



A comparison of the risks of in-breast recurrence after a diagnosis of DCIS or early invasive breast cancer

S.A. Narod MD* and E. Rakovitch MD†

ABSTRACT

Background

It is controversial whether ductal carcinoma *in situ* (DCIS) is a preinvasive marker of breast cancer or if it is part of a spectrum of small cancers with malignant potential. Comparing clinical outcomes in women with invasive and noninvasive breast lesions might help to resolve the issue.

Methods

From a database of 2641 patients with breast cancer, we selected women who had been treated with breast-conserving surgery for a cancer that was 2.0 cm or less in size, node-negative, and nonpalpable. No subject received chemotherapy. Cancers were categorized as noninvasive (stage 0, $n = 172$) or invasive (stage 1, $n = 401$) based on a review of the pathology records. We compared the actuarial risks of in-breast recurrence after invasive and noninvasive breast lesions before and after adjusting for tamoxifen and radiotherapy.

Results

The 18-year cumulative risk of in-breast recurrence was 35.2% for patients with DCIS and 12.8% for patients with small invasive cancers (hazard ratio: 2.4; 95% confidence interval: 1.5 to 3.8; $p < 0.0003$). After adjustment for radiotherapy and tamoxifen treatment, the difference was small and nonsignificant (hazard ratio: 1.4; 95% confidence interval: 0.9 to 2.4; $p = 0.22$).

Conclusions

For women with small, nonpalpable, node-negative breast cancers, the likelihood of experiencing an in-breast recurrence was associated with radiotherapy and with tamoxifen, but not with the presence of cancer cells invading beyond the basement membrane.

KEY WORDS

Breast cancer, DCIS prognostic factors, recurrence

1. INTRODUCTION

Ductal carcinoma *in situ* (DCIS) is often described as a noninvasive form of breast cancer or a precursor lesion¹. This designation is based on the histologic appearance of the lesions and on their typical clinical course. In strict terms, “noninvasive” refers to the absence of visible cancer cells beyond the basement membrane (pathology description of a lesion once it is removed and examined under the microscope). The term “noninvasive” is misleading if it is used to imply that the lesions do not have intrinsic invasive potential. The existence of DCIS with microinvasion (less than 1 mm) attests to the potential for invasion, at least for some patients. It is a matter of ongoing interest if DCIS with microinvasion should be classified with DCIS, with invasive cancer, or as part of a continuum. Further, if the invasive component exceeds 1 mm, the lesion is called “invasive breast cancer with accompanying DCIS.” Some cases of DCIS are diagnosed concurrently with invasive cancer, and other cases of DCIS are followed by an invasive breast cancer in the same breast. The subsequent diagnosis of an invasive or noninvasive cancer in the same breast is termed an in-breast “recurrence” even though the new lesion might represent a re-emergence of cancer cells that were present in the breast at the time of excision or an independent second primary cancer. Here, we use “in-breast recurrence” in that dual sense. The incidence of in-breast recurrence at 10 years after DCIS is approximately 20%^{2,3}; specifically, 20% is the actuarial risk of recurrence after surgical excision. The incidence of recurrence in the absence of surgical intervention—that is, under “watchful waiting”—is expected to be higher. A proposed nonsurgical expectant approach to DCIS management is controversial^{4,5}.

Most cases of DCIS are diagnosed through mammography⁵, and most are small and nonpalpable at

diagnosis—but the same is also true for a significant proportion of invasive cancers⁶. Tumour size and palpability are risk factors for breast cancer recurrence and mortality^{6–10}, and it is not clear how much of the difference in recurrence rates for women with DCIS and with small invasive cancers results from differences in their intrinsic potential to recur and from differences in treatment and mode of detection. If we accept that some cases of DCIS and some cases of nonpalpable invasive breast cancers will progress and that others will not, then it is appropriate to conduct a formal comparison of the two rates. A finding that the propensity for local spread is similar for women with DCIS and women with small invasive cancers would favour the position that DCIS is cancer.

2. METHODS

2.1 Study Subjects

We reviewed the electronic medical records of 2641 women who were treated for either noninvasive or invasive breast cancer at the Henrietta Banting Breast Centre of Women's College Hospital between January 1987 and December 1999. Clinical characteristics (tumour size and lymph node status) were retrieved from a review of the medical records. The designation of invasive or noninvasive was assigned after review of the pathology reports (a formal pathology review was not conducted).

For the present study, we wanted to compare women with DCIS with a similar sample of women diagnosed with invasive breast cancer. Because most cases of DCIS are identified by mammographic screening and are nonpalpable at diagnosis⁵, we restricted the study to women with invasive cancers that were nonpalpable (that is, they were diagnosed by mammography). We excluded 1622 women with a palpable cancer. Furthermore, because we wanted to restrict the comparison group to women with early-stage invasive cancers, we excluded 124 women with a cancer 2 cm or greater in size and 94 other women with node-positive disease. We also excluded 58 women who were not treated with breast-conserving surgery. We excluded 25 women with invasive cancer who were treated with chemotherapy. Information on one or more key variables was missing for 13 patients, and those women were also excluded, leaving 705 subjects in the study. Follow-up of those patients has been maintained by the database coordinator through periodic review of clinical charts and telephone contact with the patient or her physician¹¹. For deceased patients, the date and cause of death were obtained from a review of medical records and a mortality linkage with the Cancer Care Ontario database.

This investigation involved human subjects. However, informed consent was not required by the Ethics Review Board because no subject was contacted.

2.2 Survival Analysis

The patients were followed for in-breast recurrence from date of diagnosis until the first of in-breast recurrence, death from any cause, or date of last contact. We used the Kaplan–Meier method to determine the cumulative risk of in-breast recurrence from the date of diagnosis to the date of in-breast recurrence. The log-rank test was used to examine the statistical significance of the differences observed between groups in univariable analysis.

The impact of tumour size (0.1–0.9 mm vs. 1.0–2.0 cm) on in-breast recurrence was evaluated in the invasive subgroup (tumour size was not defined for the *in situ* group). A multivariate model was constructed including age of diagnosis, year of diagnosis, and radiotherapy and tamoxifen use. The impact of invasive compared with noninvasive cancer on cancer recurrence was first modelled in all subjects and then in subjects who either did or did not receive either radiotherapy or tamoxifen. All analyses were carried out with the Statistical Analysis System (SAS version 9.1.3: SAS Institute, Cary, NC, U.S.A.).

3. RESULTS

We followed the 705 women with DCIS or stage I invasive breast cancer for up to 18 years for in-breast recurrence. All patients were treated at a single hospital (Women's College Hospital), and all cases were reviewed by the same group of pathologists. Table 1 describes the study cohort. Mean follow-up was 10.0 years (range: 0.1–18 years).

Overall, by 18 years, the patients in the DCIS subgroup were more likely than the patients in the small invasive group to experience an in-breast recurrence (35.2% vs. 12.8%, log-rank $p < 0.0003$, Figure 1). However, women with DCIS were far less likely than women with small invasive cancers to have received either tamoxifen or radiotherapy as treatment (Table 1). Among the women treated with radiotherapy, the recurrence rates in the two subgroups were similar (Figure 2). Moreover, among women who received neither radiotherapy nor tamoxifen, in-breast recurrence rates were also similar (Figure 3).

We compared the recurrence rates for the two groups in a multivariable model, adjusting for treatment received. Among the women with invasive cancers, 242 had tumours 1 cm or smaller in size, and 159 women had tumours 1–2 cm in size. In those two subgroups, the 18-year in-breast recurrence rates were similar (unadjusted hazard ratio: 0.88; 95% confidence interval: 0.45 to 1.73; $p = 0.7$; and adjusted hazard ratio: 1.07; 95% confidence interval: 0.53 to 2.18; $p = 0.85$), and therefore tumour size was not included in the multivariable model.

In the multivariable model, radiotherapy and tamoxifen were both predictors of in-breast recurrence; after adjusting for those two treatments, there

was no significant difference in recurrence rates between the women with invasive and noninvasive cancers (Table II).

4. DISCUSSION

Some authors suggest that the term DCIS is misleading because it implies a *de facto* cancer^{4,5}, and some suggest replacing “DCIS” with “ductal intraepithelial neoplasia”¹². Consequently, a woman or her physician might feel pressured to treat the lesion as a cancer, and treatment might be unnecessary (it is unclear whether revision of the nomenclature would lead women to experience less—or more—distress and confusion¹³).

TABLE I Comparison of patients with ductal carcinoma *in situ* (DCIS) and small invasive cancers

Variable	Study group		p Value
	Invasive	DCIS	
Patients (n)	401	172	
Year of birth			
Median	1932.9	1936.9	<0.0001
Range	1902–1961	1907–1959	
Year of diagnosis			
Median	1993.6	1994.0	0.20
Range	1987–1999	1987–2000	
Age at diagnosis (years)			
Median	60.8	57.6	<0.001
Range	22–89	37–89	
Age group [n (%)]			
<45 Years	25 (6.2)	21 (12.2)	0.02
45–54 Years	109 (27.2)	57 (33.1)	
55–64 Years	123 (30.7)	47 (27.3)	
65+ Years	144 (35.9)	47 (27.3)	
Tumour size (mm)			
Median	9.9	Not defined	
Range	0–20		
Radiotherapy [n (%)]			
No	135 (34.1)	106 (62.7)	<0.0001
Yes	261 (65.9)	63 (37.3)	
Tamoxifen [n (%)]			
No	175 (44.3)	150 (88.8)	<0.0001
Yes	220 (55.7)	19 (11.2)	
Follow-up time (years)			
Median	10.2	9.4	0.006
Range	0.4–18	0–18	
In-breast recurrence [n (%)]			
No	364 (90.8)	137 (79.7)	<0.0002
Yes	37 (9.2)	35 (20.4)	

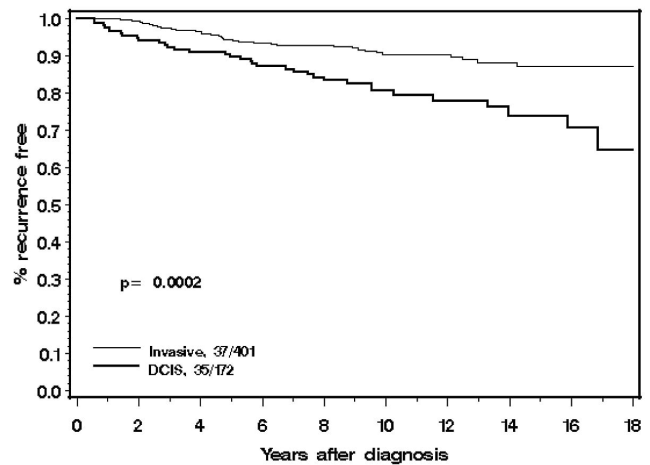


FIGURE 1 Risk of in-breast recurrence after a diagnosis of early-stage cancer, ductal carcinoma in situ (DCIS) versus invasive.

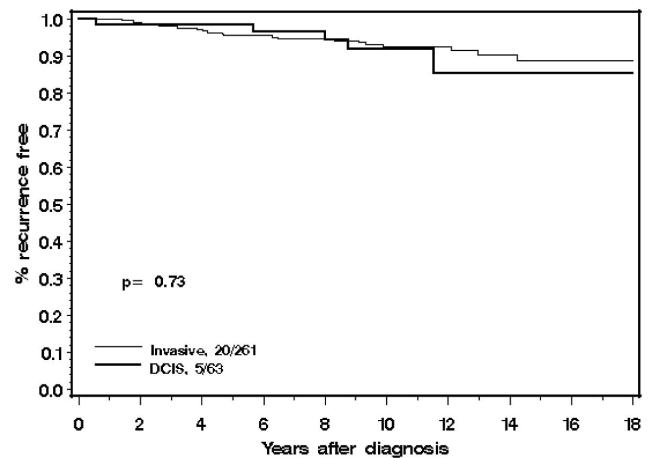


FIGURE 2 Risk of in-breast recurrence after a diagnosis of early-stage cancer, ductal carcinoma in situ (DCIS) versus invasive, with radiotherapy.

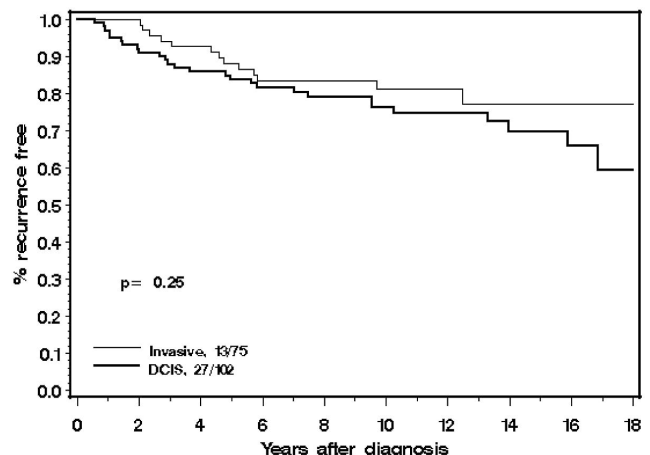


FIGURE 3 Risk of in-breast recurrence after a diagnosis of early-stage cancer, ductal carcinoma in situ (DCIS) versus invasive, without radiotherapy or tamoxifen.

TABLE II Hazard ratios for developing an in-breast recurrence

Variable	Univariate analysis			Multivariate analysis ^a		
	HR	95% CI	p Value	HR	95% CI	p Value
Presence of invasion ^b						
Yes	Reference			Reference		
No	2.37	1.49 to 3.76	<0.0003	1.41	0.82 to 2.42	0.22
Age group at diagnosis						
<45 Years	Reference			Reference		
45–54 Years	0.51	0.26 to 0.99	0.05	0.75	0.35 to 1.61	0.46
55–64 Years	0.36	0.17 to 0.73	0.005	0.70	0.24 to 2.00	0.50
65+ Years	0.36	0.18 to 0.74	0.006	0.74	0.17 to 3.18	0.69
Year of birth						
Per 10 years	1.32	1.05 to 1.65	0.02	1.26	0.78 to 2.02	0.34
Radiotherapy						
No	Reference			Reference		
Yes	0.38	0.24 to 0.62	<0.0001	0.42	0.24 to 0.73	0.002
Tamoxifen						
No	Reference			Reference		
Yes	0.46	0.27 to 0.78	0.004	0.73	0.40 to 1.35	0.32

^a Adjusted for all variables used in the univariate analyses.

^b Ductal carcinoma *in situ* (DCIS) versus invasive.

In a recent letter to the editor, Omer *et al.*⁴ reported that if DCIS were to be framed as a “high-risk condition” rather than a cancer, then more women than not (at least in their hypothetical sample) would opt for a nonsurgical treatment. We suspect that the responses of women faced with this choice in reality—rather than in a “what if” scenario—might differ, and yet the issue is nevertheless an important one. Others believe that the term “cancer” is appropriate, given that DCIS is associated with a nontrivial risk of in-breast recurrence and mortality^{2,3,14,15}. They believe that treatment is indicated and that many women who are not treated should be^{14,15}.

In-breast recurrence is not uncommon after DCIS; Collins *et al.*² estimate the risk to be roughly 20% at 10 years. Wapnir *et al.*³ estimate the risk of in-breast recurrence among DCIS patients treated with breast-conserving surgery alone to be 19.4% at 15 years. It has been argued that, given the non-inevitability of progression, DCIS falls short of cancer. Esserman *et al.*¹⁶ correctly identify overdiagnosis—defined as “the probability that a tumour if left unattended, would not become clinically apparent or cause death” and largely a consequence of screening—as a relevant issue.

Overdiagnosis becomes particularly important when associated with overtreatment: that is, as evidenced by the current trend in the United States to treat unilateral cancer with bilateral mastectomy¹⁷. But overdiagnosis is a feature of both DCIS and invasive cancers identified through screening. Several recent studies suggest that some cases of invasive

breast cancer also fail to progress^{18,19}. In particular, small node-negative cancers that are nonpalpable and diagnosed through mammographic screening might be examples of overdiagnosis^{10,20}. In two studies, progesterone receptor expression was a good predictor of indolent behaviour^{10,21}. Several authors have demonstrated that palpability is a strong prognostic factor for early-stage invasive breast cancers^{6,8,16}. Kerlikowske and colleagues²² found that, among women with DCIS, tumour palpability was a strong risk factor for in-breast invasive recurrence. Most cases of DCIS are now diagnosed through mammographic screening, and so it is apt to compare nonpalpable cases of DCIS with nonpalpable cases of invasive cancers (and to control for tumour palpability when making relevant comparisons of recurrence rates between groups). We show here that, in the absence of treatment after breast-conserving surgery for mammographically-detected cancer, the rates of in-breast recurrence are approximately the same for DCIS and for small invasive cancers. We attempted to control for differences in prognostic factors other than the presence of invasion, and therefore the comparison group was restricted to small node-negative invasive cancers. No case or control received chemotherapy. In this head-to-head comparison, the (adjusted) risk of progression to in-breast recurrence was roughly the same.

Weaknesses of our study include a relatively small sample size, the lack of a formal pathology review, and lack of inclusion of grade and other markers of malignant potential (such as comedonecrosis) in the model. Kerlikowske and colleagues²² reported

that nuclear grade was an independent predictor of local recurrence, but Collins *et al.*² did not. Likewise, we had no data on the margin status of the study patients, and positive margins have been positively associated with the risk of in-breast recurrence^{2,22}. It is likely that biomarkers will be identified in future that will better help to predict cancer recurrence after DCIS, but that possibility does not negate the validity of the present observations: When dichotomized by any predictive marker, some women will face a higher risk, and others, a lower risk of progression. Based on our data, it might be anticipated that the biomarkers that predict recurrence after DCIS are the same ones that predict recurrence after small invasive cancers.

A formal pathology review might possibly have found some cases of DCIS to be invasive (and vice versa), but we had access to the same information as the surgeon and the oncologists who decided whether to offer chemotherapy and radiotherapy. Collins *et al.*² excluded 17% of their cases after a central pathology review. All cancers in the present study were less than 2 cm in size. We did not classify tumour size in the DCIS cases, but tumour size was not a predictor of in-breast recurrence in our study.

We examined local recurrence only; the other relevant outcome is breast cancer-specific mortality. It cannot be assumed that the risks of distant recurrence and death will also be the same for the two groups, and it is our intention to expand the cohort and to follow the women for mortality. We did not distinguish between invasive and noninvasive recurrences. Some of the cases of in-breast recurrence in the DCIS group are expected to be noninvasive and a preponderance of the recurrences in the invasive group are expected to be invasive, but those data are not currently available.

5. CONCLUSIONS

The evidence presented here suggests that, in one important respect, the natural histories of DCIS and invasive breast cancer are similar. Other authors have taken a molecular approach to address this issue and have demonstrated that DCIS and adjacent invasive breast carcinomas have strikingly similar genomic profiles in terms of copy number aberrations and mutations in known cancer genes^{23–25}. Those observations suggest that, in the context of the multi-mutational model of carcinogenesis, DCIS is as advanced as its invasive counterpart. We observed a much higher overall risk of in-breast recurrence after a diagnosis of DCIS. However, that risk was the result of disparity in treatment; after adjusting for treatment, the risks were similar. Those data suggest that women with DCIS should be offered the same treatment options as women with small nonpalpable stage I breast cancers. Furthermore, when discussing options, use of the word “cancer” is appropriate. Given the high probability of an in-breast recurrence

and the availability of several effective treatments, a “watchful waiting” approach should be restricted to research trials. The LORIS (Low Risk DCIS) trial will compare current surgical treatment of low-risk DCIS with watchful waiting²⁶.

The development of an invasive in-breast recurrence is a strong predictor of mortality after a diagnosis of DCIS^{3,27–29} and increases the risk of breast cancer-specific mortality by a factor of up to 17 compared with the risk in patients without local recurrence. That understanding motivates the prevention of all invasive local recurrences—but it must be remembered that prevention of local recurrence might not result in reduced breast cancer mortality. The goals of treatment in DCIS are to prevent both in-breast recurrence and mortality from breast cancer.

In this single-institution study, the supposition that the treatments should be less aggressive for DCIS patients than for patients with mammogram-detected invasive breast cancers led to an excess number of in-breast recurrences.

6. ACKNOWLEDGMENTS

This work was funded by the Canadian Breast Cancer Foundation and the Women’s College Hospital Alternate Funding Plan.

The authors thank the Canadian Breast Cancer Foundation (Ontario Chapter) for support of the Henrietta Banting database; Ellen Rawlinson, Adriana Valentini, and Lidia Kiraly for maintaining the database; and Ping Sun for statistical support.

7. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

8. REFERENCES

1. World Health Organization. *Tumours of the Breast and Female Genital Organs*. Series: World Health Organization Classification of Tumours. Lyon, France: IARC Press; 2003.
2. Collins LC, Achacoso N, Haque R, *et al*. Risk factors for non-invasive and invasive local recurrence in patients with ductal carcinoma *in situ*. *Breast Cancer Res Treat* 2013;139:453–60.
3. Wapnir IL, Dignam JJ, Fisher B, *et al*. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. *J Natl Cancer Inst* 2011;103:478–88.
4. Omer ZB, Hwang ES, Esserman LJ, Howe R, Ozanne EM. Impact of ductal carcinoma *in situ* terminology on patient treatment preferences. *JAMA Intern Med* 2013;173:1830–1.
5. Punglia RS, Schnitt SJ, Weeks JC. Treatment of ductal carcinoma *in situ* after excision: would a prophylactic paradigm be more appropriate? *J Natl Cancer Inst* 2013;105:1527–33.
6. Narod SA. Age of diagnosis, tumor size, and survival after breast cancer: implications for mammographic screening. *Breast Cancer Res Treat* 2011;128:259–66.

7. Carter CL, Allen C, Henson DE. Relation of tumour size, lymph node status, and survival in 24,740 breast cancer cases. *Cancer* 1989;63:181–7.
8. Skinner KA, Silberman H, Sposto R, Silverstein MJ. Palpable breast cancers are inherently different from nonpalpable breast cancers. *Ann Surg Oncol* 2001;8:705–10.
9. Foulkes WD, Reis-Filho JS, Narod SA. Tumour size and survival in breast cancer—a reappraisal. *Nat Rev Clin Oncol* 2010;7:348–53.
10. Narod SA, Valentini A, Nofech-Mozes S, Sun P, Hanna W. Tumour characteristics among women with very low-risk breast cancer. *Breast Cancer Res Treat* 2012;134:1241–6.
11. Dent R, Hanna WM, Trudeau M, Rawlinson E, Sun P, Narod SA. Pattern of metastatic spread in triple-negative breast cancer. *Breast Cancer Res Treat* 2009;115:423–8.
12. Tavassoli FA. Breast pathology: rationale for adopting the ductal intraepithelial neoplasia (DIN) classification. *Nat Clin Pract Oncol* 2005;2:116–17.
13. Partridge AH, Elmore JG, Saslow D, McCaskill-Stevens W, Schnitt SJ. Challenges in ductal carcinoma *in situ* risk communication and decision-making: report from an American Cancer Society and National Cancer Institute workshop. *CA Cancer J Clin* 2012;62:203–10.
14. Rakovitch E, Nofech-Mozes S, Narod SA, *et al*. Can we select individuals with low risk ductal carcinoma *in situ* (DCIS)? A population-based outcomes analysis. *Breast Cancer Res Treat* 2013;138:581–90.
15. Wickerham DL, Julian TB. Ductal carcinoma *in situ*: a rose by any other name. *J Natl Cancer Inst* 2013;105:1521–2.
16. Esserman LJ, Thompson IM Jr, Reid B. Overdiagnosis and overtreatment in cancer: an opportunity for improvement. *JAMA* 2013;310:797–8.
17. Tuttle TM, Jarosek S, Habermann EB, *et al*. Increasing rates of contralateral prophylactic mastectomy among patients with ductal carcinoma *in situ*. *J Clin Oncol* 2009;27:1362–7.
18. Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. *N Engl J Med* 2012;367:1998–2005.
19. Kalager M, Adami HO, Bretthauer M, Tamimi RM. Overdiagnosis of invasive breast cancer due to mammography screening: results from the Norwegian screening program. *Ann Intern Med* 2012;156:491–9.
20. Lehtimäki T, Lundin M, Linder N, *et al*. Long-term prognosis of breast cancer detected by mammography screening or other methods. *Breast Cancer Res* 2011;13:R134.
21. Cancelli G, Maisonneuve P, Rotmensz N, *et al*. Progesterone receptor loss identifies luminal B breast cancer subgroups at higher risk of relapse. *Ann Oncol* 2013;24:661–8.
22. Kerlikowske K, Molinaro A, Cha I, *et al*. Characteristics associated with recurrence among women with ductal carcinoma *in situ* treated by lumpectomy. *J Natl Cancer Inst* 2003;95:1692–702.
23. Hernandez L, Wilkerson PM, Lambros MB, *et al*. Genomic and mutational profiling of ductal carcinomas *in situ* and matched adjacent invasive breast cancers reveals intra-tumour genetic heterogeneity and clonal selection. *J Pathol* 2012;227:42–52.
24. Moelans CB, de Weegs RA, Monsuurs HN, *et al*. Molecular differences between ductal carcinoma *in situ* and adjacent invasive breast carcinoma: a multiplex ligation-dependent probe amplification study. *Cell Oncol (Dordr)* 2011;34:475–82. [Erratum in: *Cell Oncol (Dordr)* 2011;34:509–10]
25. Lopez-Garcia MA, Geyer FC, Lacroix-Triki M, Marchió C, Reis-Filho JS. Breast cancer precursors revisited: molecular features and progression pathways. *Histopathology* 2010;57:171–92.
26. Soumian S, Verghese ET, Booth M, *et al*. Concordance between vacuum assisted biopsy and postoperative histology: implications for the proposed Low Risk DCIS trial (LORIS). *Eur J Surg Oncol* 2013;39:1337–40.
27. Donker M, Litière S, Werutsky G, *et al*. Breast-conserving treatment with or without radiotherapy in ductal carcinoma *in situ*: 15-year recurrence rates and outcome after a recurrence, from the EORTC 10853 randomized phase III trial. *J Clin Oncol* 2013;31:4054–9.
28. Romero L, Klein L, Ye W, *et al*. Outcome after invasive recurrence in patients with ductal carcinoma *in situ* of the breast. *Am J Surg* 2004;188:371–6.
29. Lee LA, Silverstein MJ, Chung CT, *et al*. Breast cancer-specific mortality after invasive local recurrence in patients with ductal carcinoma-*in-situ* of the breast. *Am J Surg* 2006;192:416–19.

Correspondence to: Steven A. Narod, Women's College Research Institute, 790 Bay Street, 7th Floor, Toronto, Ontario M5G 1N8.
E-mail: steven.narod@wchospital.ca

- * Women's College Research Institute, Women's College Hospital, and the Dalla Lana School of Public Health University of Toronto, Toronto, ON.
- † Department of Radiation Oncology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON.