Prognosis in Women with a Carcinoma in Situ of the Breast: 
A Population-based Study in Sweden

Fredrik Wännergren, Jonas Bergh, and Lars Holmberg
Departments of Surgery [F. W., L. H.] and Oncology [J. B.], University Hospital, S-751 85 Uppsala, Sweden

Abstract
We studied the risk of invasive breast cancer and breast cancer death after a breast carcinoma in situ during a period when mammography screening became a nationwide practice and when breast conservation was introduced.

In a study base including all 4661 women registered to the Swedish Cancer Registry for a first carcinoma in situ between 1960 and 1992, we selected a cohort of 3398 women diagnosed between 1980 and 1992. The recruitment period was chosen according to the reporting routines for the registry.

The corrected survival was 97.4% after 10 years. The risk of invasive cancer was similar in the ipsilateral and contralateral breast. Women diagnosed between 1989 and 1992 ran a relative risk of 0.1 (95% confidence interval, 0.0–0.9) of dying of breast cancer, as compared with women diagnosed from 1980–1982. Residence in counties where mammography screening was available was associated with a relative risk of 0.2 (95% confidence interval, 0.0–2.1) for breast cancer death in the age groups screened.

Screening mammography may have contributed to the improvement of prognosis over this time period. This study cannot distinguish between lead time effects and a “true” improvement in prognosis. The increased use of breast conservation was not associated with a worse prognosis in the group as a whole. The study indicates that at least 50% of invasive cancers occurring after treatment for in situ lesions may be new cancers.

Introduction
Women treated for DCIS1 run a higher than normal risk of developing invasive breast cancer in the same breast (1–8). In retrospective studies of small series of patients, a reevaluation of biopsies judged to be benign lead to a reclassification of lesions to DCIS. The risk of developing a subsequent ipsilateral invasive or in situ cancer was up to 50% after ~10 years in these studies (2, 4, 6). In studies of the outcome after breast-conserving treatment for DCIS, the cumulative incidence of new ipsilateral events varies from 4–45%, with a follow-up time of 3–8 years (9–14). Half or more of the new ipsilateral events are invasive cancers (2, 4, 9–14). In the NSABP B17 study where 818 women with DCIS were randomly assigned to undergo lumpectomy with or without postoperative breast irradiation, 13.3% of the ipsilateral events after a mean follow-up of 43 months were located in a quadrant other than the primary, indicating that these were new events rather than recurrences (13). Postoperative radiotherapy considerably lowers the risk of a new ipsilateral event. In the NSABP B17 study, the risk was 50% less after radiotherapy than after lumpectomy alone (13). The rate of ipsilateral recurrences after mastectomy is low (2–5% after up to 9 years of follow-up; Refs. 8, 9, and 15–18).

Few of the studies of prognosis after treatment for DCIS have published data on contralateral breast cancer events, but the NSABP group reported that 2.3% of 790 patients had a new contralateral event after a mean follow-up of 43 months, and 61% of these were invasive cancers (13). In a register study from Washington, the cumulative incidence of contralateral breast cancer was 2.4% and 6.1% after 5 and 10 years, respectively, in 1929 patients with DCIS. Sixty-six percent of these cancers were invasive (19).

The risk of dying of breast cancer after a primary diagnosis of DCIS is largely unknown. In a meta-analysis including 585 patients treated with mastectomy and 308 patients treated with local excision, the overall survival was 97–99% after a mean follow-up of approximately 7 years (10). The generally good prognosis after treatment for DCIS requires large patient series and long-term follow-up to evaluate the risk of dying of breast cancer, and hitherto no studies have reported estimates of the breast cancer corrected survival rate. Thus, it is not known how the risk of dying of breast cancer in women who have been treated for DCIS is linked to new invasive cancers.

Even less is known about the natural history of LCIS. LCIS is said to be a general risk factor for invasive breast cancer, with similar risks for both breasts (3, 10, 20–21). The risk of a subsequent invasive cancer is reported to be 7–11 times higher than the risk of a breast cancer in the general female population (17, 22–24). No estimates of the risk of dying of breast cancer after primary LCIS have been reported.

The aim of this study was to analyze the risk of new invasive cancers—ipsilateral and contralateral—after a previous CIS of the breast and the risk of dying of breast cancer in a large Swedish population-based cohort. In a study base including all 4661 women registered in the SCR for a first CIS between 1960 and 1992, we selected a cohort of 3398 women diagnosed between 1980 and 1992, whom we followed for the events of interest. We were especially interested in time trends

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2 To whom requests for reprints should be addressed, at Department of Surgery, University Hospital, S-751 85 Uppsala, Sweden. Phone: 46-18-663000; Fax: 46-18-504114.
3 The abbreviations used are: DCIS, ductal carcinoma in situ; LCIS, lobular CIS; BCS, breast-conserving therapy; NSABP, National Surgical Adjuvant Breast Project; SCR, Swedish Cancer Registry; CDR, Causes of Death Registry; CI, confidence interval; RH, relative hazard.
because the period of diagnosis covers the 1980s when mammography screening and BCS were introduced. In this cohort, we could not distinguish between DCIS and LCIS.

The study was approved by the Ethics Committee at Uppsala University Hospital.

Materials and Methods

The SCR. The SCR, established in 1958, has a high degree of completeness and includes 90–99% of all cases diagnosed with invasive cancer (25–27). The law requires that all malignant tumors, including CIS of the breast, be notified to the registry, but some benign lesions must also be reported. During 1991, ~40,000 cancers were registered, of which ~5,000 were breast cancers. The total population of Sweden was 8.6 million. In 1978 about 80% of cancers of all types were histologically confirmed (26), and in 1991 and 1993 the percentage was 97 (Statistics Sweden).

Up to 1980, DCIS was reported as invasive ductal cancer, but from 1980 onward, it was classified as in situ, as was LCIS also. In a validity control of the registry in the southern part of Sweden, the correctness of registration of CIS of the breast was found to be 93.8% and the completeness was 78.0% from 1982–1988. Correctness and completeness during 1989 and 1991 rose to 95.9% and 94.6%, respectively (27). There are no data on the correctness and completeness of “recurrences” after CIS or invasive breast cancer. The SCR also includes data from the national CDR. The CDR has recently been validated concerning breast cancer deaths in more than 2000 women. In Sweden, the correctness of registration of CIS of the breast was estimated to be 93.8% and the completeness was 78.0% from 1982–1988.

Study Base. In Fig. 1, we present the design of the study. Among women with subsequent invasive cancer, we could not distinguish between a new ipsilateral and contralateral cancer and whether the first sign of relapse occurred outside the breasts.

Methods. The following data were collected: age at diagnosis, date of diagnosis, date of diagnosis and location (ipsilateral versus contralateral) of a subsequent invasive breast cancer, date of death, and cause of death. We could not distinguish between LCIS and DCIS as the primary diagnosis for the cohort. We received information on the reporting hospital and were, thus, able to categorize the patients into those from counties where mammography screening was in use and counties where it was not.

The medical records were collected from the time of the primary diagnosis in women whose breast cancer was entered as the direct or indirect cause of death in the CDR (n = 78) or who later developed invasive cancer reported to the SCR, but were still alive (n = 94). Twenty-four of the women who died of breast cancer had a subsequent invasive breast cancer after the primary CIS, but this was not reported to the SCR. These 24 women were added to the 94 others. In 11 of these 24 patients, we could not verify the time of the new event and, instead, we used the time of death in our calculations of the probability of subsequent development of invasive cancer. We also collected medical records of women reported to have died of breast cancer from the years before death and the death certificates. On the basis of this information, we determined the cause of death and the correctness of the primary diagnosis.

Among women with subsequent invasive cancer, we could not distinguish between a new ipsilateral cancer and what clinically could have been classified as a true relapse. However, we could distinguish between ipsilateral and contralateral cancers and whether the first sign of relapse occurred outside the breasts.

Using the study base of 4661 women, we have also conducted a case-control study where we studied the risk for a subsequent invasive breast cancer or later breast cancer death after a primary DCIS.4 A case in this study was defined as a woman with a primary DCIS who later died of breast cancer or a woman with invasive cancer in either breast who was reported to the SCR at least 3 months after the diagnosis of DCIS. Four controls with a primary CIS were selected in each case. The controls were matched for the year of diagnosis and region of residence. When we selected the controls in this study we could not distinguish between DCIS and LCIS, and the 550 controls that were diagnosed between 1980 and 1992 were used as a sample to validate the cohort data. In the sample, all medical records from the time of the initial diagnosis, including the original histopathological report, were collected from the hospital where the patient was initially treated. We studied the correctness of registration and estimated the frequency of LCIS, the proportion of breast-conserving surgery, and mammographically-detected lesions over time.

Statistics. Life-table plots of overall and breast cancer-related survival and of relapse-free survival were constructed for the cohort of 3398 patients. Cox regression models were made to study the effects of age, time period, and screening activity on the risk of dying of breast cancer and the risk of developing subsequent invasive breast cancer. The age groups chosen were <40, 40–49, 50–59, 60–69, 70–79 and >79 years. The total study period was divided into the periods 1980–1982, 1983–1985, 1986–1988, and 1989–1992. In the analyses of the effects of screening, we compared regions having fully developed screening with those having no screening programs during each time period. Because not all women were offered screening in counties where randomized studies of mammography screening took place, these counties were excluded in the anal-

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4 Unpublished results.
yses of screening effects. We included only the 40–69 years age group in the analysis of screening effects because this age group is most often included in the screening programs. We studied models of age and time period and age and screening activity, but we did not study screening and time period together because of colinearity (in the latest period 1989–92, the screening was almost nationwide). Statistical Analysis Software was used in all statistical calculations.

Results

In the total cohort of 3398 women, the mean age at diagnosis was 58.6 years, ranging from 15.6–97.4 years. The mean age at diagnosis was stable during the study period (1980, 57.5 years; 1985, 58.8 years; 1992, 58.5 years). The number of cases reported annually increased during the period.

In our sample of 550 patients, the percentage of pure LCIS was 11.6. The percentages of LCIS over time were 14.4, 12.1, 6.7, and 12.9, respectively, during the time periods 1980–1982, 1983–1985, 1986–1988, and 1989–1992. In 4.5% of cases, the lesions were mixed (i.e., DCIS and LCIS). During the study period, the percentages of lesions detected by mammography increased from 26.8 in the first period to 58.8 in the last period. The use of breast-conserving surgery increased over time, and the percentages during each time period were 42.8, 40.2, 48.5, and 73.3, respectively. The histopathological reports showed that 11.1% of the lesions were invasive carcinomas, but many of these cases had a minimal area of invasiveness, and the lesion was referred to as microinvasive DCIS. In 2.2% of the lesions, the final diagnosis was benign. In 5.6%, there was a history of an earlier breast carcinoma, which was most common in the first time period [1980–1982 (13%)]. The percentages of women treated with radiotherapy postoperatively increased from 6.7 from 1980–1982 to 10.5 from 1989–1992; in the whole sample the percentage was 8.7.

During the follow-up period (mean, 4.3 years; 14,699 person-years of observation), 30 of the 78 deaths reported to be caused by breast cancer were classified by us as caused by breast cancer after studying the medical records and death certificates. Three of these 30 women had primarily a suspicious microinvasive cancer according to the pathological report, but were reported as a CIS. Only 5 of the 78 women with a death reported to be caused by breast cancer were autopsied. In 3 of the 78 women, we did not obtain the individual medical records. These deaths were included in the analyses as breast cancer deaths, and the total number of breast cancer deaths in the study were, thus, 33. In 45 of the 78 women, the cause of death was not related to breast cancer according to the medical records. Altogether, there were 255 other deaths.

One hundred fifteen women had a subsequent invasive breast cancer during follow-up. There were 53 ipsilateral and 42 contralateral events. In 16 of the 115 women, the first sign of relapse was generalized disease, and in one woman the relapse was an autopsy finding. One woman subsequently developed cancer in both breasts at the same time, and in three women information on the site of recurrence was lacking. The number of deaths due to breast cancer, the number of cases of subsequent invasive cancer, and the total number of patients in each age group in the different time periods are presented in Table 1.

The cumulative risk of subsequently developing invasive cancer is illustrated in Fig. 2. The risk was stable during the postoperative follow-up, a finding confirmed by calculating the yearly hazard of developing invasive breast cancer during the first 10 years of follow-up (data not shown). The cumulative risk was similar for ipsilateral and contralateral events, and the annual hazards were almost identical on the two sides.

At follow-up, the overall survival and the survival related to breast cancer deaths (corrected survival) were: 5 years, 90.9% (CI 95%, 89.7–92.2) and 99.1% (CI 95%, 98.7–99.5); 10 years, 81.6% (CI 95%, 79.2–84.0) and 97.4% (CI 95%, 96.3–98.5); and 12 years, 77.7% (CI 95%, 74.3–81.1) and 96.5% (CI 95%, 95.0–98.1), respectively. The corrected survival by time period is shown in Fig. 3. The 95% CIs are given for the longest follow-up only. The prognosis improved over time in each study period (log rank test, P = 0.005). A similar pattern was seen regarding the risk of a subsequent invasive breast cancer (log rank test, P = 0.03).

Cox analyses of corrected survival and relapse-free survival were performed with respect to time period and age group, with no allowance for screening activity. The results are shown in Table 2. The time period reference was 1980–1982, and the age-group reference 50–59 years. The risk of dying of breast cancer was highest in the youngest and the oldest age groups, but only in patients over 70 was it statistically significantly different from the reference group. The risk of a subsequent invasive cancer increased with age at diagnosis, but this finding was not statistically significant. As expected from the findings shown in Fig. 3, there was a trend toward a better prognosis in the latter part of the period studied. The survival was statistically significantly better in the last interval (1989–1992). The risk of developing a subsequent invasive cancer also tended to be lower in the latest time periods and was similar to the risk of death from breast cancer. In other models, we analyzed only age and only the time period of diagnosis, but these models had less fit than the model with both age and time period included (data not shown).

### Table 1 Number of BCDs and patients with invasive cancer over total number of patients in the cohort 1980–1992 with a primary diagnosis of CIS of the breast by age group and time period of diagnosis

<table>
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<tbody>
<tr>
<td>&lt;40</td>
<td>0 (0)/29</td>
<td>0 (2)/49</td>
<td>2 (2)/47</td>
<td>0 (0)/74</td>
<td>2 (4)/199</td>
</tr>
<tr>
<td>40–49</td>
<td>3 (7)/92</td>
<td>3 (8)/135</td>
<td>1 (4)/196</td>
<td>0 (7)/371</td>
<td>7 (26)/794</td>
</tr>
<tr>
<td>50–59</td>
<td>3 (11)/91</td>
<td>1 (4)/112</td>
<td>0 (5)/157</td>
<td>0 (6)/476</td>
<td>4 (26)/836</td>
</tr>
<tr>
<td>60–69</td>
<td>4 (11)/66</td>
<td>1 (7)/99</td>
<td>2 (9)/211</td>
<td>1 (7)/531</td>
<td>8 (34)/907</td>
</tr>
<tr>
<td>70–79</td>
<td>4 (8)/85</td>
<td>4 (8)/83</td>
<td>1 (3)/127</td>
<td>0 (1)/277</td>
<td>9 (26)/502</td>
</tr>
<tr>
<td>≥80</td>
<td>0 (0)/23</td>
<td>2 (3)/40</td>
<td>1 (2)/35</td>
<td>0 (0)/62</td>
<td>3 (5)/160</td>
</tr>
<tr>
<td>Total</td>
<td>14 (37)/366</td>
<td>11 (32)/518</td>
<td>7 (25)/773</td>
<td>1 (2)/741</td>
<td>33 (115)/3398</td>
</tr>
</tbody>
</table>

*BCD, breast cancer death; inv. ca, invasive cancer.*
We also attempted to analyze the effect of time periods separate from the introduction of screening; we made an analysis of the risk of dying from breast cancer by period of diagnosis up to 1988 and restricted it to women not covered by screening. The results showed a reduction in the RHs over time, but not so large as in the analysis of all women: 1983–1985 [1.0 (0.4–2.7)] and 1986–1988 [0.6 (0.2–1.7)], with the period 1980–1982 as reference.

A Cox regression model of RH of breast cancer death and subsequent invasive breast cancer to study the influence of mammography screening was performed. Women under 40 and over 69 years of age and women in counties where randomized trials of screening were being undertaken were excluded from this analysis. The reference groups were “no screening” and “50–59 years of age”. Fourteen women died from breast cancer, and 62 women developed an invasive breast cancer in this subgroup of 2121 women from the cohort. The risk of dying of breast cancer was five times lower in women from regions where mammography screening was fully developed than in those without a screening program, but the estimate was not statistically significant [RH, 0.2 (0.0–2.1)]. The risk to develop a subsequent invasive breast cancer was almost the same in those without a screening program, but the estimate was not statistically significant [RH, 0.2 (0.0–2.1)]. The risk to develop a subsequent invasive breast cancer was almost the same in both groups [RH, 0.9 (0.5–1.7)]. In a life-table analysis, there was no statistically significant difference in survival between the women coming from counties with screening programs and those coming from counties without screening after 4 years, which was the longest follow-up from screening counties.

Discussion
Our key finding concerning the main question under study—the time trends—is that women with a CIS of the breast had a better prognosis when diagnosed between 1989 and 1992 than from 1980–1983. To understand how changing diagnostic and treatment policies influence the change in prognosis, the cohort study provides information as in an ecological study: we have no individual data. However, the analysis comparing counties and periods with different screening policies suggests that screening may contribute to improved prognosis. During the 1980s, participation in screening programs was high (well over 80% in all programs), therefore, it is likely that detection with mammography is the main contributor to incident cases in counties with mammography screening programs. On the other hand, if screening is responsible for much of the improvement in prognosis, we cannot say whether we observed a lead time effect, or a natural history of CIS of a more benign type than the one detected in an ordinary clinical setting, or a really improved prognosis. We could not determine whether the histopathological criteria changed during this period, but the cohort study was done when reporting routines to the cancer registry were uniform. The increasing use of breast conservation over the years, may, indeed, increase the risk of subsequent invasive cancer events, but its effect has not been detected at the group level—one factor that contributes to this is probably the increasing use of postoperative radiotherapy.

Another important outcome of this study is that we can substantiate the findings of a few other larger studies (10, 19) that although these women run a considerably higher risk of developing invasive breast cancer than a normal background population, their prognosis is good, with a breast cancer corrected survival of more than 97% at 10 years. This has implications for information to patients and for interpretation of the clinical value of data on risk factors. Because events (i.e., breast...
cancer death and later development of invasive breast cancer) are so few, even risk groups with a rather high RH would still have a fair prognosis, and the presence of a risk factor would not necessarily require aggressive therapeutic action. For example, if we study age as a risk factor, women in the 50–59 years reference group had a 10-year failure of ~2%, and women in the 70–79 years age group had a RH of 4.0 and, thus, a 10-year failure of 8%. Usually, risk factors have been associated with smaller RHs than four. Our findings should, thus, be used only very cautiously in clinical management and should be regarded more as clues to understanding the natural history of the disease. In accord with other studies on invasive breast cancer (29–30), we found the same biphasic risk pattern regarding age and breast cancer death, whereas the pattern for subsequent invasive cancer was more difficult to interpret because of the large CIs and possibly different patterns of ipsilateral and contralateral cancers.

Nearly half of the morbidity in subsequent invasive cancers consists of contralateral events in the cohort. Hence, more than half of the invasive cancers after a previous in situ lesion are new cancers because many subsequent ipsilateral cancers are new cancers as well (13). In the cohort, <15% of the women had LCIS. Altogether, this challenges the old dogma that the cancer morbidity after DCIS is almost solely due to local recurrences and LCIS is “only” a marker of susceptibility to cancer (3, 10, 20–21). The ratio of contralateral to ipsilateral invasive cancers is obviously influenced by the use of BCS and of contralateral prophylactic mastectomy. Increasing use of adjuvant radiotherapy to the remaining breast after BCS, however, should result in local control similar to that with mastectomy (13). Prophylactic mastectomy was used in only a few cases during this time period (i.e., in a sample of 64 women with LCIS and 69 women with DCIS, 8 women with LCIS underwent a prophylactic contralateral mastectomy). Based on this sample, we estimated that a prophylactic contralateral mastectomy was performed in 1.2% of the whole cohort.

One of the limitations of this study is the correctness and completeness of the Swedish Cancer Registry. Although, the overall correctness and completeness concerning breast cancer in situ is high (27), we might suspect an underreporting of relapses or new cancers in women with an earlier CIS. We found 24 women with a subsequent invasive cancer not reported to the registry who later died from breast cancer. Women with a subsequent invasive cancer, but still alive, may be undetected. We can also suspect that a later ipsilateral or generalized breast cancer may be under-reported, whereas a contralateral cancer might be regarded as a new cancer and, therefore, more often correctly reported. Of the 24 unreported cases, 8 were ipsilateral events, 15 were generalized disease, and 1 was a contralateral cancer. Our conclusion is that ipsilateral cancer events may be under-reported, especially if they are concomitant with generalized disease. However, deaths are

![Fig. 3. The corrected survival by time period after a primary diagnosis of CIS. The 95% CIs are given.](image)

<table>
<thead>
<tr>
<th>Table 2</th>
<th>RHs from Cox regression model of RH of breast cancer death and of invasive breast cancer subsequent to breast CIS by age group and time period of diagnosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and time periods</td>
<td>Breast cancer death (n = 33)</td>
</tr>
<tr>
<td>40–49 years</td>
<td>1.4 (0.3–7.6)</td>
</tr>
<tr>
<td>50–59 years</td>
<td>1.6 (0.5–5.3)</td>
</tr>
<tr>
<td>60–69 years</td>
<td>Ref*</td>
</tr>
<tr>
<td>70–79 years</td>
<td>2.4 (0.7–8.0)</td>
</tr>
<tr>
<td>≥80 years</td>
<td>4.0 (1.2–13.0)</td>
</tr>
<tr>
<td>1980–1982</td>
<td>Ref*</td>
</tr>
<tr>
<td>1983–1985</td>
<td>0.7 (0.3–1.6)</td>
</tr>
<tr>
<td>1986–1988</td>
<td>0.5 (0.2–1.3)</td>
</tr>
<tr>
<td>1989–1992</td>
<td>0.1 (0.0–0.9)</td>
</tr>
</tbody>
</table>

*a Ref, reference.*
not missed, and the determination of breast cancer as cause of death in the registries are very similar to those obtained in studies of medical records (28, 31).

The completeness of the registry for CIS was lower in the first part of the study period (78% from 1982–1988) compared with the rate between 1989 and 1991, which was 94.6% (27). This might be due to the change in reporting of DCIS in the early 1980s. However, we could not detect a difference in the ratio between reported LCIS and DCIS during the study period reflecting any selective underreporting, and we have no reason to believe that the difference in between periods should bias the survival analyses.

Finally, this study has several implications for research. Women with CIS of the breast should be analyzed separately in clinical studies (e.g., in studies of screening). It is likely that the period of diagnosis, mode of detection, and age at diagnosis confound comparisons of treatments and risk factors in non-randomized studies or in studies comparing different series of patients. The margin for therapeutic improvement is small, and very large numbers of patients are needed to detect modest therapeutic effects.

References


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