade, and tumor size. It is therefore perhaps not surprising that no clinical or histopathologic characteristics have been found to be consistently associated with recurrence.

The primary purpose of this study was to examine clinical and histopathologic characteristics, as defined by criteria created by the DCIS Consensus Conference Committee *(15)*, that predict type of recurrence (DCIS or invasive cancer) in a large population-based cohort of women with DCIS who were treated by

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lumpectomy alone. In addition, we determined the absolute risk of recurrence as a function of these factors.

Subjects and Methods

Subjects

The study sample included women who were aged 40 years or older when diagnosed with DCIS and who were treated by lumpectomy alone at one of 63 hospitals located in one of nine greater San Francisco Bay Area counties from January 1983 through December 1994. We did not include women aged 30–39 years in our study (N = 80 potentially eligible women) because most DCIS lesions are detected mammographically and women aged 30–39 years are not recommended for routine screening mammography. We used data from the Surveillance, Epidemiology, and End Results (SEER)[1] program of Northern California to identify 1568 women aged 40 years or older who had reportedly initially received lumpectomy alone; these women represented 42% of all women diagnosed with DCIS in the nine counties of the greater San Francisco Bay Area during the study time period *(10)*. We excluded a total of 229 women who had DCIS that was treated by mastectomy or by lumpectomy and radiation within 6 months of the initial diagnosis, who had a prior diagnosis of breast cancer, who died within 6 months of the initial diagnosis, or whose initial DCIS lesion was found to be invasive cancer on standardized pathology review. Of the 1339 eligible participants, 82 women could not be located, 24 women did not speak fluent English, Cantonese, Spanish, or Russian (the languages we used to conduct the telephone interviews), 193 women refused to participate, and four women had a doctor's request not to be contacted. Thus, the study cohort consisted of 1036 women for an overall participation rate of 77%. If we exclude the 110 women who could not be located, did not speak English, Cantonese, Spanish, or Russian, or had a doctor's request not to be contacted from the total number of eligible subjects, the overall participation rate was 84%.

This study was reviewed and approved by the University of California, San Francisco, Committee on Human Research. Study participants provided verbal and/or written informed consent.

Telephone Interviews

We obtained demographic information and a breast health history from each woman during a 30-minute telephone interview that was conducted in English, Cantonese, Spanish, or Russian from January 1997 through September 1999. To obtain information for women who were deceased or not able to participate in an interview because of illness (n = 169), we interviewed a proxy and/or conducted a medical record review. The interview included questions about breast procedures a woman had undergone, family history of breast cancer, reproductive history, mode of DCIS detection, menopausal status and self-reported height and weight at the time of DCIS diagnosis, and history of oral contraceptive use and postmenopausal hormone therapy before and after the initial DCIS diagnosis. Women aged 40–54 years at the time of initial DCIS diagnosis were considered to be postmenopausal if both of their ovaries had been removed, if their menstrual periods had stopped permanently (no menstruation for at least 6 months), or if they were using postmenopausal hormone therapy. If interview or chart review information was missing, women aged 55 years or older at the time of initial DCIS diagnosis were considered to be postmenopausal and those younger than 55 years were categorized as having an unknown menopausal status.

Standardized Pathology Review

Paraffin-embedded tissue samples and/or hematoxylin–eosin-stained slides of DCIS tissue were requested from the original pathology laboratories for all women who had disease recurrence (case subjects) and for a random sample of women who did not have disease recurrence (control subjects); two control subjects were matched by year of diagnosis to each case subject. There were no statistically significant differences in the demographic or breast health history characteristics between the control subjects selected for standardized pathology review and those not selected (data not shown). Disease recurrence was defined as DCIS or invasive breast cancer diagnosed in the ipsilateral breast that contained the initial DCIS lesion or at a distant site more than 6 months after the initial diagnosis and treatment of DCIS. For all analyses, women who had both DCIS and invasive cancer in tissue samples of recurrent disease were categorized as having a recurrence as invasive cancer. To classify a woman as having recurrent disease, we investigated the nature of all breast procedures reported by the woman during the telephone interview and obtained pathology reports for breast biopsies performed after the initial diagnosis. In addition, we obtained the death certificates for all deceased women to determine if the cause of death was metastatic breast cancer. Women who developed only contralateral breast cancer during the study period were included in the study as control subjects.

We reviewed the hematoxylin–eosin-stained slides to verify the initial diagnoses of DCIS and to verify the diagnoses of recurrent disease. If the slides we requested were inadequately prepared, destroyed, or not released, we used the paraffin-embedded tissue samples to prepare additional slides. We obtained 79% of the original slides or blocks for initial events and 84% of the original slides or blocks for recurrent events. A total of 45% of case (N = 65) and control (N = 131) subjects had additional tissue excised within 6 months of lumpectomy (re-excision). We performed pathology review of the re-excision specimens for 89% of these case and control subjects to accurately estimate tumor margins and tumor size. Histopathologic evaluation of case and control subjects was based on consensus committee recommendations for the classification of DCIS *(15)* and performed by study pathologists (I. Cha or B.-M. Ljung) who were blinded to the clinical outcome. Agreement of at least 80% on identification of histopathology characteristics was established on a training set of DCIS cases prior to reviewing study cases. Disagreements were resolved by consensus.

Nuclear grade, type and quantity of necrosis, cell polarity, architectural growth pattern, and type of calcification were classified according to consensus definitions *(15)*. We estimated lesion size by directly measuring the largest dimension on the slide showing the most extensive disease. In addition, if DCIS was present on more than one slide, we took into account the number of slides containing DCIS of the total number of slides available to estimate lesion size. When DCIS was present on more than one slide, we assumed that each section was 0.3 cm

in thickness and multiplied the number of slides that contain DCIS by 0.3 cm. The larger of these two measurements was used to estimate lesion size. In some cases, not all of the original slides for a specimen were available for review, and the sequence of the slides relative to the gross specimen was not always known. Thus, the lesion sizes we report here are best estimates, given the available pathology material and information.

Tumor margin width was determined by direct measurement of the smallest single distance between the edge of the tumor and the inked tumor margin or cautery artifact. Margins were considered positive if there was ink on the tumor. Tumor margins were classified as uncertain if margin status was unknown or could not be assessed. Tumor margins in women who underwent re-excision and in whom no additional DCIS was found were reported as being at least 10 mm in width.

Statistical Analysis

All statistical significance tests were two-sided. We used Cox proportional hazards models to determine relative risks (RRs) for various clinical factors among women in the cohort who recurred compared with women who did not recur and Wald's statistic to calculate *P* values for these comparisons. The data were found to conform to proportional hazards assumptions. Univariate conditional logistic regression models were used to determine histopathologic predictors of recurrence among case and control subjects. We dichotomized pathologic lesion size at 10 mm so that our results could be compared with those of other studies *(16–19)*. We used multivariate conditional logistic regression models to determine independent clinical and histopathologic predictors of recurrence and type of recurrence (DCIS versus invasive cancer). We had 80% statistical power to calculate odds ratios (ORs) of 2.2 or larger for histopathologic characteristics associated with a DCIS recurrence and ORs of 2.3 or larger for histopathologic characteristics associated with a recurrence as invasive cancer for characteristics that had a prevalence of 25% or greater among the control subjects.

To estimate the 5-year probability of recurrence for the population-based cohort by clinical and histopathologic characteristics, the results of the matched case–control study were converted to Kaplan–Meier survival curves as described in the "Appendix." Recurrence as invasive cancer and recurrence as DCIS are competing events. To adjust for the competing risks, we used a conditional probability function *(20)*. This function results in a monotone increasing function defined as the probability of a recurrence of interest by time *t* given the absence of a recurrence of non-interest by time *t* (*see* "Appendix" for more details).

Because there were only 10 deaths due to breast cancer during the follow-up period (January 1983 through September 1999) among the 1036 women in the cohort, we were only able to estimate a woman's chance of dying of invasive breast cancer during the 10 years after a DCIS diagnosis. We calculated this for women whose initial DCIS lesion was detected by palpation versus those whose lesion was detected by mammography and for women with high-, intermediate-, or low-nuclear-grade DCIS lesions according to the decade of age at diagnosis. To estimate a woman's risk of dying of invasive breast cancer during the next 10 years, we used the Markov model described in the "Appendix," and in the model we used the estimated 5-year probabilities of recurrence as invasive cancer calculated as noted above and the reported age-specific 10-year probabilities of dying of breast cancer among women newly diagnosed with invasive cancer from 1992 through 1998 by the SEER program *(10)*. For the Markov model, we assumed that the probability of recurrence as invasive cancer was constant over time (Fig. 1).

Results

Absolute Risks of Recurrence

From January 1983 through September 1999, 209 of the 1036 women in our study cohort (20.2% overall) developed a recurrence (median follow-up = 77.9 months); 112 women (10.8%) had recurrence as local DCIS, 71 women (6.9%) had recurrence as local invasive cancer, 19 women (1.8%) had recurrence as regional invasive cancer, and seven women (0.7%) had recurrence as distant invasive cancer. Among the 97 women who had recurrence as invasive cancer, 10 women died of metastatic breast cancer. The 5-year risk of recurrence as invasive cancer was lower than the 5-year risk of recurrence as DCIS (8.2%, 95% CI = 6.6% to 9.8% versus 11.7%, 95% CI = 9.9% to 13.3%) (Fig. 1).

Univariate Results of Clinical Factors Associated With Recurrence

All recurrences combined. Women aged 40–49 years were at increased risk of a recurrence as either DCIS or invasive cancer compared with women aged 70 and older, but the increase was of borderline statistical significance (OR = 1.4, 95% CI = 1.0 to 2.1; *P* = .05) (Table 1). Body mass index, use of hormone replacement therapy before or after the initial DCIS diagnosis, oral contraceptive use, family history of breast cancer, menopausal status, race/ethnicity, and DCIS detection method were not associated with recurrence. We obtained similar results when we repeated this analysis excluding women for whom we obtained information by proxy.

Invasive cancer recurrences compared with DCIS recurrences. Compared with women whose initial DCIS lesion was detected by mammography, women whose initial DCIS lesion was detected by palpation were at increased risk of recurrence as invasive cancer (OR = 2.7, 95% CI = 1.2 to 6.1). Women aged

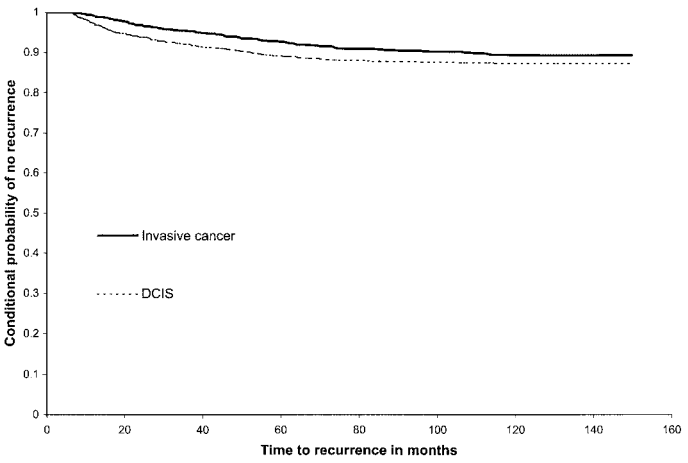

Fig. 1. Competing risk plot of the conditional probability of a recurrence as ductal carcinoma *in situ* (DCIS) and as invasive cancer.

Table 1. Prevalence of risk factors among women initially treated for ductal carcinoma *in situ* (DCIS) by lumpectomy alone according to recurrence (DCIS or invasive cancer) status*

Variable†	No recurrence, % (N = 827)	Recurrence, % (N = 209)	Relative risk (95% CI)	P‡
Age at diagnosis, y				
40–49	21	30	1.4 (1.0 to 2.1)	.05
50–59	25	24	1.0 (0.7 to 1.5)	.9
60–69	23	20	0.9 (0.6 to 1.3)	.5
≥70	31	26	1.0 (referent)	
Race/ethnicity§				
White	78	80	1.0 (referent)	
African American	7	7	1.0 (0.6 to 1.8)	.9
Hispanic	8	8	1.0 (0.6 to 1.7)	.9
Asian	7	5	0.7 (0.3 to 1.2)	.2
Family history of breast cancer§‖				
Negative	74	69	1.0 (referent)	
Positive	26	31	1.2 (0.9 to 1.7)	.2
Menopausal status§				
Postmenopausal	83	78	1.0 (referent)	
Premenopausal	17	22	1.3 (0.9 to 1.8)	.13
Oral contraceptive use§¶				
No	61	50	1.0 (referent)	
Yes	39	50	1.4 (1.0 to 1.9)	.09
Postmenopausal hormone therapy before diagnosis§				
No	59	63	1.0 (referent)	
Yes	41	37	0.9 (0.7 to 1.3)	.7
Postmenopausal hormone therapy after diagnosis§				
No	75	73	1.0 (referent)	
Yes	25	27	1.0 (0.7 to 1.4)	1.0
Body mass index, kg/m^2§				
<25	65	69	1.0 (referent)	
≥25	35	31	0.9 (0.7 to 1.2)	.6
Detection method§#				
Mammography	81	79	1.0 (referent)	
Palpation	19	21	1.2 (0.9 to 1.8)	.3

*Excludes women with a history of breast cancer and women who had radiation therapy or mastectomy. CI = confidence interval.

†Missing data: 2.5% for race/ethnicity, 15.8% for family history, 1.4% for menopausal status, 11.6% for oral contraceptive use, 10.3% for postmenopausal hormone therapy before diagnosis, 12.0% for postmenopausal hormone therapy after diagnosis, 9.1% for body mass index, and 16.7% for detection method.

‡Two-sided; calculated with Wald statistic.

§Relative risk was age-adjusted.

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

¶Oral contraceptives or hormone injections for contraception.

#Palpable mass found by the woman or by her physician upon physical examination.

Table 2. Univariate results of histopathologic factors associated with recurrence (ductal carcinoma *in situ* or invasive cancer)

Factor*	Control subjects, %† (N = 279)	Case subjects, %† (N = 152)	Odds ratio (95% confidence interval)	P‡
Tumor size				
>10 mm	28	39	1.7 (1.1 to 2.6)	.02
≤10 mm	72	61	1.0 (referent)	
Margins				
Positive	25	35	3.0 (1.5 to 6.1)	.002
Uncertain	21	26	2.9 (1.4 to 5.9)	.004
1–1.9 mm disease-free	21	19	2.1 (1.0 to 4.5)	.05
≥2 to <10 mm disease-free	8	8	2.4 (0.9 to 6.1)	.08
≥10 mm disease-free	25	12	1.0 (referent)	
Nuclear grade§				
High	34	55	3.8 (2.0 to 7.3)	<.001
Intermediate	35	32	2.1 (1.1 to 3.9)	.02
Low	31	13	1.0 (referent)	
Necrosis type				
Comedo	39	47	1.3 (0.9 to 2.1)	.2
Focal/punctuate	61	53	1.0 (referent)	
Quantity of necrosis				
Extensive	18	28	1.7 (1.1 to 2.8)	.03
Moderate/scant	82	72	1.0 (referent)	
Cell polarity‖				
Poor	48	67	2.7 (1.3 to 5.7)	.008
Moderate	35	24	1.4 (0.6 to 3.0)	.4
Good	17	9	1.0 (referent)	
Architectural growth pattern§				
Cribriform	41	33	0.7 (0.3 to 1.9)	.5
Solid	42	52	1.1 (0.4 to 2.7)	.9
Micropapillary	8	6	0.7 (0.2 to 2.4)	.7
Papillary	6	8	1.0 (referent)	
Clinging	3	1	Not calculable	
Calcification				
Psammomatous	16	9	0.6 (0.3 to 1.3)	.2
Dystrophic	41	50	1.2 (0.7 to 2.0)	.4
Other	12	12	1.1 (0.6 to 2.3)	.7
None	31	29	1.0 (referent)	

*Missing data: 2.1% for tumor size, 6.5% for margins, 7.4% for nuclear grade, 8.1% for type of necrosis, 0.2% for extent of necrosis, 8.6% for cell polarity, 8.4% for architectural growth pattern, and 8.4% for calcification.

†Control subjects were a random sample of women with ductal carcinoma *in situ* who did not have disease recurrence and were matched by year of diagnosis to the case subjects, who were women who had disease recurrence.

‡Two-sided; calculated with likelihood ratio test.

§For lesions with more than one type of nuclear grade, an overall grade was assigned according to the highest grade present. For lesions with more than one type of architectural growth pattern, an overall pattern was assigned according to the pattern present in the highest percentage. If equal percentages of two or more growth patterns were present, the pattern associated with the lowest number was selected for the overall pattern: cribriform (1), solid (2), micropapillary (3), papillary (4), or clinging (5).

‖Cell polarity is the degree of radial orientation of the apical portion of tumor cells toward intercellular (lumen-like) spaces.

40–49 years versus those aged 70 years or older and women who were premenopausal versus those who were postmenopausal were at an increased risk of recurrence as DCIS (OR = 2.3, 95% CI = 1.1 to 4.6 and OR = 1.9, 95% CI = 1.0 to 3.7, respectively) (data not shown).

Univariate Results of Histopathologic Factors Associated With Recurrence

All recurrences combined. An increased risk of a recurrence as DCIS or invasive cancer was associated with initial DCIS lesions that were larger than 10 mm, had positive or uncertain margins, were of high or intermediate nuclear grade, or had extensive necrosis or poor cell polarity (Table 2). Necrosis type, architectural growth pattern, and type of calcification were not associated with recurrence. The 5-year risks of recurrence for women with high-nuclear-grade lesions and women with low-nuclear-grade lesions were 25.2% (95% CI = 23.0% to 27.4%) and 9.3% (95% CI = 7.8% to 11.0%), respectively (Fig. 2), and the risk of recurrence remained higher for women with high-nuclear-grade lesions than for women with low- and intermediate-nuclear-grade lesions for at least 10 years after initial DCIS diagnosis. The 5-year risks of recurrence for women with pos-

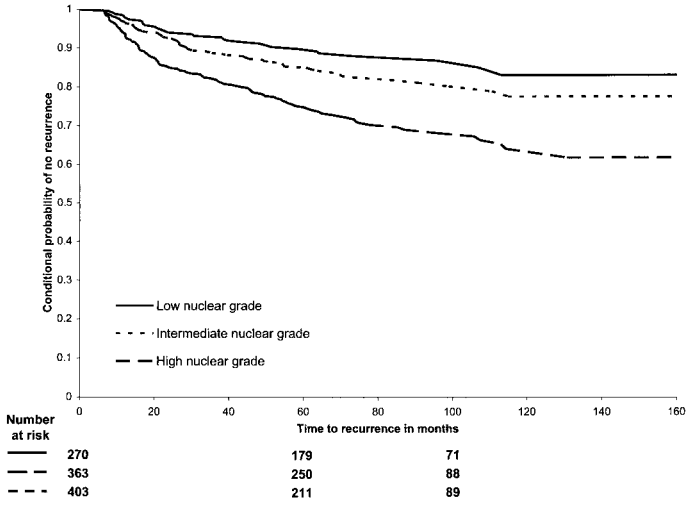

Fig. 2. Kaplan–Meier curves, generated from simulations (*see* Appendix), showing the proportion of women free of recurrence (as either ductal carcinoma *in situ* [DCIS] or invasive cancer) according to the nuclear grade of the initial DCIS lesion.

itive margins and women with disease-free margins of 10 mm or larger were 23.0% (95% CI = 20.2% to 26.0%) and 9.0% (95% CI = 7.2% to 11.1%), respectively (Fig. 3).

Invasive cancer recurrences compared with DCIS recurrences. Women who had high-nuclear-grade DCIS lesions had an increased risk of recurrence as invasive cancer compared with women who had low-nuclear-grade lesions (OR = 2.3, 95% CI = 0.9 to 5.6) (data not shown). Women who had DCIS lesions with psammomatous calcifications had a decreased risk of recurrence as invasive cancer compared with women who had DCIS lesions with no calcifications (OR = 0.3, 95% CI = 0.1 to 0.9) (data not shown).

Risk of recurrence as DCIS was elevated for women with high- and intermediate-nuclear-grade lesions versus those with low-nuclear-grade lesions (OR = 6.3, 95% CI = 2.4 to 16.5 and OR = 2.7, 95% CI = 1.1 to 6.6, respectively; data not shown).

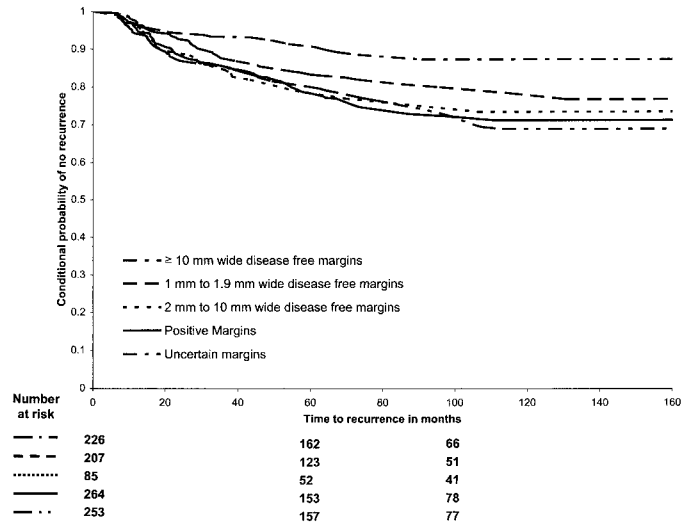

Fig. 3. Kaplan–Meier curves, generated from simulations (*see* Appendix), showing the proportion of women free of recurrence (as either ductal carcinoma *in situ* [DCIS] or invasive cancer) according to tumor margin status.

In addition, the following DCIS lesions were associated with recurrence as DCIS: lesions that were larger than 10 mm versus those 10 mm or smaller on pathology review (OR = 2.1, 95% CI = 1.2 to 3.8), had positive margins versus 10 mm or larger disease-free margins (OR = 5.2, 95% CI = 1.7 to 16.1), had uncertain margins versus 10 mm or larger disease-free margins (OR = 8.4, 95% CI = 2.4 to 29.1), had disease-free margins of 1–1.9 mm versus disease-free margins of 10 mm or larger (OR = 4.5, 95% CI = 1.3 to 15.3), had disease-free margins of 2–9.9 mm versus disease-free margins of 10 mm or larger (OR = 4.3, 95% CI = 1.0 to 18.8), had extensive versus moderate or scant necrosis (OR = 1.9, 95% CI = 1.0 to 3.6), or had poorly developed versus well-developed cell polarity (OR = 3.6, 95% CI = 1.3 to 10.0) (data not shown).

Multivariate Results of Clinical and Histopathologic Factors Associated With Recurrence

Conditional logistic regression analysis showed that positive margins, disease-free margins of 1–1.9 mm, disease-free margins 2 mm or larger but smaller than 10 mm, uncertain margins, and DCIS lesions of high or intermediate nuclear grade were independently associated with recurrence (of DCIS and invasive cancer combined) (Table 3).

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs) from final conditional logistic regression multivariate models of clinical and histopathologic factors independently associated with recurrence*

Variable	Invasive cancer† OR (95% CI)	DCIS‡ OR (95% CI)	Invasive cancer or DCIS§ OR (95% CI)
Age at diagnosis 40–49 y (versus 50 y or older)	NA	2.3 (1.1 to 4.8)	1.4 (0.9 to 2.4)
Detection by palpation (versus mammography)‖	4.9 (1.7 to 14.2)	NA	NA
Margins			
Positive	2.7 (0.7 to 9.4)	6.9 (1.9 to 25.2)	3.5 (1.6 to 7.5)
Uncertain	1.2 (0.4 to 3.5)	11.4 (2.4 to 53.9)	3.0 (1.4 to 6.7)
1–1.9 mm disease-free	0.9 (0.3 to 3.0)	6.5 (1.6 to 26.1)	2.5 (1.1 to 5.9)
≥2 to <10 mm disease-free	1.1 (0.2 to 6.3)	6.6 (1.1 to 38.1)	3.1 (1.1 to 9.0)
≥10 mm disease-free	1.0 (referent)	1.0 (referent)	1.0 (referent)
Nuclear grade			
High	4.5 (1.2 to 16.3)	6.2 (2.0 to 19.1)	4.6 (2.2 to 9.5)
Intermediate	1.8 (0.6 to 6.1)	1.7 (0.6 to 4.5)	2.1 (1.1 to 4.2)
Low	1.0 (referent)	1.0 (referent)	1.0 (referent)
Tumor size >10 mm (versus ≤10 mm)	NA	1.9 (0.9 to 4.1)	NA

*DCIS = ductal carcinoma *in situ;* NA = not applicable because not included in multivariate model.

†Initial model included detection method, margin status, nuclear grade, and type of calcification.

‡Initial model included age, tumor size, margin status, nuclear grade, and cell polarity.

§Initial model included age, tumor size, margin status, nuclear grade, quantity of necrosis, and cell polarity.

‖Palpable mass found by the woman or by her physician upon physical examination.

High-nuclear-grade lesions were independently associated with recurrence as invasive cancer and with recurrence as DCIS (Table 3). The 5-year risk of recurrence as invasive cancer was higher for women with high-nuclear-grade lesions (11.8%, 95% CI = 9.9% to 14.1%) than for those with low-nuclear-grade lesions (4.8%, CI = 3.7% to 6.8%) (Table 4). Recurrence as invasive cancer was more likely in women whose initial DCIS lesions were detected by palpation than in women whose initial DCIS lesions were detected by mammography (OR = 4.9, 95% CI = 1.7 to 14.2) (Table 3). Initial DCIS lesions that were detected by palpation were associated with a high 5-year risk of recurrence as invasive cancer (11.6%, 95% CI = 11.3% to 12.0%) compared with initial DCIS lesions that were detected by mammography (6.6%, 95% CI = 6.2% to 7.1%) (Table 4). Women who were aged 40–49 years at diagnosis were more likely to have a recurrence as DCIS than women who were 50 years or older at diagnosis; women who had positive or uncertain margins, disease-free margins of 1–1.9 mm in width, or disease-free margins of at least 2 mm but less than 10 mm were more likely to have a recurrence as DCIS than women who had lesions with disease-free margins of 10 mm or larger (Table 3). The 5-year risk of recurrence as DCIS was highest for women aged 40–49 years at diagnosis (15.1%, 95% CI = 13.6% to 16.8%), women with high-nuclear-grade lesions (17.1%, 95% CI = 15.5% to 18.7%), and women with DCIS lesions that had positive margins (15.6%, 95% CI = 13.6% to 17.1%) (Table 4). The 5-year risk of recurrence as DCIS was lowest for women with low-nuclear-grade lesions (4.8%, 95% CI = 3.8% to 5.8%) and for women with disease-free margins of 10 mm or larger (3.4%, 95% CI = 2.1% to 4.4%).

Estimated Risk of Death From Breast Cancer

We used the estimates of the risk of recurrence presented in Table 4 to estimate the absolute risk of dying of invasive cancer within 10 years of the initial DCIS diagnosis. The 10-year absolute risk of death was greatest for women who were aged 40 years at diagnosis and whose DCIS was detected by palpation (2.5%, 95% CI = 2.4% to 2.5%) or whose DCIS had a high nuclear grade (2.5%, 95% CI = 2.1% to 3.0%) (Table 5) and lowest for women who were aged 70 years at diagnosis and whose DCIS lesions had a low nuclear grade (0.8%, 95% CI = 0.6% to 1.2%) or were detected by mammography (1.2%, 95% CI = 1.1% to 1.2%) (Table 5). The 10-year absolute risk of death from other causes was greater for women of all ages who had DCIS that was initially detected by mammography than the 10-year absolute risk of death from invasive breast cancer.

Discussion

We examined the clinical and histopathologic characteristics of women with DCIS who were treated by lumpectomy alone to identify which factors were associated with recurrence as DCIS versus recurrence as invasive breast cancer and to determine the 5-year absolute risks of recurrence as a function of these factors. Nuclear grade was the factor most strongly associated with recurrence but was not more strongly associated with recurrence as DCIS than recurrence as invasive cancer or vice versa. Women with high-nuclear-grade DCIS had relatively high 5-year risks of recurrence as invasive cancer and as DCIS of 11.8% and 17.1%, respectively, whereas women with low-nuclear-grade DCIS had relatively low 5-year risks of recurrence as invasive cancer and as DCIS of 4.8% and 4.8%, respectively. Women whose initial DCIS lesion was detected by palpation had a higher risk of recurrence as invasive cancer than women whose DCIS lesion was initially detected by mammography (5-year risks of recurrence of 11.6% and 6.6%, respectively).

Results of recent studies *(11,12,21–28)* of DCIS lesions detected primarily by mammography suggest that the incidence of a subsequent invasive breast cancer for lesions treated by wide excision alone is low. On the basis of these findings, it appears that 5%–10% of DCIS cases have the potential to progress to

Table 4. Estimate of 5-year absolute risk of recurrence for factors independently associated with recurrence*

Variable	Risk of invasive cancer, % (95% CI)	Risk of DCIS, % (95% CI)	Risk of invasive cancer or DCIS, % (95% CI)†
Overall risk	8.2 (6.6 to 9.8)	11.7 (9.9 to 13.3)	17.6 (15.1 to 19.9)
Age at diagnosis, y			
40–49	9.6 (9.2 to 10.2)	15.1 (13.6 to 16.8)	23.2 (17.4 to 28.6)
≥50	7.7 (7.2 to 8.4)	9.3 (7.4 to 11.6)	15.8 (13.2 to 18.4)
Mode of detection			
Palpation‡	11.6 (11.3 to 12.0)	8.6 (7.1 to 10.2)	21.2 (14.5 to 27.5)
Mammography	6.6 (6.2 to 7.1)	14.1 (11.4 to 17.8)	16.8 (13.9 to 19.6)
Margin status			
Positive	10.1 (8.0 to 13.8)	15.6 (13.6 to 17.1)	23.0 (20.2 to 26.0)
Uncertain	8.8 (6.7 to 10.7)	12.8 (10.9 to 14.7)	19.6 (16.8 to 22.6)
1–1.9 mm disease-free margins	7.0 (4.2 to 13.5)	11.3 (9.7 to 13.1)	16.8 (14.5 to 19.7)
≥2 to <10 mm disease-free margins	10.7 (5.7 to 18.2)	13.0 (10.1 to 17.3)	21.4 (16.9 to 27.4)
≥10 mm disease-free margins	6.3 (4.5 to 7.7)	3.4 (2.1 to 4.4)	9.0 (7.2 to 11.1)
Nuclear grade			
High	11.8 (9.9 to 14.1)	17.1 (15.5 to 18.7)	25.2 (23.0 to 27.4)
Intermediate	7.8 (6.5 to 9.3)	9.6 (8.5 to 10.8)	16.0 (14.1 to 17.9)
Low	4.8 (3.7 to 6.8)	4.8 (3.8 to 5.8)	9.3 (7.8 to 11.0)

*DCIS = ductal carcinoma *in situ;* CI = confidence interval.

†The risk of recurrence as invasive cancer plus DCIS is not equal to the sum of the risk of invasive cancer or DCIS because they are competing risks. Risk calculation is based on 97 women with an invasive recurrence, 112 women with a DCIS recurrence, and 827 women without a recurrence.

‡Palpable mass found by the woman or by her physician upon physical examination.

Table 5. Estimates of 10-year absolute risks of death from invasive cancer after a diagnosis of ductal carcinoma *in situ* (DCIS) and from other causes for factors independently associated with an invasive recurrence by age at time of DCIS diagnosis*

Risk factor and decade of age at DCIS diagnosis	Risk of death from invasive cancer, % (95% CI)	Risk of death from other causes, %
High nuclear grade		
40s	2.5 (2.1 to 3.0)	2.1
50s	2.4 (2.0 to 2.8)	4.6
60s	2.3 (1.9 to 2.7)	11.1
70s	2.0 (1.7 to 2.4)	25.2
Intermediate nuclear grade		
40s	1.7 (1.4 to 2.0)	2.0
50s	1.6 (1.3 to 1.9)	4.5
60s	1.5 (1.3 to 1.8)	11.1
70s	1.4 (1.1 to 1.6)	25.4
Low nuclear grade		
40s	1.0 (0.8 to 1.5)	1.9
50s	1.0 (0.7 to 1.4)	4.5
60s	0.9 (0.7 to 1.3)	11.2
70s	0.8 (0.6 to 1.2)	25.6
Detection by palpation*		
40s	2.5 (2.4 to 2.5)	2.1
50s	2.3 (2.3 to 2.4)	4.6
60s	2.2 (2.2 to 2.3)	11.1
70s	2.0 (2.0 to 2.0)	25.2
Detection by mammography		
40s	1.4 (1.3 to 1.5)	2.0
50s	1.3 (1.2 to 1.4)	4.5
60s	1.3 (1.2 to 1.4)	11.1
70s	1.2 (1.1 to 1.2)	25.2

*Palpable mass found by the woman or by her physician upon physical examination.

invasive cancer within 5 years of initial excision and that a similar percentage of cases have the potential to recur as DCIS. The 5-year recurrence rate for invasive disease reported here, 8.2%, is similar to recurrence rates reported in recently published studies *(11,12,29)* of women with DCIS treated by lumpectomy alone.

Clinical and histopathologic characteristics of women diagnosed with DCIS who are at a low risk of recurrence and thus may avoid radiation and/or tamoxifen therapy have not been consistently identified by clinical trials *(30)*. Results of a number of small studies *(16–18,25,29,31–40)* suggest that women whose initial DCIS lesions have comedo necrosis or high nuclear grade have a high recurrence rate (13%–38%) over 5–10 years, whereas women with low-nuclear-grade DCIS lesions or lesions without comedo necrosis have a low recurrence rate (5%–7%). Results of some studies have also suggested that women who received lumpectomy alone were more likely to have a recurrence if their lesions were 10 mm or larger *(17,22,37,41–43)* or they had margin widths less than 1 mm *(44–47)*, but other studies *(16,19,29,33,39,44,45,48)* have not confirmed these findings. In a non–population-based observational study of women with DCIS who were treated with lumpectomy and radiation that adjusted for margin status, histologic subtype, and nuclear grade, the combination of comedo carcinoma subtype and high nuclear grade was associated with local recurrence within the first 5 years after treatment *(33)* but not at 10 years after treatment *(49)*. The National Surgical Adjuvant Breast and Bowel Project B17 trial assessed the influence of margin width, lesion size, nuclear grade, and comedo necrosis on recurrence and showed that, after adjusting for type of treatment, only moderate to marked comedo necrosis was associated with disease recurrence *(16)*. The European Organization for Research and Treatment of Cancer (EORTC) 10853 trial assessed the influence of margin width, lesion size, nuclear grade, and comedo necrosis on recurrence and showed that, after adjusting for type of treatment, only cribriform and comedo growth patterns and involved margins were associated with disease recurrence *(19)*.

Randomized controlled trials are not the optimal type of study for evaluating prognostic factors that influence disease recurrence because participants in randomized trials are self-selected and thus may not accurately reflect the range of disease, distribution of risk factors, or outcomes seen in the community *(50)*. Our results are directly applicable to women with different histologic types of DCIS because this population-based study included sufficient numbers of women with each histologic category of DCIS. After taking into account clinical characteristics, margin status, histologic subtype, and lesion size, we found that nuclear grade was most strongly associated with recurrence of invasive breast cancer and DCIS after treatment with lumpectomy alone. Moreover, the association between nuclear grade and recurrence persisted for at least 10 years after the initial DCIS diagnosis (Fig. 2).

We found that no single histopathologic characteristic of the initial DCIS lesion predicted the type of recurrence, consistent with results of other reports *(16,29,33,40,45,51)*. Women who had DCIS lesions of either low or high nuclear grade had recurrences as either invasive cancer or as DCIS. Only one other study *(52)* has examined clinical and histopathologic predictors by type of recurrence using a multivariate model. In that study, after adjusting for age at diagnosis, margin width, lesion size, comedo necrosis, and mode of detection, only high nuclear grade and lower volume of re-excision were associated with a recurrence of invasive cancer among 95 patients treated by lumpectomy and radiation. We found that whether or not the pathology margins were disease-free was associated with the type of recurrence, in that disease-free margins were more strongly associated with a lower risk of recurrence as DCIS than with a lower risk of recurrence as invasive cancer. This finding is consistent with results from univariate analyses reported in a study *(45)* of women treated by lumpectomy and radiation, which also found that disease-free margins were associated with a decreased risk of recurrence as DCIS but not of recurrence as invasive cancer. Together, these findings suggest that recurrences as DCIS are likely due to persistence of neoplastic cells from the original DCIS lesion. This hypothesis is supported by the observation that, in most cases, neoplastic cells in DCIS recurrences are clonally related to cells in the original DCIS lesions *(53)*.

Younger age *(13,19,44,45,48,52)* and premenopausal status *(29,44)* at the time of DCIS diagnosis have been associated with an increased risk of disease recurrence. However, different studies have used different definitions for younger age: younger than 40 years *(19,44,45)*, younger than 45 years *(48,52)*, and younger than 49 years *(13)*. Results of a study *(45)* of women with DCIS who were treated with lumpectomy and radiation showed that the 10-year crude incidence of a DCIS recurrence was higher than that of an invasive cancer recurrence among women aged 30–39 years (19% versus 15%) and 40–49 years (9% versus

4%), but similar among women aged 50–59 years (4% versus 4%). Incidence of an invasive cancer recurrence was highest among women aged 30–39 years *(45)*. We found, as have other studies *(13,19,44,45,48,52)*, that younger age at diagnosis was associated with an increased risk of recurrence. Moreover, when we examined the relationship between age and the type of recurrence, younger age at diagnosis was associated with an increased risk of recurrence as DCIS but not of recurrence as invasive cancer. However, we did not include women aged 30–39 years in our study, which may account for our observation that younger age at diagnosis was not associated with an increased risk of an invasive cancer recurrence.

Results of other studies *(13,19,37,39)* have suggested that DCIS lesions that are detected by palpation are more likely to be associated with recurrence than are those detected mammographically. Our study is the first, to our knowledge, to report that DCIS lesions detected by palpation and treated by lumpectomy alone are more likely to recur as invasive cancer than as DCIS. We found that approximately seven of 100 women whose DCIS was detected by mammography had an invasive recurrence within 5 years, compared with approximately 12 of 100 women whose DCIS was detected by palpation. A possible explanation for this finding is that women with palpable DCIS may have a greater stromal response, which is directly linked to risk of an invasive cancer recurrence, than women with nonpalpable DCIS. Another possible explanation is that palpable DCIS lesions may be more aggressive than nonpalpable lesions, just as palpable invasive cancer lesions tend to be more aggressive than nonpalpable invasive lesions *(54)*. It is also possible that very small foci of invasive cancer were not identified on pathology review of palpable DCIS lesions because the entire DCIS lesion was not fully sectioned and reviewed.

Our study has several strengths. First, it is the largest population-based study of women with DCIS treated by lumpectomy alone to measure both clinical and histopathologic characteristics and disease recurrence status. Second, we conducted standardized pathology reviews for women who had disease recurrence (case subjects) and a random sample of women with DCIS who did not have disease recurrence (control subjects), which enhanced our ability to determine which histology features were associated with recurrence. In particular, our ability to obtain re-excision samples for review increased the likelihood of accurately classifying tumor size and margin status. Third, we collected DCIS cases from 63 hospitals, thereby minimizing the chance of selection bias due to specific clinical practices at some hospitals and not others. Fourth, our large sample size allowed us to examine clinical and histopathologic factors independently associated with type of recurrence (DCIS versus invasive cancer) by using a multivariate model.

Our study also has several limitations. First, clinical factors were assessed retrospectively, raising the possibility of recall bias. However, factors that a woman might attribute as causes of recurrence and thus remember more readily when questioned, such as presence of family history of breast cancer and hormone replacement therapy use, were not associated with recurrence, suggesting that recall bias did not greatly affect our results. Second, the median follow-up for our cohort was 6.5 years. Results of other studies *(16,33,45,47,49)* have suggested that margin status and comedo carcinoma subtype in combination with high nuclear grade are associated with recurrence within 5 years after treatment but not with recurrence during a longer follow-up. We will continue to monitor this population-based cohort to examine whether the risk of recurrence as invasive cancer substantially increases over time among women with low- or intermediate-nuclear-grade lesions.

Results of the National Surgical Adjuvant Breast and Bowel Project B17 trial showed that 13.4% of DCIS patients randomly assigned to receive treatment by lumpectomy alone experienced recurrence as invasive cancer by 8 years after treatment compared with 3.9% of DCIS patients randomly assigned to receive treatment by lumpectomy and radiation *(11)*. This finding suggests that an estimated 9.5% of DCIS patients who receive lumpectomy may benefit from adjuvant radiation treatment within the first 8 years after treatment *(11)*. These findings also suggest that the great majority (86.6%) of such patients remains disease-free after lumpectomy alone and would, therefore, undergo radiation therapy unnecessarily. Results of other studies *(11,45,49)* suggest that women with DCIS who are initially treated by lumpectomy or lumpectomy and radiation and who later present with local invasive cancer recurrence have a very low likelihood of developing distant metastasis after treatment for recurrent disease; moreover, the incidence of distant metastasis at the time of first recurrence is rare (<1% within 5 years of treatment). Our findings suggest that, for the 80% of women who have mammographically detected DCIS, the risk of dying from an invasive breast cancer recurrence within 10 years of a DCIS diagnosis is 1.2% to 1.4%. Thus, in the short term, most women diagnosed with DCIS, particularly those women with co-morbid illnesses, are at a low risk of dying of breast cancer and could be spared unnecessary adjuvant therapies.

In conclusion, our results suggest that the mode of DCIS detection and the nuclear grade of the lesion are the most important factors in predicting an invasive cancer recurrence and should be assessed when helping women to decide whether to undergo adjuvant therapies. The 5-year risk of recurrence as invasive cancer was higher (11.6%) among women whose DCIS was detected by palpation and lower (6.6%) for those whose DCIS was detected by mammography. The 5-year risk of recurrence as invasive breast cancer was 4.8% among women with low-nuclear-grade DCIS, as compared with 11.8% for those with high-nuclear-grade lesions. These findings suggest that women with palpable or high-nuclear-grade DCIS lesions are at relatively high risk for recurrence as invasive cancer if treated by lumpectomy alone and may be appropriate candidates for additional treatment. By contrast, women with mammographically detected or low-nuclear-grade (and possibly intermediate-nuclear-grade) lesions may reasonably decide to undergo lumpectomy alone followed by mammographic surveillance. Further study is needed to examine whether measurements of molecular markers can further help estimate an individual's risk for recurrence to avoid over- and undertreatment of women with DCIS.

Appendix: Constructing Survival Curves From Case–Control Data for Population-Based Estimates of the Risk of Recurrence

To estimate the absolute risks of recurrence for the population-based cohort by clinical and histopathologic characteristics, we converted the results from the matched case–control study to survival curves by using the following method. First, we assigned a

simulated value for a variable of interest to each member of the cohort not included in the case–control study and to those members selected for the case–control study who had missing values. We generated the simulated value based on the prevalence of the variable of interest among the control and case subjects. After all participants in the entire cohort had been assigned a value for a variable of interest, we used standard methods to generate Kaplan–Meier survival curves. We repeated this process 1000 times, each time using a new, simulated value assigned for the variable of interest that was based on the same proportion calculated for case and control subjects. Finally, we generated an overall Kaplan–Meier curve by averaging the Kaplan–Meier curves at each event time point, *t*. We repeated this process for each clinical and histopathologic variable of interest. The 95% confidence intervals for the averaged Kaplan–Meier curves were obtained by evaluating the .025 and .975 quantiles at each time point, *t*. All survival estimates and simulations were generated with the use of the statistical package R *(55)*.

The same procedure was implemented to estimate the conditional probability function of the recurrence of interest at time *t* given the absence of a recurrence of non-interest (e.g., the probability of having a recurrence as invasive cancer at 5 years, given that the patient has not had a recurrence as DCIS by 5 years). The Kaplan–Meier estimation method was replaced with the conditional probability function. We used the R code available at http://www.math.yorku.ca/Who/Faculty/Monette/S-news/ 2235.html to estimate the conditional probability function survival curves.

We verified this approach by testing it on a variable that was known for the entire cohort, age at diagnosis. We estimated the 5-year absolute risk of recurrence according to age at diagnosis using three different methods. For the first method, we used the entire cohort to calculate a true risk estimate. For the second method, we used only women who were included in the case–control study. For the third method, we used the procedure for assigning simulated values noted earlier to assign an age at diagnosis to individuals not included in the case–control study. Our goal was to test how closely the second and third methods provided values that approached the true estimate obtained for the entire cohort. For the "true" estimate, all 1036 women were included and the absolute risk of recurrence at 5 years was 0.23 for women aged 49 years or younger at diagnosis and 0.16 for women aged 50 years or older at diagnosis. For the second method, only the 431 women included in the case–control study were included and the absolute risk at 5 years was 0.38 for women aged 49 years or younger at diagnosis and 0.30 for women aged 50 years or older at diagnosis. For the third method, the procedure outlined above resulted in 5-year absolute risks of 0.23 for women aged 49 years or younger at diagnosis and 0.16 for women aged 50 years or older at diagnosis. It is apparent that the second approach is biased, whereas the third approach accurately assimilated estimates for the cohort. Thus, the third method is sufficiently accurate to translate clinical and histopathologic characteristics found to be associated with disease recurrence in a case–control study into estimates of the absolute risk of recurrence.

Markov Model for Risk of Death Following Recurrence as Invasive Breast Cancer

Fig. 4 shows the Markov model used for our calculations. We assumed that for a woman diagnosed with DCIS to die from breast cancer, she must first have had a recurrence as invasive breast cancer.

We estimated four transition probabilities. We used the following equation to estimate the probability of transition from DCIS to recurrence as invasive breast cancer:

$\lambda = -1n(S(t))/t,$

where $S(t)$ is the specific risk group–estimated recurrence-free survival at *t* years after diagnosis. For example, the estimated 5-year risk of invasive cancer recurrence was 8.2% for all women, regardless of risk factor status (Table 4). This estimated risk leads to an estimate of 0.017 for the annual transition probability from initial DCIS diagnosis to recurrence as invasive breast cancer. For women with high-nuclear-grade DCIS, the estimated 5-year risk of invasive cancer recurrence was 11.8%. This estimated risk leads to an estimate of 0.025 for the same transition.

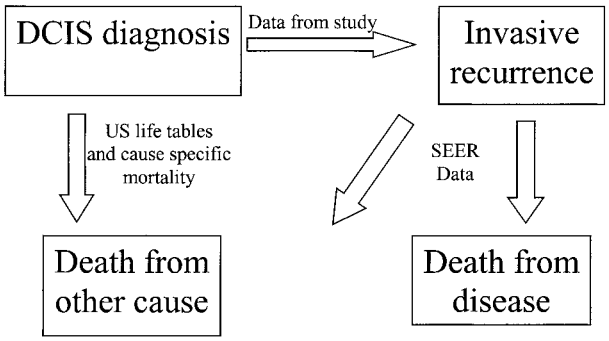

Fig. 4. Markov model for predicting outcomes following a ductal carcinoma *in situ* (DCIS) diagnosis. Boxes indicate health states, arrows indicate transitions, and text outside the boxes indicates sources for estimates of transition probabilities. SEER = Surveillance, Epidemiology, and End Results Program.

For the transition from DCIS to death from a cause other than breast cancer we obtained cause- and age-specific breast cancer mortality rates for women in the United States from the Centers for Disease Control and Prevention Web site (http://www.cdc.gov/nchs/datawh/statab/unpubd/mortabs/gmwk210_10.htm). We then subtracted these mortality rates from the 'qx' column in the 1988 U.S. Life Table for females, which we obtained from the same URL noted above, to estimate the 1-year transition probabilities for U.S. women, given their exact age at DCIS diagnosis.

We used SEER survival data for women diagnosed with invasive breast cancer from 1988 through 1998 to estimate transition probabilities of invasive cancer to death from breast cancer and of invasive cancer to death from other causes, given an exact age at diagnosis.

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NOTES

[1]*Editor's note:* SEER is a set of geographically defined, population-based central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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