*Curr Oncol*, Vol. 21, pp. e418-425; doi: http://dx.doi.org/10.3747/co.21.1563

ORIGINAL ARTICLE

# Factors associated with breast cancer mortality after local recurrence

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## ABSTRACT

### Purpose

We aimed to identify risk factors for mortality after local recurrence in women treated for invasive breast cancer with breast-conserving surgery.

### Experimental Design

Our prospective cohort study included 267 women who were treated with breast-conserving surgery at Women's College Hospital from 1987 to 1997 and who later developed local recurrence. Clinical information and tumour receptor status were abstracted from medical records and pathology reports. Patients were followed from the date of local recurrence until death or last follow-up. Survival analysis used a Cox proportional hazards model.

### Results

Among the 267 women with a local recurrence, 97 (36.3%) died of breast cancer within 10 years (on average 2.6 years after the local recurrence). The actuarial risk of death was 46.1% at 10 years from recurrence. In a multivariable model, predictors of death included short time from diagnosis to recurrence [hazard ratio (HR) for <5 years compared with ≥10 years: 3.40; 95% confidence interval (CI): 1.04 to 11.1; $p = 0.04$], progesterone receptor positivity (HR: 0.35; 95% CI: 0.23 to 0.54; $p < 0.001$), lymph node positivity (HR: 2.1; 95% CI: 1.4 to 3.3; $p = 0.001$), and age at local recurrence (HR for age >45 compared with age ≤45 years: 0.61; 95% CI: 0.38 to 0.95; $p = 0.03$).

### Conclusions

The risk of death after local recurrence varies widely. Risk factors for death after local recurrence include node positivity, progesterone receptor negativity, young age at recurrence, and short time from diagnosis to recurrence.

## KEY WORDS

Breast cancer, recurrence, mortality, prognostic factors

## 1. INTRODUCTION

Multiple studies show that, after treatment of invasive breast cancer with breast-conserving surgery, the risk of developing subsequent distant metastases and death is greater for women who experience a local recurrence than for women without a local recurrence[1–5]. The mortality rate is increased by a factor of 2 or 3 after local recurrence, but the risk varies between patients. For some patients, chemotherapy is given at the time of local recurrence with the goal of preventing progression ("salvage therapy"), but there are no standard indications for chemotherapy use[6]. Recently, investigators of the CALOR study, a randomized trial, reported that disease-free survival was improved if chemotherapy was given, in particular for women with estrogen receptor (ER)–negative disease[7]. The identification of factors that predict distant recurrence and death after a woman experiences local recurrence might help to guide treatment recommendations and to illuminate the natural history of breast cancer. It is expected that some of the risk factors that predict mortality from the time of the initial diagnosis will overlap with factors that predict mortality after local recurrence, but some factors might be distinct to one or the other process. The identification of discordant factors could promote a better understanding of the steps in cancer progression.

Much research has been conducted on risk factors for recurrence of breast cancer, but relatively little on risk factors for mortality after a local recurrence, or on how various treatments given after a local recurrence affect mortality. Factors that have been associated with a poor outcome after local

recurrence include the extent of recurrent disease, lack of hormone receptor expression, lymph node status of the primary tumour, older age at diagnosis, and a short disease-free interval[3,6,8].

Gene expression profiling indicates that breast cancer comprises at least 4 distinct entities, and patterns of both locoregional and systemic recurrence can vary by subtype[8–11]. For example, in patients with triple-negative breast cancer, the rate of progression from first diagnosis to local recurrence appears to be similar to that in patients of other molecular subgroups; however, the triple-negative phenotype is associated with relatively short intervals from first diagnosis to distant metastases and from distant metastases to death[12]. It is not known if the triple-negative phenotype also predicts time from local recurrence to death. In the present study, we set out to estimate breast cancer mortality rates after local recurrence following breast-conserving surgery and to identify predictors of long-term survival.

## 2. METHODS

### 2.1 Study Patients

We studied a cohort of women with invasive breast cancer who were treated at the Henrietta Banting Breast Centre (HBBC) between 1987 and 1997. The HBBC database is a hospital-based cohort of women diagnosed with primary breast cancer at Women's College Hospital (WCH) with systematic pathologic evaluation. The HBBC database was established to systematically record data on clinical presentation, treatment, and outcome in women with breast cancer who received primary surgical treatment at Women's College Hospital. Patients are referred from family practitioners and other physicians in the surrounding medical community to 1 of 5 teaching surgeons practicing at HBBC. Women were included in the study if they were diagnosed with invasive breast cancer at Women's College Hospital from January 1987 to December 1997 and were entered into the HBBC database. For this study, only women who were treated with breast-conserving surgery and who experienced a local or locoregional recurrence were included. Of the 267 patients who met those criteria, 209 had a local recurrence only and 58 had a locoregional recurrence. Those two groups are combined in the analysis and, for convenience, are referred to as a "local recurrence" group. Medical records and pathology reports were reviewed. Patient information was recorded at accrual, and included details about the patient's age at diagnosis (in years), all treatments received for the primary cancer (surgery, chemotherapy, tamoxifen therapy, and radiation), tumour grade, lymph node status and pathology-determined size of the primary tumour (millimetres), all local and distant recurrences, and dates and causes of death. We did not record treatments given after the first recurrence or analyze the effect of treatment for recurrence on mortality. Pathology reports pertained to specimens obtained at the time of diagnosis of the primary cancer (and not of the recurrence).

### 2.2 Immunohistochemistry

For each patient in the database, a set of representative paraffin-embedded slides was requested for antibody staining in the reference laboratory. Staining was performed between 2000 and 2004. The ER and progesterone-receptor (PR) status were determined by immunohistochemistry. For ER and PR analysis, Novocastra antibodies were obtained from Leica Biosystems (Concord, ON), and receptor positivity was accepted at cut-off levels of more than 10%. A paraffin-embedded slide was not available for 25% of the patients, and in those cases, ER and PR status were determined by a review of the pathology records. These early assays were biochemical, using a cut-point of 10 fmol/mg protein. For those patients, human epidermal growth factor receptor 2 (HER2) status did not determine patient treatment, but was obtained for research purposes. Overexpression of the HER2 protein was evaluated using the CB11 monoclonal antibody (Novocastra: Leica Biosystems) in representative paraffin sections of each tumour, using the peroxidase–antiperoxidase technique for immunohistochemical assay. Positivity for HER2 was defined as strong complete membrane staining in at least 10% of tumour cells. For the present study, triple-negative breast cancers were defined as those that were ER-negative, PR-negative, and HER2-negative. Breast cancers that were positive for any of the receptors were defined as "other."

### 2.3 Follow-Up

Follow-up has been maintained by the database coordinator through review of clinical charts and telephone contact with patients. Locoregional relapses and subsequent surgery during the 90-day postsurgical period were considered to be part of primary management: distant recurrence during that period disqualified the patient from the study. Relapses after 90 days were considered to be events. Relapses were dated and reviewed by 2 medical oncologists; initial interobserver agreement was greater than 95%. For 85% of the patients, follow-up had continued for 3 or more years, and 75% of the patients were under active follow-up (or had died). For deceased patients, date and cause of death were obtained from the medical records. In the present study, patients were followed from date of local recurrence until date of death. The cause of death was established by medical chart review and by linkage to the Ontario Cancer Registry.

### 2.4 Analysis

In the survival analysis, patients were followed from date of first local or locoregional recurrence until death from breast cancer, death from another cause, or last date that they were known to be alive. Kaplan–Meier survival analyses of distant recurrence-free survival were carried out for relevant subgroups. The log-rank test was used to examine the statistical significance of the between-group differences observed. A multivariable survival analysis conducted using the Cox proportional hazards model incorporated a number of covariates. Treatments were considered to be covariates (tamoxifen: yes/no; radiotherapy: yes/no; chemotherapy: yes/no). In that analysis, chemotherapy refers to primary treatment and not to salvage chemotherapy. In the final model, variables were included only when their hazard ratios (HRS) were significantly different from unity in the full multivariable model.

## 3. RESULTS

In the HBBC database, 2294 women were treated for invasive breast cancer between 1987 and 1997. Of those patients, 1742 were treated with breast-conserving surgery, and of the latter patients, 267 experienced a local recurrence (15.3%) and are the subject of the present report (Table I). Of the 267 study patients, 97 died of breast cancer within 10 years of experiencing a local recurrence—on average, 2.6 years (range: 1 month–9.9 years) after the local recurrence. The actuarial risk of death after a local recurrence was 36.6% at 5 years and 46.1% at 10 years.

We conducted a survival analysis to identify factors predicting death after local recurrence (Table II). The HR for each potential risk factor was estimated in a univariable analysis, and then a multivariable analysis was performed. In the univariable analysis, factors that predicted mortality included age at first diagnosis, age at local recurrence, short interval from diagnosis to recurrence, use of chemotherapy, large tumour size at initial diagnosis, positive lymph nodes, ER negativity, PR negativity, and HER2 positivity (Table II). In the multivariable analysis, 5 variables were significant independent predictors of death after local recurrence: short time from initial diagnosis to local recurrence, positive lymph node status, negative PR status, young age at recurrence, and locoregional compared with local recurrence. In women who experienced a locoregional occurrence, mortality was almost 4 times the mortality observed in women who experience local recurrence alone.

In the univariate model, time from initial diagnosis to recurrence was a strong predictor of mortality after a diagnosis of local recurrence (Figure 1). For women who experienced a local recurrence within 5 years of diagnosis, the 10-year mortality rate from date of recurrence was 53.1%;

TABLE I Characteristics of the 267 study patients

| *Characteristic* | *Value [n (%)]* |
|---|---|
| Age at diagnosis | |
| ≤45 Years | 86 (32.2) |
| 46–55 Years | 82 (30.7) |
| ≥56 Years | 99 (37.1) |
| Age at recurrence | |
| <45 Years | 49 (18.4) |
| 46–55 Years | 72 (27.0) |
| ≥56 Years | 146 (54.7) |
| Time from diagnosis to local recurrence | |
| 0–4.99 Years | 166 (62.2) |
| 5–9.99 Years | 55 (20.6) |
| ≥10 Years | 46 (17.2) |
| ER status | |
| Negative | 76 (30.6) |
| Positive | 172 (69.4) |
| Missing | 19 |
| PR status | |
| Negative | 104 (42.6) |
| Positive | 140 (57.4) |
| Missing | 23 |
| HER2 status | |
| Negative | 119 (73.0) |
| Positive | 44 (27.0) |
| Missing | 104 |
| Initial chemotherapy | |
| No | 200 (75.2) |
| Yes | 66 (24.8) |
| Missing | 1 |
| Initial radiotherapy | |
| No | 96 (36.4) |
| Yes | 168 (63.6) |
| Missing | 3 |
| Tamoxifen | |
| No | 175 (65.5) |
| Yes | 92 (34.5) |
| Initial tumour size | |
| 0–2 cm | 163 (61.0) |
| 2–5 cm | 95 (35.6) |
| >5 cm | 9 (3.4) |
| Initial node status | |
| Negative | 138 (61.6) |
| Positive | 86 (38.4) |
| Missing | 43 |

ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2.

for women who experienced a local recurrence 5–10 years from diagnosis, the 10-year actuarial mortality from date of recurrence was 34.8%; for women who experienced a local recurrence 10 or more years from diagnosis, the 10-year actuarial mortality from date of recurrence was 18.8%.

We also classified the cancers as "triple-negative" or "other." In the univariate analysis, the HR for death after recurrence was 2.51 (95% CI: 1.41 to 4.47; $p = 0.002$) for triple-negative compared with other tumours, and in the adjusted analysis (after removing ER, PR, and HER2 as individual covariates), the HR was 1.87 (95% CI: 1.02 to 3.40; $p = 0.04$) for triple-negative compared with other tumours. The 10-year mortality rate after local recurrence was 66.5% for women for triple-negative cancer and 45.3% for women with

TABLE II Factors that predict breast cancer–specific mortality after local recurrence

| *Factor* | *Univariate analysis* | | | *Multivariate analysis* | | |
|---|---|---|---|---|---|---|
| | *HR* | *95% CI* | p *Value* | *HR* | *95% CI* | p *Value* |
| Age at first primary[a] | | | | | | |
| ≤45 Years | | Reference | | | Reference | |
| 46–55 Years | 0.77 | 0.47 to 1.25 | 0.29 | 1.23 | 0.74 to 2.06 | 0.43 |
| ≥56 Years | 0.70 | 0.43 to 1.12 | 0.14 | 0.74 | 0.43 to 1.29 | 0.29 |
| Age at recurrence[a] | | | | | | |
| ≤45 Years | | Reference | | | Reference | |
| 46–55 Years | 0.54 | 0.32 to 0.91 | 0.02 | 0.84 | 0.47 to 1.51 | 0.56 |
| ≥56 Years | 0.44 | 0.27 to 0.70 | 0.0005 | 0.71 | 0.40 to 1.24 | 0.23 |
| Time from initial diagnosis to local recurrence | | | | | | |
| ≥10 Years | | Reference | | | Reference | |
| 0–4.99 Year | 5.07 | 1.60 to 16.1 | 0.006 | 3.19 | 0.96 to 10.6 | 0.06 |
| 5–9.99 Years | 2.61 | 0.75 to 9.04 | 0.13 | 2.05 | 0.57 to 7.37 | 0.27 |
| ER status | | | | | | |
| Negative | | Reference | | | Reference | |
| Positive | 0.51 | 0.34 to 0.77 | 0.001 | 0.94 | 0.57 to 7.37 | 0.81 |
| PR status | | | | | | |
| Negative | | Reference | | | Reference | |
| Positive | 0.35 | 0.23 to 0.53 | 0.0001 | 0.38 | 0.23 to 0.65 | 0.0003 |
| HER2 status | | | | | | |
| Negative | | Reference | | | Reference | |
| Positive | 1.73 | 1.07 to 2.80 | 0.03 | 0.99 | 0.58 to 1.67 | 0.96 |
| Initial chemotherapy | | | | | | |
| No | | Reference | | | Reference | |
| Yes | 2.12 | 1.40 to 3.21 | 0.0004 | 1.19 | 0.64 to 2.20 | 0.59 |
| Initial radiotherapy | | | | | | |
| No | | Reference | | | Reference | |
| Yes | 1.32 | 0.86 to 2.02 | 0.20 | 1.44 | 0.85 to 2.43 | 0.18 |
| Initial size | | | | | | |
| 0–2 cm | | Reference | | | Reference | |
| 2–5 cm | 2.44 | 1.62 to 3.67 | 0.0001 | 1.29 | 0.81 to 2.05 | 0.28 |
| >5 cm | 3.09 | 1.22 to 7.81 | 0.02 | 1.61 | 0.60 to 4.32 | 0.34 |
| Initial node status | | | | | | |
| Negative | | Reference | | | Reference | |
| Positive | 2.62 | 1.69 to 4.06 | 0.0001 | 1.41 | 0.77 to 2.60 | 0.27 |
| Recurrence | | | | | | |
| Local | | Reference | | | Reference | |
| Locoregional | 3.62 | 2.42 to 5.43 | <0.0001 | 3.33 | 2.11 to 5.27 | <0.0001 |

[a] Age at diagnosis and age at recurrence were added in model separately because of colinearity.
HR = hazard ratio; CI = confidence interval; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2.

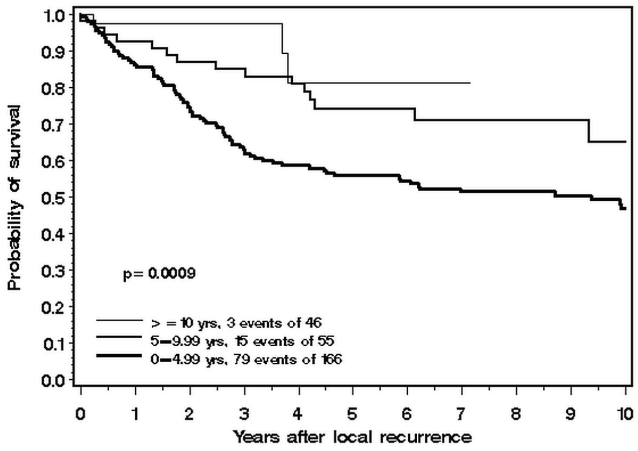


*FIGURE 1 Risk of death after local recurrence, by time from initial diagnosis to local recurrence.*

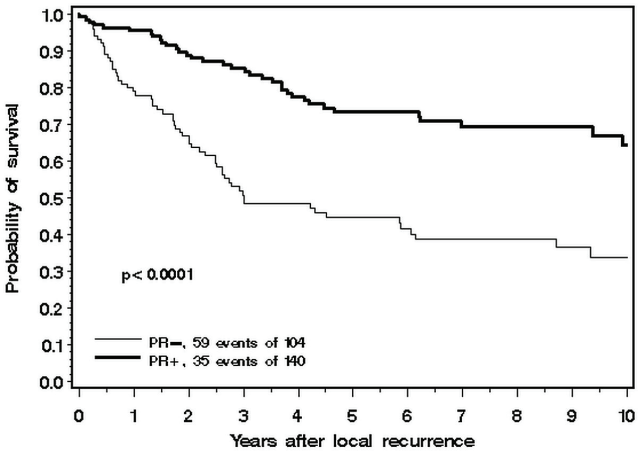


*FIGURE 2 Risk of death after local recurrence, by progesterone receptor (PR) status.*

other forms of cancer. In the triple-negative group, ER and PR are typically considered to be equivalent, but on closer inspection, that understanding was found not to be the case. Women were much less likely to die of breast cancer after a local recurrence when their tumour expressed PR than when it was PR-negative (adjusted HR: 0.35; 95% CI: 0.23 to 0.54; $p < 0.001$; Figure 2), but the same was not true for ER expression (adjusted HR: 0.92; 95% CI: 0.56 to 1.53; $p = 0.8$). The beneficial prognostic effect of PR positivity on survival was present for both ER-positive breast cancers (HR: 0.31; 95% CI: 0.17 to 0.56; $p < 0.001$; Figure 3) and ER-negative breast cancers [HR: 0.48; 95% CI: 0.15 to 1.15; $p = 0.22$ (only 18 women in the study had ER-negative, PR-positive breast cancer)].

Positive lymph node status at baseline was also an independent prognostic variable (HR: 2.1; 95% CI: 1.4 to 3.3; $p = 0.001$, Figure 4). Among women who had a lymph node–positive breast cancer that was also PR-negative, the mortality rate at 10 years was 82.1%. In addition, if the local recurrence occurred within 5 years of the initial diagnosis, the 10-year actuarial mortality rate was 88.2%. Among women with lymph node–negative, PR-positive breast cancer, the 10-year actuarial mortality rate was 20.2%

The probability of death after local recurrence declined with increasing age at first diagnosis (Table II). When age was divided into three categories, older age category was predictive of death in the univariate but not in the multivariable analysis (Table III). The HR for death was 0.73 (95% CI: 0.49 to 1.10) for women first diagnosed after age 45 compared with women first diagnosed at age 45 or younger ($p = 0.13$). In a second analysis, age at local recurrence was substituted for age at diagnosis. The results were more discriminatory: The univariate HR for death was 0.47 for women diagnosed with local recurrence after age 45 compared with women diagnosed at age 45 or younger ($p = 0.0006$, Figure 5).

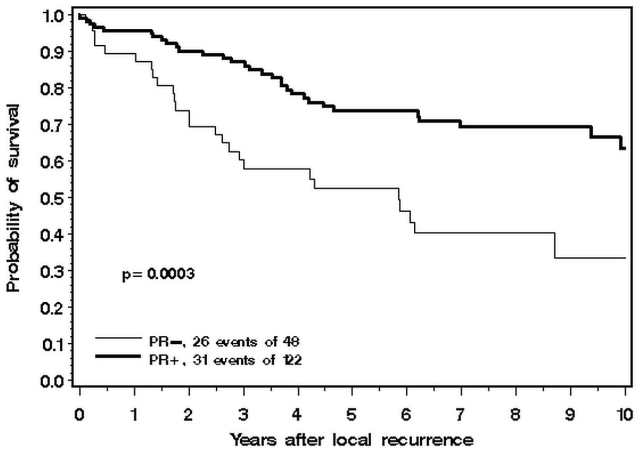


*FIGURE 3 Risk of death after local recurrence, by progesterone receptor (PR) status, estrogen receptor–positive patients only.*

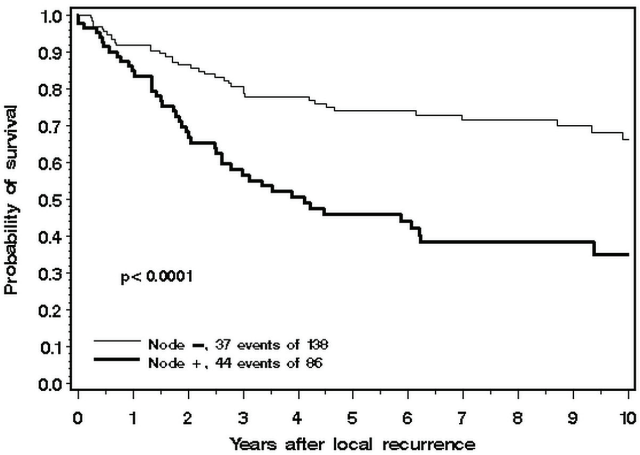


*FIGURE 4 Risk of death after local recurrence, by lymph node status.*

TABLE III Factors that predict breast cancer–specific death, final model

| *Factor* | *Multivariate analysis* | | |
|---|---|---|---|
| | *HR* | *95% CI* | p *Value* |
| Time from initial diagnosis to local recurrence | | | |
| 0–4.99 Year | 3.01 | 0.92 to 9.81 | 0.07 |
| 5–9.99 Years | 2.03 | 0.57 to 7.21 | 0.27 |
| ≥10 Years | | Reference | |
| PR status | | | |
| Negative | | Reference | |
| Positive | 0.37 | 0.24 to 0.57 | <0.0001 |
| Initial node status | | | |
| Negative | | Reference | |
| Positive | 1.72 | 1.08 to 2.76 | 0.002 |
| Age at local recurrence | | | |
| ≤45 Years | | Reference | |
| 46–55 Years | 0.86 | 0.49 to 1.50 | 0.59 |
| 56+ Years | 0.64 | 0.38 to 1.06 | 0.09 |
| Recurrence | | | |
| Local | | Reference | |
| Locoregional | 3.07 | 1.99 to 4.76 | <0.0001 |

HR = hazard ratio; CI = confidence interval; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2.

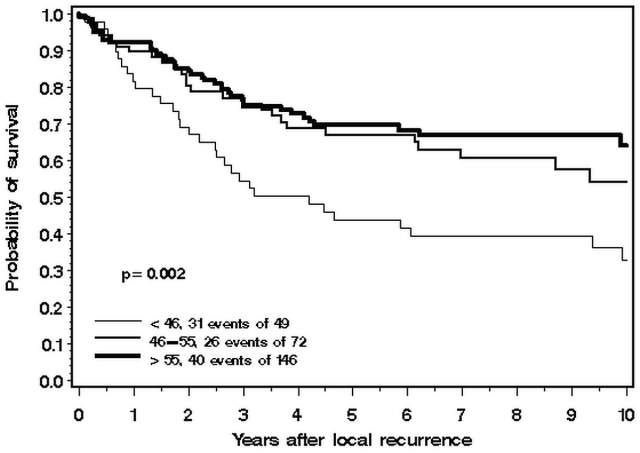


FIGURE 5 *Risk of death after local recurrence, by age at local recurrence.*

## 4. DISCUSSION AND CONCLUSIONS

Our study showed that two of the strongest predictors of mortality among women who experience a local recurrence after treatment for breast cancer are time to recurrence and negative PR status. Other important factors include lymph node status and age at recurrence. One important distinction between factors that predict local recurrence *per se* and those that predict mortality after local recurrence is PR status. At initial diagnosis, the 10-year mortality after local recurrence was 35.7% for women who had a PR-positive cancer compared with 66.1% for women who had a PR-negative cancer. The tendency is to subdivide breast cancer cases into subgroups of triple-negative, luminal, and so on, but interestingly, in terms of mortality after local recurrence, the effects of ER and PR status were distinct: PR was a strong prognostic factor among ER-positive cancers (Figure 3). The luminal or triple-negative dichotomy has been widely accepted because it is a good predictor of local recurrence[8–11]; however, the classification scheme falls short in this clinical context, in which PR status and ER status are not equivalent. Montagna *et al.* reported that survival after local recurrence was much inferior for patients with triple-negative breast cancer than for other patients[8]. They did not look at PR status independently of ER status, and it is possible that patients in that study with ER-positive, PR-negative breast cancers had a prognosis that was equally poor as that for patients with triple-negative cancer. In our study, ER and PR status were classified according to the examination of the primary tumour; results might be different if we were to assess the hormone receptor status of the recurrence.

Much attention has been paid to prognostic factors at the time of diagnosis. The information in our study is relevant for women who experience a local recurrence after breast-conserving surgery and suggests that, in this scenario, not all of the initial prognostic variables remain relevant. Women younger than 45 when they experienced a local recurrence were more likely than women who were diagnosed at a later age to die of their disease. That observation is consistent with early age of onset being a risk factor for local recurrence[13]; women with early-onset breast cancer are more likely to experience a recurrence and, once they do, are more likely to succumb to their disease. It is not clear which factors contribute to the relatively poor prognosis in young women[14]. In our study, age of primary diagnosis was correlated with several other prognostic factors (data not shown) and was not an independent predictor in the final model. In contrast to the present study, a prior study of 200 women with local recurrence found that early age of diagnosis was a good prognostic factor[15]; however, the study authors did not adjust for other prognostic factors.

In our study, the 5-year survival rate after local recurrence was 63%. That rate is within the 60%–70% range cited by Fisher *et al.*[1], whose study (NSABP-B06) treated patients from 1981 to 1984. Our patients were treated from 1987 to 1997. Despite progress made in the adjuvant treatment of breast cancer since 1992, it is not clear if the life expectancy of women who experience a local recurrence has subsequently increased[1,4], and it will be important to follow our cohort and others for updated analyses. Similarly, it

has been reported that little improvement has been observed since the early 1980s in the survival of women with distant metastases[16].

It has previously been reported that the survival experience after local recurrence is relatively poor if the recurrence occurs early[2–4]. In one study, 5-year overall survival was 44% for local recurrences that occurred within 3 years of initial treatment, compared with 87% for women who experienced a later recurrence[4]. In a recent report from the National Surgical Adjuvant Breast and Bowel Project, the rate of overall survival was 49% for women with an interval from initial diagnosis to local recurrence of less than 2 years; it was 85% percent for women whose cancers recurred later[2]. In another study, the actuarial rate of distant metastases after local recurrence was 92% when the interval from primary treatment was less than 2 years, 53% for intervals of 2–5 years, and 22% for intervals longer than 5 years[5].

In the present study, we analyzed all local recurrences as a single category. The effect of time since diagnosis on recurrence risk might indicate that we have included a mixture of true recurrences and second primary cancers. In a recent study, Yi *et al.*[17] suggest that approximately one half of in-breast tumour recurrences are true local recurrences of the original cancer; the other half represent new primaries. In that study, the risk of distant metastasis was higher for women categorized as having a true local recurrence than for those categorized as having a second primary. In the present study, we were unable to subclassify the in-breast tumour recurrences because we lacked details of the recurrence histology or the location within the breast. However, if, on average, true recurrences occur earlier than second primary cancers, and if, as Yi *et al.* propose, mortality is greater after true recurrences than after second primaries, then a relationship between time to recurrence and mortality is to be expected.

It might be expected that patients who recur after treatment with radiotherapy or chemotherapy will have more aggressive disease than those who recur but who did not receive either treatment. In the univariate analysis, patients who recurred after receiving chemotherapy had a much worse prognosis than did those in whom chemotherapy was not given; however, chemotherapy was not significant in the multivariable model. The effect of radiotherapy was similar, but the effect size was smaller. In the study by Yi *et al.*[17], prior chemotherapy was a significant adverse prognostic factor among women with local disease recurrence in a univariable analysis (a multivariable analysis was not done). In the CALOR trial[7], prior chemotherapy was a nonsignificant predictor of poor survival after local recurrence (odds ratio: 1.97; $p = 0.12$).

A local recurrence is associated with an increase in the risk of distant recurrence and death from breast cancer (reviewed in Sirohi *et al.*[6]). In our study, among young women with a PR-negative, node-positive breast cancer who experienced local recurrence, the case-fatality rate exceeded 80%. However, prevention of local recurrence by mastectomy or radiotherapy is not accompanied by a commensurate reduction in mortality[18–21]. That observation is the basis for the conventional belief that local recurrence is a marker for breast cancer that has spread beyond the breast at the time of surgery, with the recurrence not being the source of the metastases—a situation that would not be expected to be the case if the recurrence represented a second primary cancer. However, an extended follow-up time would be required to demonstrate that prevention of second primary cancers (through mastectomy) has an impact on long-term mortality[22]. Long-term studies have, in general, supported the equivalence of mastectomy and breast-conserving surgery in terms of mortality[18,19], but it is not clear whether these studies in the general population are relevant for young women with PR-negative, node-positive breast cancers.

The present study did not include information on the treatment of local recurrences (chemotherapy or surgical resection), and we did not consider those secondary treatments in our analysis. It is possible that results might be different in patients who receive chemotherapy at the time of recurrence. The International Breast Cancer Study Group's CALOR trial[7] reported that chemotherapy after a local recurrence was effective in reducing the 5-year mortality rate to 12% from 24%. Women with ER-positive or ER-negative disease both appeared to benefit from chemotherapy. For women with ER-negative disease, disease-free survival improved to 67% from 35% with chemotherapy ($p = 0.007$). For women with ER-positive disease, overall survival improved to 94% from 80% ($p = 0.12$). The study was small, the follow-up was short, and the authors have not yet reported results by PR status. Nevertheless, these early data support the use of chemotherapy for selected women with breast cancer at the time of local recurrence or thereafter. Based on the very high risks of mortality observed here, we suggest that young women with a recurrence after a PR-negative, node-positive breast cancer might be among those who would most benefit from chemotherapy.

## 5. CONFLICT OF INTEREST DISCLOSURES

The authors declare no financial conflicts of interest.

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