Risk Factors for Subsequent Invasive Breast Cancer and Breast Cancer Death after Ductal Carcinoma in Situ: A Population-based Case-Control Study in Sweden

Fredrik Wärnberg, Jonas Bergh, Matthew Zack, and Lars Holmberg

In a case-control study derived from a cohort of 4661 women with a primary carcinoma in situ of the breast, we investigated age at diagnosis, mode of detection, tumor characteristics, and primary therapy, as prognostic factors for developing invasive breast cancer or dying from breast cancer. From all of the women with a primary carcinoma in situ reported to the Swedish Cancer Registry from 1960 through 1992, we selected as cases all of the women with a ductal carcinoma in situ who later died of breast cancer (n = 39) or who developed a subsequent invasive cancer in either breast (n = 118). From this cohort, we also selected controls matched to the cases by year of diagnosis and health care region. We conducted univariate and multivariate analyses to study the association between risk of invasive cancer or death and the different risk factors. Large size, diameter ≥25 mm [odds ratio (OR), 3.5; 95% confidence interval (CI), 1.1–11.4] and multifocality (OR, 3.9; 95% CI, 1.2–12.7) increased the risk of breast cancer death in univariate analysis. Postoperative radiotherapy (OR, 0.1; 95% CI, 0.0–1.0) and mastectomy (OR, 0.1–95% CI, 0.0–0.5) lowered the risk of an ipsilateral invasive cancer in multivariate analysis. The risk pattern by treatment category differed between those who had an ipsilateral invasive cancer and those who either had a contralateral cancer or died from breast cancer. The driving forces behind local and generalized disease may differ. Because confounding by indication may influence the effects of different treatments, the results should be interpreted with caution.

Introduction

During the last decade, the proportion of CIS among all of the detected cases of breast cancer in Sweden has increased, mainly because of the introduction of a nation-wide mammography-screening program. During the 1960s and 1970s, CIS constituted ~1–2% of all of the breast cancers reported to the SCR, but today this percentage is ~10%. DCIS has increased more than LCIS because DCIS is often detected by mammography, whereas LCIS is not.

Women treated for DCIS have a higher risk of ipsilateral invasive breast cancer ≤11 times that of women without DCIS (2–8). After mastectomy, the recurrence risk of both invasive and CIS is low, 0–10% after ≤9 years of follow-up (9–13). After BCS, the reported recurrence risk of ipsilateral events varies from 4 to 45% over a follow-up time of 3–8 years (9, 13–18). One-half or more of these new ipsilateral events are invasive (2, 9, 13–18). Radiotherapy after BCS lowers this recurrence risk considerably. In the NSABP B17 study (16), for example, after a mean follow-up of 43 months, XRT reduced the average annual incidence rate of ipsilateral breast cancer by more than 50%; more than 10% of the ipsilateral cancers were located in a quadrant other than the one with the primary cancer, which indicated that these might be new cancers rather than recurrences.

The risk of contralateral breast cancer after DCIS resembles that reported for women with invasive breast cancer. In a register study from Washington State, the cumulative incidence of contralateral breast cancer in 1929 patients with DCIS was 2.4% after 5 years and 6.1% after 10 years; 66% of these cancers were invasive (19). In the NSABP study, 2.3% of the 790 patients had a new contralateral event during a follow-up of 43 months (mean), of which 61% were invasive (16). In a Swedish cohort including 3398 women with a primary CIS diagnosed from 1980 through 1992, the cumulative incidence of subsequent invasive cancer was approximately 8% after 10 years, with equal risks ipsilaterally and contralaterally (20).

The risk of dying from breast cancer after a primary diagnosis of DCIS has been studied little and mostly in smaller institutional series, because such breast cancer deaths are uncommon. In a meta-analysis of 585 patients treated with mastectomy and 308 patients treated with local excision after a primary DCIS, only 1–3% had died after ~7 years follow-up (13). In our own population-based cohort study involving more than 3,000 women, only 2.6% had died from breast cancer after a primary diagnosis of DCIS, after 10 years follow-up (20).

The aim of this study was to determine whether easily identifiable clinical characteristics in women with a primary diagnosis of DCIS affected their risk of subsequent ipsilateral and contralateral invasive breast cancer and of breast cancer death. For this purpose, we designed a case-control study in two...
parts (with either new invasive cancers or breast cancer deaths as cases) nested within a population-based cohort.

Materials and Methods
The SCR. The SCR, established in 1958, is very complete because 90–99% of all of the diagnosed cancer cases are reported (21–23). Swedish law mandates that all of the malignant tumors, CIS of the breast, and some benign lesions be reported to the Registry. Before 1980, DCIS was reported as invasive ductal cancer, but since then, it has been classified as CIS. In a study of the validity of the Registry in southern Sweden, the correctness of registration of CIS during 1982–1988 was 93.8%, and the completeness, 78.0% (23); both correctness and completeness improved during 1989–1991 to 95.9 and 94.6%, respectively (23).

The Cancer Registry also includes data from the national CDR. In a recent validation study of more than 2,000 female breast cancer deaths, the registered cause of death in the CDR disagreed with that from autopsy reports and medical records in only 4.6% of the reported deaths (24). For this study, the data from these Registries were available up to December 31, 1992. This study has been approved by the Ethics Committee at Uppsala University Hospital.

Study Base. From 1960 through 1992, 6882 patients were reported to the SCR with a diagnosis of CIS. We excluded all of the women who had received a diagnosis of invasive breast cancer previously (n = 421) or on the same day or within 3 months after the diagnosis of the CIS (n = 1357), as well as all of the duplicates (n = 107) and all of the men (n = 36). The final study base consisted of 4661 women with a primary CIS of the breast, from whom we selected all of the cases and controls.

Cases and Controls. We split the case-control study into two parts, one relating to subsequent invasive cancer and the other relating to breast cancer death. We collected all of the women’s medical records from the time of the initial diagnosis, including the original histopathological report, from the hospitals where the women was initially treated and the medical records of the cases that died of breast cancer for the years before death. From these medical records, we abstracted data on the mode of detecting DCIS, its palpability, its location, and the primary therapy. From the histopathological reports, we abstracted data on tumor size, multifocality, margins, and histopathological subtype. No review of the histopathological slides was done. Because the histopathological subtype was not registered in the SCR during the study period, we excluded from both parts of the study all of the cases and controls with LCIS only, with invasive foci, or with only a unifocal lesions (we did not distinguish between unifocal and multicentric lesions); (f) tumor size of \( \geq 25 \) mm. This cutoff was chosen because it has been reported that microinvasion is more common in lesions measuring \( > 25 \) mm (26, 27).

For the analysis of risk factors related to subsequent invasive cancer in either breast, we defined a case as a woman with an invasive cancer reported to the SCR at least 3 months after the diagnosis of DCIS. We excluded as cases, those women in whom only metastases outside the breast were diagnosed; but we included women with a subsequent invasive cancer in either breast who later died of breast cancer (these women are, thus, cases for both parts of the study).

To each of these cases, we matched four controls, by year of diagnosis and by health care region. The controls had to be alive without a subsequent invasive cancer at the time of diagnosis of a breast cancer in the case but could later themselves become a case. For two of the cases, fewer than four controls were eligible.

Statistical Methods. Using the SAS procedure, PROC PHREG (25), we calculated ORs and their 95% CIs from univariate and multivariate conditional logistic regression models based on the matched case-control sets, to associate risk factors with subsequent invasive breast cancer, either ipsilateral or contralateral, or with breast cancer death. The risk factors that we studied included the following: (a) three age groups categorized as indicator variables: \( \leq 49 \) years old, 50–59 years old (the reference group), and \( \geq 60 \) years; (b) three different surgical treatments: BCS (sector resection or biopsy) without XRT (the reference group), BCS with XRT, and mastectomy; (c) two modes of detection (those detected clinically and those diagnosed by mammography prior to a clinical examination, either as an individually targeted screening or in a population-based program); (d) palpability of the lesion; (e) multifocal versus unifocal lesions (we did not distinguish between multifocal and multicentric lesions); (f) free margins (if the histopathological reports mentioned “free” margins; we assumed margins as free if the reports did not mention margins) versus having unclear or doubtful margins; and (g) tumor size of \( < 25 \) mm versus \( \geq 25 \) mm. This cutoff was chosen because it has been reported that microinvasion is more common in lesions measuring \( > 25 \) mm (26, 27).

Results
From 1960 through 1992, subsequent invasive breast cancer developed in 162 women with DCIS, and breast cancer later caused death according to the SCR in 113 women with DCIS. To these cases we matched 638 and 452 controls, respectively. Of the 1365 medical records requested on these cases and controls, we obtained 1281 (94%): 81% (104/129) from those diagnosed in the 1960s, 92% (323/341) from those diagnosed in the 1970s, and 95% (854/895) from those diagnosed from 1980 through 1992. We obtained 96% (263/275) of the records from the cases and 93% (1018/1090) from the controls.

Of the 1281 cases and controls whose records were obtained, 711 were excluded from the analyses (Table 1). For 113 women, the histopathological report showed invasive cancer most often described as microinvasion. Nineteen tumors diagnosed only by cytology were mainly clinically invasive cancers, many of them either inoperable or in patients with generalized disease. Of the 113 women reported to have died from breast cancer, 4 had no available medical records, 21 died from other causes according to the medical records, and 49 were excluded because of other reasons. Most of those excluded were controls (n = 386), whose originally matched cases no longer fulfilled the criteria for being a case.

The 570 women remaining in the study included 70 cases with a subsequent ipsilateral cancer, 48 with a subsequent contralateral cancer, 39 cases who died from breast cancer, and their corresponding controls (Table 2). Because an ipsilateral or contralateral invasive breast cancer developed in 19 of the women
before they died from breast cancer, these 19 women are counted twice because they were included in both parts of the study. In 10 of these 19 cases, we ascertained the occurrence of their invasive breast cancer after the diagnosis of DCIS, not from the SCR reports, but only after scrutinizing their medical records. These 10 cases were, thus, included in the study of subsequent invasive breast cancer, and 20 new matched controls were selected from those eligible in the study of breast cancer deaths.

Of the 39 women who died from breast cancer, an ipsilateral invasive cancer developed in 15, 7 of whom had undergone a mastectomy. A contralateral invasive cancer developed in four women. In 19 women, generalized disease developed without a mastectomy. A contralateral invasive cancer developed in 22 women, 7 of whom had undergone a mastectomy. Not surprisingly, size and treatment category may be mutually confounding, because larger tumors were more common in older women. Not surprisingly, size and treatment category may be mutually confounding, because XRT or mastectomy is chosen more often than breast conservation alone for larger tumors. Tumor size ≥25 mm and multifocality significantly increased the risk of breast cancer death (Table 3). The 50–59-year-old group had nonsignificantly lower risk of breast cancer death than either the younger or the older age groups. Mode of detection, palpability, free margins, and type of treatment did not seem to affect this risk.

Compared with BCS without XRT, BCS with XRT and mastectomy significantly lowered the risk of new ipsilateral invasive cancers. Palpable tumors also lowered this risk but not statistically significantly. No other risk factor appeared to affect risk.

Multivariate Conditional Logistic Regression. In building the statistical models, a palpable tumor, larger histopathological tumor size, and clinical mode of detection were highly correlated. To avoid potential collinearity, we kept tumor size in the multivariate models, because this determinant gave a better fit (as determined by comparing the log likelihood of the models) in the models than the other two (palpability and mode of detection) did. In one model, we substituted palpability of the tumor for tumor size if the size was missing, and we substituted mode of detection if both size and palpability were missing. The estimates or model fits did not change materially (data not shown). Because much of the information about multifocality and margins of excision was missing, these determinants were unstable in the multivariate models and were omitted from the models because they did not contribute to the model fit.

The final models included age group, size, and treatment category (Table 4). Comparing how the ORs changed from the univariate analysis through the possible intermediate two-factor models [age + size; age + treatment; size + treatment (data not shown)] to the final model further clarified their relationship.

For breast cancer deaths, adding tumor size both diminished and type of treatment were also probably mutually confounding because adding size to the models enhanced the protective effect of mastectomy and XRT on ipsilateral breast cancer occurrence. In the models for contralateral invasive breast cancer, size and type of treatment were mutually confounding because adding size to the models substantially diminished the effect of BCS with XRT on contralateral invasive cancer occurrence.

Discussion
In this study of outcomes after DCIS, the numbers of subsequent invasive cancers and deaths exceeded those in other DCIS studies.
Prognosis in Breast CIS Patients

Clearly defined if the thermore, although the histopathological reports were usually events, this power is still low for studying patient subsets. Further, histopathological reports. Even with a comparably large number of low statistical power and the variable quality of information in the original medical records were identified and retrieved. Similarly since that time. Finally, a very high proportion of the selection of controls. Matching controls to cases on the year of diagnosis and on health care region minimized the possible effects of periodic or local differences in reporting. Within each health care region, regional breast cancer working groups have established guidelines for treatment since the end of the 1970s. Thus, within each region and period, treatment protocols have been similar since that time. Finally, a very high proportion of the original medical records were identified and retrieved.

The main methodological limitations of this study include the number of cases and the corresponding years of follow-up in the underlying cohort were large. This case-control study was nested in a clearly defined population-based cohort of all of the women with a CIS of the breast reported to the SCR during 33 years. The completeness both of registration and follow-up is high, and determination of causes of death has been validated. The population-based cohort allowed an unbiased selection of controls. Matching controls to cases on the year of diagnosis and on health care region minimized the possible effects of periodic or local differences in reporting. Within each health care region, regional breast cancer working groups have established guidelines for treatment since the end of the 1970s. Thus, within each region and period, treatment protocols have been similar since that time. Finally, a very high proportion of the original medical records were identified and retrieved.

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As in most observational studies, the estimates of the effect of different treatment strategies must be interpreted very cautiously. Confounding by severity or other selection mechanisms may heavily influence these estimates, particularly because the multivariate models show that tumor size and choice of treatment were mutually confounded. The decision to give radiotherapy at a time when this was not a routine practice was probably based on patient characteristics that could have influenced the prognosis. However, for confounding alone to explain very low (such as ≤0.25) or high (such as ≥4.0) ORs, the effect of this confounder on the outcome must be very strong (28, 29). Theoretically, it would also have been preferable if we could have separated the ipsilateral invasive events into true recurrences and new tumors, but any attempt to do so was deemed unreliable.

Tumor size is an important, clinically relevant, prognostic factor for subsequent ipsilateral cancer, contralateral cancer, or breast cancer death. This relevance implies different preventive strategies for women with previous DCIS. The strong protective effect on ipsilateral cancer recurrence from postoperative irradiation or mastectomy was expected (30). However, postoperative irradiation and mastectomy did not protect against contralateral cancer or breast cancer death. After treatment for invasive breast cancer, the risk of a contralateral cancer is believed to be equal or slightly increased after postoperative irradiation (relative risk, 1.0–1.3; Refs. 31–33). Bilateral mammography thus remains necessary during follow-up for those undergoing only BCS, and mammography for the opposite breast remains necessary for those undergoing BCS with XRT.

### Table 3 Variables associated univariately with breast cancer death and development of invasive cancer in either breast after a primary DCIS of the breast

<table>
<thead>
<tr>
<th>Variable</th>
<th>Breast cancer death OR (95% CI) [cases/controls]</th>
<th>Subsequent invasive cancer OR (95% CI) [cases/controls]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ipsilateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contralateral</td>
</tr>
<tr>
<td>Total</td>
<td>[39/99]</td>
<td>[70/185]</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>[48/129]</td>
</tr>
<tr>
<td>&lt;50 yr</td>
<td>1.5 (0.5–4.3) [13/37]</td>
<td>0.6 (0.3–1.2) [19/69]</td>
</tr>
<tr>
<td>50–59 yr</td>
<td>Ref* [7/28]</td>
<td>Ref [17/37]</td>
</tr>
<tr>
<td>≥59 yr</td>
<td>2.5 (0.8–7.8) [19/34]</td>
<td>1.2 (0.6–2.6) [34/79]</td>
</tr>
<tr>
<td>Mode of detection, mammography vs. clinical</td>
<td>0.8 (0.3–2.0) [37/98]</td>
<td>0.9 (0.4–1.8) [68/183]</td>
</tr>
<tr>
<td>Palpable, yes vs. no</td>
<td>1.2 (0.5–2.6) [38/98]</td>
<td>0.5 (0.3–1.0) [60/184]</td>
</tr>
<tr>
<td>Free margins, no or doubtful vs. yes</td>
<td>1.7 (0.3–10.3) [30/84]</td>
<td>1.3 (0.4–3.9) [45/160]</td>
</tr>
<tr>
<td>Size, ≥25 mm vs. &lt;25 mm</td>
<td>3.5 (1.1–11.4) [24/65]</td>
<td>1.0 (0.4–2.2) [43/117]</td>
</tr>
<tr>
<td>Size, multifocal or multicentric vs. unifocal</td>
<td>3.9 (1.2–12.7) [24/65]</td>
<td>1.1 (0.5–2.5) [43/117]</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCS</td>
<td>Ref [13/32]</td>
<td>Ref [10/29]</td>
</tr>
<tr>
<td>BCS + XRT</td>
<td>0.3 (0.0–0.8) [19]</td>
<td>0.1 (0.0–0.8) [21/13]</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>1.1 (0.5–2.8) [25/57]</td>
<td>0.2 (0.1–0.4) [18/104]</td>
</tr>
</tbody>
</table>

*Ref, Reference group with an odds ratio 1.0.

### Table 4 Variables associated multivariately with breast cancer death and development of invasive cancer in either breast after a primary DCIS of the breast

<table>
<thead>
<tr>
<th>Variable</th>
<th>Breast cancer death OR (95% CI) [cases/controls]</th>
<th>Ipsilateral cancer OR (95% CI) [cases/controls]</th>
<th>Contralateral cancer OR (95% CI) [cases/controls]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>[39/99]</td>
<td>[70/185]</td>
<td>[48/129]</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 yr</td>
<td>1.6 (0.8–8.3) [13/37]</td>
<td>0.7 (0.2–2.4) [19/69]</td>
<td>0.7 (0.2–2.7) [17/51]</td>
</tr>
<tr>
<td>50–59 yr</td>
<td>Ref* [7/28]</td>
<td>Ref [17/37]</td>
<td>Ref [13/26]</td>
</tr>
<tr>
<td>≥59 yr</td>
<td>1.2 (0.2–7.5) [19/34]</td>
<td>0.9 (0.2–3.4) [34/79]</td>
<td>1.2 (0.3–4.3) [18/52]</td>
</tr>
<tr>
<td>Size, ≥25 mm vs. &lt;25 mm</td>
<td>2.9 (0.8–10.1) [24/65]</td>
<td>2.3 (0.7–7.0) [43/117]</td>
<td>1.7 (0.5–5.1) [25/73]</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCS + XRT</td>
<td>1.4 (0.1–18.1) [1/9]</td>
<td>0.1 (0.0–1.0) [2/13]</td>
<td>3.6 (0.3–43.5) [6/4]</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>1.8 (0.4–7.6) [25/57]</td>
<td>0.1 (0.0–0.5) [18/104]</td>
<td>0.7 (0.2–2.9) [30/82]</td>
</tr>
</tbody>
</table>

*Ref, Reference group with an odds ratio 1.0.
We could not corroborate the reports of other studies on DCIS (15, 34) that younger age at diagnosis entails a higher risk of a local recurrence. However, a biphasic pattern regarding age and risk of breast cancer death after an invasive breast cancer has earlier been noted (35, 36).

Apart from the unfavorable prognostic influence of tumor size, the pattern of risk by treatment category for ipsilateral new invasive cancers differs from that for breast cancer death and contralateral cancer. This difference challenges the idea that the main path from a primary DCIS to breast cancer death runs from local progression in the breast to invasiveness, then to metastases, and ultimately to death. However, most of the deaths may arise from patients who actually had an invasive cancer from the start, but where the invasiveness was not diagnosed. The probability of overlooking an invasive part of the tumor increases with increasing tumor size. Much effort must be invested in finding those cases to be able to adjust treatment and avoid later breast cancer deaths. Also, remnants of DCIS in the remaining breast or the mastectomy scar may progress to invasiveness and still be capable of metastasizing without giving any clinical signs of local recurrence. In general, however, this explanation is difficult to reconcile with the very low propensity of DCIS to metastasize to axillary lymph nodes (10, 26).

References
18. Rutqvist, L. E., and Wallgren, A. Inconsistencies in breast carcinoma registra-
20. Mattsson, B., and Wallgren, A. Completeness of the Swedish Cancer Regis-
22. Garne, J. P., Aspgren, K., and Möller, T. Validity of breast cancer registra-
26. Lagios, M. D., Westdahl, P. R., Margolin, F. R., and Rose, M. R. Duct carcinoma in situ: relationship of extent of noninvasive disease to the frequency of occult invasion, multicentricity, lymph node metastases, and short-term treat-
31. Storm, H. H., Anderssen, M., Boice, J. D., Blettner, M., Stovall, M., Mourid-
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