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Original Paper

Histological Determinants for Different Types of Local Recurrence after Breast-conserving Therapy of Invasive Breast Cancer

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The purpose of this study was to determine which histological factors are associated with an increased risk for local recurrence in the breast after breast-conserving therapy for early breast cancer (TNM stage I and II) and whether risk patterns vary according to menopausal status and type of local recurrence. Through complete follow-up of the patients of eight regional radiation oncology departments, two cancer institutes and one surgical clinic in The Netherlands, 360 patients were identified with local recurrence in the breast after having received breast-conserving therapy (local tumour excision, axillary dissection and irradiation of the whole breast and a boost to the tumour bed) during the 1980s. For each case, two controls with a follow-up of similar duration without local recurrence were randomly selected. Histological slides of the primary tumour were reviewed. Among premenopausal patients the risk of recurrence for those younger than 35 years was significantly higher than that for premenopausal patients of 45 years or older (relative risk (RR) 2.9; 95% confidence interval (95% CI) 1.3–6.6, $P<0.05$). The risk of recurrence at or near the site of the primary tumour was most significantly increased for patients with high grade extensive intraductal component (EIC) adjacent to the primary tumour (RR 4.1; 95% CI 1.7–9.8, $P<0.01$). Microscopic margin involvement was an important risk indicator for diffuse recurrence and recurrence in the skin of the breast, especially in the presence of vascular invasion (RR 25; 95% CI 4.0–150, $P<0.001$). To prevent local recurrence at or near the site of the primary tumour, local excision with a 1–2 cm margin of healthy tissue and a 15 Gy boost seemed adequate local treatment for patients with well differentiated EIC. In contrast, a wider surgical margin, a higher boost dose or mastectomy should be considered for patients with poorly differentiated EIC. Microscopic margin involvement in the presence of vascular invasion significantly increases the risk of diffuse recurrence or recurrence in the skin. **© 1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

RANDOMISED STUDIES set up to compare breast conservation therapy (BCT) with mastectomy have demonstrated equal survival rates for the two therapeutic modalities [1–5]. However, a recent overview of randomised trials revealed substantially different effects on the rates of local recurrence in the breast, depending on the type of local treatment [6]. Whereas the impact of differences in local control after BCT on breast cancer-related death is still equivocal [7–9], the detrimental effect of local recurrence on the patient's quality of life is obvious. Risk factors for local recurrence after BCT have been studied extensively to improve patient selection and to find a balance between recurrence risk and cosmetic outcome. A higher risk of recurrence has been found for younger patients [10–15], patients with larger tumours [16], infiltrating tumours with an extensive intraductal component (EIC) [17–20], vascular invasion [21, 22], and microscopic margin involvement [11, 21, 23, 24].

Patients with local recurrence represent a clinically and biologically heterogeneous group. When recurrence occurs at or near the site of the primary tumour it probably represents clonogenic outgrowth of the residual tumour and is classified as 'true' recurrence or 'marginal miss'; in other cases recurrence is found at a clear distance from the primary tumour bed, probably representing a second primary tumour. None the less, in most studies these different types of recurrence have not been analysed separately, which could have weakened or obscured certain risk factors. In addition, the analyses were often limited by the small number of patients with local recurrence. We conducted a population-based multicentre case–control study in The Netherlands of 360 patients with local recurrence after BCT and two matched controls per patient with a follow-up of similar duration without local recurrence. In order to determine which factors are associated with an increased risk of local recurrence various histological characteristics of the patients with local recurrence and their matched controls were compared after a pathological review of the primary tumour.

PATIENTS AND METHODS

Patients

A case–control study of local recurrence after BCT was conducted among approximately 7000 consecutive patients with TNM stage I and II breast cancer [25] who received BCT in the period 1980–1992. Patient data were obtained from eight departments of radiotherapy, two cancer institutes and one department of surgery in The Netherlands, which maintained complete records on all their patients with invasive breast cancer, including information on the date of local recurrence in the breast, and axillary or distant recurrence of disease. In all institutes follow-up was completed at least until 1994. During follow-up, 360 patients with local recurrence after BCT were identified. Local recurrence was defined as a new tumour occurring in the preserved breast or overlying skin at least 3 months after the date of local excision or re-excision.

For each subject with local recurrence, 2 controls were randomly selected from the same institute. The main requirement was that each control had survived without local recurrence for at least as long as the time between BCT and diagnosis of the recurrence for the corresponding case. Other matching factors included menopausal status (premenopausal versus postmenopausal) and postsurgical axillary nodal status (node-positive versus node-negative). In one institute cases and controls were matched on age ($\leq$50 or $>$50 years of age) due to missing data on menopausal status. In another institute more than 2 controls were selected for some postmenopausal cases. Overall, 769 controls were matched to the 360 patients with local recurrence. The patients of the Netherlands Cancer Institute were part of a previously published study on risk factors for local recurrence after BCT [22].

Treatment

BCT generally consisted of wide local excision of the tumour with an attempted margin of at least 1 cm of healthy tissue and axillary dissection, followed by 45–50 Gy whole breast irradiation in fractions of 1.8 or 2.0 Gy five times a week. An additional boost was given to the tumour bed by an external beam technique, using either photons or electrons, or by the use of iridium 192 interstitial implants. Total boost doses varied between 15 and 25 Gy but were sometimes higher for iridium 192 implants. Adjuvant systemic therapy was given only to axillary node-positive patients; in general premenopausal patients received six cycles of adjuvant cyclophosphamide, methotrexate and 5-fluorouracil (CMF) combination chemotherapy, given after the completion of radiotherapy, whereas postmenopausal patients received 20 mg of tamoxifen daily for at least 1 year.

Data collection

All data were entered into a central database at the Eindhoven Cancer Registry. Local investigators used the complete medical records to obtain detailed data recorded on standardised forms. Complete treatment details were obtained for all cases and their matched controls. Information on the extent and localisation of local recurrence was collected to classify the cases according to the type of recurrence.

Representative slides of the primary tumour were available for review for 326 of the 360 cases with breast recurrence (91%) and 716 of the 769 controls (93%). During 1995 and 1996 the slides were reviewed by three pathologists; one reviewing 60% and the other two receiving 20% each. They used standardised forms and well-defined criteria. The case–control status was unknown to the reviewing pathologists. The largest tumour diameter and the size of the tumour specimen were taken from the original pathology report. The tumours were classified according to WHO criteria. The microscopic aspect of the tumour margin was classified as clearly outlined (round or stellate) or poorly outlined (diffuse or multinodular). The extent of the intraductal component was considered moderate if the number of ducts with intraductal cancer in breast tissue directly adjacent to the primary tumour was between 2 and 9. When 10 or more ducts were involved the intraductal component was classified as extensive (EIC+). Tumours predominantly consisting of ductal carcinoma *in situ* (DCIS) with focal areas of invasion were also classified as EIC+. DCIS was classified as cytonuclear high grade (with a comedo or solid pattern) or low grade (with a non-comedo, i.e. cribriform or micropapillary pattern). Vascular invasion was considered to be present if distinct tumour emboli were seen in more than three endothelium-lined vessels, including both blood and lymphatic vessels. Margins were considered microscopically involved when invasive and/or intraductal carcinoma was found on the surface of the specimen and doubtful if the

Table 1. *Number of cases and controls available for the analysis and the period during which they underwent breast-conserving therapy (BCT), according to institute*

Institute	Cases ($n = 279$)	Controls ($n = 555$)	Period of BCT*
Leiden University Medical Centre	66	124	1980–1992
Dr Daniël den Hoed Cancer Centre, Rotterdam	47	90	1981–1984
Dr Bernard Verbeeten Instituut, Tilburg	42	83	1981–1987
Netherlands Cancer Institute, Amsterdam	38	67	1980–1987
Comprehensive Cancer Centre South, Eindhoven	35	107	1981–1990
Radiotherapeutisch Instituut Friesland, Leeuwarden	15	24	1983–1990
Radiotherapeutisch Instituut Stedendriehoek, Deventer	18	30	1984–1990
Medisch Spectrum Twente, Enschede	6	11	1986–1989
Academic Hospital Maastricht	5	8	1985–1989
Zeeuws Radiotherapeutisch Instituut, Vlissingen	4	7	1990–1992
Academic Medical Centre, Amsterdam	3	4	1986–1990

*Follow-up was completed until 1994.

tumour was seen at a distance of less than one high power field diameter from the resection plane. Otherwise the margin was called free. The mitotic activity index (MAI) was defined as the number of mitotic figures in 10 adjacent high-power fields (HPF) [26]. The mitotic figures were counted in the most cell-rich areas in the invasive tumour margins, avoiding necrotic areas. The tumours were divided into three categories: ≤ 5, 6–19 and ≥ 20 mitotic figures/HPF.

We excluded 87 patients (34 cases (9%) and 53 controls (7%)) from the analysis for whom histopathological slides of the primary tumour were not available and 39 patients (11 cases (3%) and 28 controls (4%)) whose primary tumours showed intraductal cancer only, as determined at the pathology review. Also excluded were 28 cases (8%) (and their matched controls) with local recurrence more than 3 months after the diagnosis of distant metastases. After these exclusions, 279 case–control pairs (78%) remained available for the analysis (Table 1).

Statistical methods

The relative risks of local recurrence associated with patient and tumour characteristics were estimated by comparison of the distribution between the case and her matched controls by means of conditional logistic regression methods for individually matched pairs [27]. Relative risk estimates (RR), two-sided P values, and 95% confidence intervals (95% CI) were calculated with the microcomputer programme EGRET (SERC, Seattle, Washington, U.S.A.); comparisons between different levels of determinants were based on likelihood-ratio tests. Multivariate analyses were performed to account simultaneously for potentially confounding effects for the group as a whole; they were stratified according to menopausal status and the localisation of local recurrence (at or near the excision area versus diffuse or with skin involvement). The variables included in the multivariate models were: age at date of breast-conserving surgery, pathological tumour diameter, histological type, aspect of tumour margin, mitotic index, the extent and grade of the intraductal component, vascular invasion and microscopic margin involvement. By matching controls according to institute, we incorporated adjustment for important confounders such as radiotherapy technique and dose, which were highly standardised within the institutes. By matching for menopausal status and postsurgical nodal status we adjusted for the potential confounding effect of adjuvant systemic treatment. Therefore, additional adjustment for treatment-related factors in the multivariate analyses was not considered necessary. Subjects with unknown values for the variables determined at pathology review were excluded from the multivariate analyses unless they were incorporated as a separate category (as was the case for outline of the tumour margin and microscopic margin involvement).

Table 2. *Patient and treatment characteristics*

	Cases ($n = 279$)	Controls ($n = 555$)
Variable	n (%)	n (%)
Period of BCT		
1980–1983	88 (32)	168 (30)
1984–1987	126 (45)	266 (48)
1988–1992	65 (23)	121 (22)
Menopausal status		
Premenopausal	171 (61)	320 (58)
Postmenopausal	108 (39)	235 (42)
Postoperative nodal status (pN)		
Negative	184 (66)	368 (66)
Positive	95 (34)	187 (34)
Re-excision		
Yes	57 (20)	115 (21)
No	219 (78)	433 (78)
Unknown	3 (1)	7 (1)
Boost type		
External (electrons or photons)	172 (62)	383 (69)
Iridium implant	91 (33)	162 (29)
None	3 (1)	5 (1)
Unknown	13 (5)	5 (1)
Total radiotherapy dose (Gy)		
≤ 65	69 (25)	149 (27)
66–70	82 (29)	166 (30)
71–75	32 (11)	63 (11)
>75	29 (10)	50 (9)
Unknown	67 (24)	127 (23)
Interval between surgery and start radiotherapy (weeks)		
≤ 6	202 (72)	413 (74)
>6	75 (27)	138 (25)
Unknown	2 (1)	4 (1)
Adjuvant systemic treatment		
No	167 (60)	324 (58)
Yes	57 (20)	129 (23)
Unknown	55 (20)	102 (18)

RESULTS

Of the 279 cases 219, (78%) developed local recurrence as the first sign of failure, and 60 (22%) exhibited recurrence within 3 months before or after distant metastases. Of all recurrences 152 (54%) were detected within 3 years of BCT, 78 (28%) between 3 and 5 years, and 49 (18%) more than 5 years after BCT. In 160 (57%) cases recurrence was localised at or near the site of the primary tumour (25 together with distant metastases) and in 33 (12%) local recurrence occurred elsewhere in the breast, at a clear distance from the primary tumour bed (four together with distant metastases). 42 cases (15%) had diffuse recurrence with multiple localisations or extending through the parenchyma of the entire breast (14 with distant metastases), and 29 (10%) had recurrence in the skin of the breast (14 with distant metastases). For 15 cases (5%) insufficient information was available to classify the recurrence according to the above criteria.

The matching procedure resulted in an equal distribution among cases and controls of the year of diagnosis, menopausal status, postoperative nodal status and treatment characteristics (Table 2).

Risk factors for the total group

Table 3 shows the unadjusted and adjusted RR's for local recurrence for the total group. Adjustment for all variables simultaneously substantially altered the risk estimates. In the multivariate analysis, age at BCT was a significant predictor of local recurrence. The relative risk of 0.96 ($P<0.01$) indicates that an increase in age of one year resulted in a 4% decrease of the recurrence risk. Significantly increased risks were found for patients with high grade EIC (RR 3.0, $P<0.01$) and high grade intraductal component of minimal or moderate extent (RR 1.8, $P<0.05$). The significantly elevated recurrence risk for patients with microscopically involved tumour margins or doubtful involvement of the margins (RRs 2.0, $P<0.01$ and 1.8, $P<0.01$ respectively) disappeared in the multivariate analysis, suggesting a relation with other factors. The significant predictive effect of the mitotic activity index (MAI) in the univariate analysis also disappeared in the multivariate analysis. This was explained by the strong association between MAI and the grade of the intraductal component. Patients with lobular breast cancer appeared to have a recurrence risk similar to that found for patients with ductal cancer. The risk of recurrence for

Table 3. Unadjusted and adjusted relative risks (RR) for local recurrence, all patients

Variable	Cases/controls (279/555)	Unadjusted RR (95% CI)		Adjusted RR* (95% CI)	
Age, per year increase		0.96§	(0.94–0.98)	0.96‡	(0.93–0.99)
Tumour diameter (cm)					
0–2.0	199/413	1.0	(–)	1.0	(–)
≥2.1	78/135	1.2	(0.86–1.7)	1.1	(0.74–1.7)
ND	2/7				
Histological type					
Ductal	229/406	1.0	(–)	1.0	(–)
Lobular/mixed	26/62	0.75	(0.45–1.2)	1.0	(0.45–2.2)
Other	24/87	0.46‡	(0.28–0.76)	0.62	(0.33–1.2)
Mitotic index (per 10 HPF)					
≤5	92/257	1.0	(–)	1.0	(–)
6–19	99/169	1.6†	(1.1–2.2)	1.1	(0.65–1.8)
≥20	74/98	2.0§	(1.3–3.0)	1.5	(0.82–2.6)
ND	14/31				
Outline of tumour margin					
Clearly outlined	171/386	1.0	(–)	1.0	(–)
Poorly outlined	51/68	1.6†	(1.1–2.4)	1.6	(0.89–2.8)
ND	57/101	1.9	(0.79–4.5)	1.7	(0.47–5.9)
Intraductal component					
No	76/203	1.0	(–)	1.0	(–)
Minimal/moderate, low grade	52/162	0.92	(0.60–1.4)	0.95	(0.55–1.6)
Minimal/moderate, high grade	83/109	2.1§	(1.4–3.2)	1.8†	(1.1–3.0)
Extensive, low grade	16/28	1.7	(0.83–3.5)	1.9	(0.84–4.4)
Extensive, high grade	42/28	4.3§	(2.4–7.7)	3.0‡	(1.5–6.0)
ND	10/25				
Vascular invasion					
No	167/377	1.0	(–)	1.0	(–)
Yes/doubtful	88/142	1.5†	(1.1–2.2)	1.1	(0.72–1.8)
ND	24/36				
Microscopic margin					
Free	115/289	1.0	(–)	1.0	(–)
Involved	37/50	2.0‡	(1.2–3.2)	1.7	(0.91–3.1)
Doubtful	57/84	1.8‡	(1.2–2.7)	1.6	(0.92–2.7)
ND	70/132	1.3	(0.87–2.0)	1.4	(0.82–2.3)

*All variables listed fitted simultaneously. Adjusted relative risks are based on 231 case–control sets. †$P<0.05$, ‡$P<0.01$ §$P<0.001$. ND, not determined.

patients with other, less common histological types, such as tubular and medullary cancer tended to be lower. The decrease in risk, however, was not significant. Patients with tumours >2 cm did not show a higher risk of recurrence.

Risk factors according to menopausal status

After stratification according to menopausal status the effects on the risk of recurrence changed considerably for some variables (Table 4). The effect of age and microscopic margin involvement were much more pronounced in premenopausal patients, the risk for patients younger than 35 years being 2.9 times higher risk ($P<0.05$) compared with that for premenopausal patients of 45 years or older. For premenopausal patients the risk appeared to be higher for high grade EIC (RR 2.1) as well as low grade EIC (RR 3.0, $P<0.05$), whereas for postmenopausal patients only those with high grade EIC were at an increased risk (RR 8.4, $P<0.01$). Among the postmenopausal patients those with a high grade intraductal component of minimal or moderate extent were also exposed to a markedly increased risk of recurrence (RR 5.3, $P<0.001$).

Risk factors for recurrence at or near the site of the primary tumour

After adjustment for all morphological variables the RRs were significantly increased for patients with a poorly outlined tumour margin (RR 2.6, $P<0.05$) and for patients with high grade EIC (RR 4.1, $P<0.01$). Among patients for whom the tumour margin was considered doubtful the risk of recurrence at or near the site of the primary tumour was increased (RR 1.7), although this was not statistically significant. The risk for patients with medullary or tubular cancer or other rare histological tumour types was 0.6 times lower compared with those with ductal cancer; however, this

Table 4. Adjusted relative risks (RR) for local recurrence, according to menopausal status

	Premenopausal			Postmenopausal		
Variable	Cases/controls (171/320)	Adjusted RR* (95% CI)		Case/controls (108/235)	Adjusted RR* (95% CI)	
Age group (years)						
>45	43/105	1.0	(–)			
35–44	89/179	1.2	(0.67–2.0)			
<35	39/36	2.9†	(1.3–6.6)			
Age group (years)						
≥65				11/39	1.0	(–)
55–64				39/90	1.4	(0.39–4.8)
<55				58/106	1.5	(0.46–4.9)
Tumour diameter (cm)						
0–2.0	122/240	1.0	(–)	77/173	1.0	(–)
≥2.1	47/75	1.2	(0.72–2.4)	31/60	0.70	(0.28–1.7)
ND	2/5			0/2		
Histological type						
Ductal	135/234	1.0	(–)	94/172	1.0	(–)
Lobular/mixed	19/30	1.4	(0.49–3.8)	7/32	0.36	(0.08–1.7)
Other	17/56	0.65	(0.30–1.4)	7/31	0.47	(0.14–1.5)
Mitotic index (per 10 HPF)						
≤5	55/131	1.0	(–)	37/126	1.0	(–)
6–19	56/101	0.99	(0.52–1.9)	43/68	1.2	(0.51–3.0)
≥20	50/69	1.5	(0.70–3.2)	24/29	1.7	(0.61–4.5)
ND	10/19					
Intraductal component						
No	48/100	1.0	(–)	28/103	1.0	(–)
Minimal/moderate, low grade	31/89	0.79	(0.38–1.6)	21/73	1.0	(0.38–2.7)
Minimal/moderate, high grade	46/78	1.2	(0.60–2.3)	37/31	5.3§	(2.1–13.8)
Extensive, low grade	15/18	3.0†	(1.1–8.4)	1/10	0.23	(0.02–2.8)
Extensive, high grade	26/22	2.1	(0.84–5.1)	16/6	8.4‡	(2.4–29.8)
ND	5/13			5/12		
Vascular invasion						
No	102/214	1.0	(–)	65/163	1.0	(–)
Yes/doubtful	58/86	1.3	(0.75–2.3)	30/56	1.1	(0.45–2.7)
ND	11/20			13/16		
Microscopic margin						
Free	67/157	1.0	(–)	48/132	1.0	(–)
Involved	21/33	2.6†	(1.1–5.8)	16/17	1.2	(0.37–4.0)
Doubtful	38/50	2.5†	(1.2–5.3)	19/34	1.1	(0.41–3.0)
ND	45/80	1.7	(0.86–3.4)	25/52	1.7	(0.63–4.4)

*All variables listed fitted simultaneously. Adjusted relative risks are based on 144 case–control sets for the premenopausal group and on 87 sets for the postmenopausal group. †$P<0.05$, ‡$P<0.01$, §$P<0.001$. ND, not determined.

difference in risk was not statistically significant. Tumour size and vascular invasion were not significantly associated with recurrence at or near the site of the primary tumour.

Risk factors for diffuse recurrence or recurrence in the skin

It was not possible to fit all variables simultaneously in a multivariate model due to the small number of patients in some subgroups. In the univariate analysis microscopic margin involvement was the most important risk factor for diffuse breast recurrence or recurrence in the skin (RR 11, $P<0.001$) (Table 6). A 3.5-fold higher risk was observed ($P<0.01$) when involvement of the tumour margin was considered doubtful. The presence of vascular invasion was associated with a 2.4 times higher risk ($P<0.05$) compared with those without vascular invasion. There appeared to be a significant relationship between microscopic margin involvement and the presence of vascular invasion. Vascular invasion was present in 13 of the 20 patients (65%) with a microscopically involved tumour margin but only in 24 of the 99 patients (24%) with free margins. By creating an interaction term of vascular invasion and margin involvement a 25-fold (95% CI 4.0–150) higher risk of diffuse or skin recurrence was found for patients with margin involvement in the presence of vascular invasion compared with those with microscopically free margins without vascular invasion ($P<0.001$). The risk of recurrence for patients with histological tumour types other than ductal or lobular cancer was significantly decreased (RR 0.26, $P<0.05$). The RR was not significantly increased for patients with EIC. Since there were no case subjects with low grade EIC, low and high grade EIC were taken as one category in the analysis to meet the conditions for convergence of the conditional logistic model. Those with a high grade intraductal component of minimal or moderate extent showed a significantly higher risk (RR 2.1, $P<0.05$). Tumour diameter, mitotic index and aspect of tumour margin showed no significant association with recurrence risk.

Recurrence elsewhere in the breast

Because there were only 33 patients with recurrence elsewhere in the breast the association with the variables could only be assessed in a univariate analysis (Table 6). Only patients with a mitotic index ≥20 showed a higher risk of recurrence elsewhere in the breast (RR 4.9; 95% CI 1.2–21, $P<0.05$).

Table 5. Unadjusted and adjusted relative risks (RR) for local recurrence at or near the site of the primary tumour

Variable	Cases/controls (160/322)	Unadjusted RR (95% CI)		Adjusted RR* (95% CI)	
Age, per year increase		0.95§	(0.92–0.98)	0.96†	(0.93–1.00)
Tumour diameter (cm)					
0–2.0	108/237	1.0	(–)	1.0	(–)
≥2.1	50/79	1.4	(0.91–2.2)	1.1	(0.61–1.9)
ND	2/6				
Histological type					
Ductal	131/246	1.0	(–)	1.0	(–)
Lobular/mixed	13/33	0.76	(0.38–1.5)	1.2	(0.37–3.6)
Other	16/43	0.65	(0.35–1.2)	0.60	(0.25–1.4)
Mitotic index (per 10 HPF)					
≤5	56/152	1.0	(–)	1.0	(–)
6–19	58/97	1.5	(0.94–2.4)	1.3	(0.67–2.6)
≥20	40/59	1.9†	(1.1–3.2)	1.8	(0.83–4.0)
ND	6/14				
Outline of tumour margin					
Clearly outlined	94/225	1.0	(–)	1.0	(–)
Poorly outlined	28/28	2.1†	(1.2–3.9)	2.6†	(1.1–6.1)
ND	38/69	1.8	(0.57–5.7)	2.1	(0.26–16.0)
Intraductal component					
No	35/112	1.0	(–)	1.0	(–)
Minimal/moderate, low grade	33/95	1.2	(0.65–2.1)	1.2	(0.58–2.6)
Minimal/moderate, high grade	42/68	2.2‡	(1.3–4.0)	1.7	(0.85–3.3)
Extensive, low grade	10/14	2.6	(0.97–7.6)	2.5	(0.82–7.8)
Extensive, high grade	32/17	6.4§	(3.0–13.7)	4.1‡	(1.7–9.8)
ND	8/16				
Vascular invasion					
No	101/221	1.0	(–)	1.0	(–)
Yes/doubtful	45/79	1.5	(0.87–2.5)	1.0	(0.56–2.0)
ND	14/22				
Microscopic margin					
Free	66/163	1.0	(–)	1.0	(–)
Involved	22/40	1.4	(0.73–2.5)	1.0	(0.47–2.2)
doubtful	33/41	2.1‡	(1.2–3.7)	1.7	(0.84–3.6)
ND	39/78	1.1	(0.67–1.9)	1.3	(0.63–2.5)

*All variables listed fitted simultaneously. Adjusted relative risks are based on 132 case–control sets. †$P<0.05$, ‡$P<0.01$, §$P<0.001$. ND, not determined.

Table 6. Unadjusted relative risks for diffuse local recurrence, local recurrence in the skin or local recurrence elsewhere in the breast

Variable	Diffuse recurrence or recurrence in skin			Recurrence elsewhere in the breast		
	Cases/controls (71/138)	Unadjusted RR (95% CI)		Cases/controls (33/59)	Unadjusted RR (95% CI)	
Age, per year increase		0.97	(0.93–1.01)		0.94	(0.87–1.02)
Tumour diameter (cm)						
0–2.0	50/108	1.0	(–)	29/46	1.0	(–)
≥2.1	21/30	1.7	(0.86–3.5)	4/12	0.41	(0.11–1.6)
ND				0/1		
Histological type						
Ductal	55/96	1.0	(–)	30/41	1.0	(–)
Lobular/mixed	11/14	1.4	(0.58–3.5)	2/9	0.35	(0.07–1.7)
Other	5/28	0.26*	(0.09–0.79)	1/9	0.16	(0.02–1.3)
Mitotic index (per 10 HPF)						
≥5	20/56	1.0	(–)	9/28	1.0	(–)
6–19	26/46	1.7	(0.8–3.7)	11/19	1.6	(0.51–5.3)
≥20	20/25	2.0	(0.9–4.5)	11/7	4.9*	(1.2–20.6)
ND	5/11			2/5		
Outline of tumour margin						
Clearly outlined	38/92	1.0	(–)	29/45	1.0	(–)
Poorly outlined	21/25	2.0	(0.99–3.9)	1/9	0.19	(0.02–1.6)
ND	12/21	0.89	(0.09–8.8)	3/5	2.0	(0.13–32.0)
Intraductal component						
No	25/52	1.0	(–)	13/20	1.0	(–)
Minimal/moderate, low grade	13/42	0.67	(0.31–1.5)	4/15	0.45	(0.13–1.6)
Minimal/moderate, high grade	27/25	2.1*	(1.0–4.4)	10/13	1.3	(0.39–4.5)
Extensive, low grade	0/8	0.69	(0.23–2.1)	3/3	2.3	(0.40–13.5)
Extensive, high grade	5/7			2/3	1.1	(0.15–8.4)
ND	1/4			1/5		
Vascular invasion						
No	32/86	1.0	(–)	21/42	1.0	(–)
Yes/doubtful	32/38	2.4*	(1.2–4.8)	10/17	1.1	(0.41–3.2)
ND	7/14			2/0		
Microscopic margin						
Free	25/74	1.0	(–)	16/31	1.0	(–)
Involved	14/6	11.1‡	(3.1–39.4)	0/3	0.43	(0.11–1.6)
Doubtful	19/22	3.5†	(1.5–8.5)	3/13		
ND	13/36	1.3	(0.47–3.5)	14/12	2.9	(0.85–9.7)

*$P<0.05$, †$P<0.01$, ‡$P<0.001$. ND, not determined.

DISCUSSION

Our multicentre case–control study is the largest study on histological determinants for local recurrence after BCT so far, enabling the identification of risk patterns for different types of local recurrence and according to menopausal status. The case–control design proved to be an efficient way of studying determinants for local recurrence after BCT, considering the small actuarial rate of recurrence of 0.5–2% per year. In contrast to the cohort approach, information on the risk factors of interest, such as data from the pathology review, was only needed for patients with recurrence and a matched sample of patients from the remaining cohort. The case–control design had already proven to be valuable in the study of second malignancies as a sequel to cancer therapy [28], which also have a low incidence. The relative risk estimates resulting from a case–control study are comparable with those obtained from a cohort study. However, only the relative risks associated with the various risk factors can be calculated, not the absolute recurrence rates which are usually presented in cohort analyses.

The data suggest that there is a continuously increasing risk of recurrence with decreasing age. The highest risk of recurrence is found for patients younger than 35 years. As in most other studies this higher risk could not be explained by any of the other risk factors in the analysis [10–12, 14, 15].

Though lobular cancer is characterised by a high incidence of multicentricity and has been associated with bilaterality, we did not observe an increased risk of local recurrence for these patients, which is in agreement with other studies [29–34]. Compared with ductal and lobular carcinoma, the less common tumour types, such as medullary and tubular carcinoma, appeared to be less likely to recur.

Patients with larger tumours have been reported to be at higher risk for local recurrence [16]. The lack of any of such association in our study might be explained by the relatively small proportion of patients with larger tumours; of all patients only 5% had tumours larger than 3 cm (data not shown).

The extent as well as the grade of the intraductal component contributed significantly to the risk of local recurrence at

or near the site of the excision, especially for postmenopausal patients (Table 5). EIC was first described as a determinant for local recurrence by the Boston group in 1984 [17], and its role has been confirmed by others [18, 19]. EIC, according to the Boston group, is defined as intraductal carcinoma accounting for greater than 25% of the tumour area, as well as any intraductal carcinoma in breast tissue immediately adjacent to the tumour. The main difference with our definition lies in the emphasis that we put to the presence of DCIS in the normal tissue adjacent to the tumour. A surgical margin of 1–2 cm is required to allow optimal pathological analysis. If margins are too narrow EIC is not evaluable according to our definition. Approximately half of the tumours meeting the Boston criteria of EIC will not be classified as such according to our definition because they lack the extensive intraductal carcinoma in the surrounding normal tissue.

The association between EIC and local recurrence has been explained by the more extensive, multifocal nature of such tumours. In a careful analysis of mastectomy specimens, Holland and associates showed that the likelihood and the number of residual cancer foci were elevated for patients with EIC [35]. Our finding that high grade EIC is of greater importance than low grade EIC may be attributed to the higher malignant potential of the cells left behind after local excision. Our results are similar to the findings of the Boston group [17], which found a 5-year actuarial local recurrence risk of 39% for those patients with a combination of an EIC and a high nuclear grade within the infiltrating or intraductal component. In later reports of the Boston group, however, this effect was no longer present [23, 36]. Evidence for the importance of the grade of the EIC is also provided by studies on local excision with or without radiotherapy for non-invasive breast cancer [37, 38]. Here, patients with a tumour of the comedo-type or with a high nuclear grade were also found to be at greater risk for local failure and subsequent development of invasive breast cancer.

In contrast to our study, several studies have found that EIC is no longer a risk factor for local recurrence in patients with uninvolved margins [22, 23, 39]. Wide excisions are therefore recommended for patients with a EIC-positive tumour to obtain negative margins. Our results indicate that local excision with a 1–2 cm margin of healthy tissue and a 15 Gy boost are adequate local treatment for most patients with low grade EIC. However, more extensive surgery, a higher boost dose or mastectomy should be considered for patients with high grade EIC to achieve an acceptable rate of local control.

Microscopic margin involvement appeared to be the most important risk factor for diffuse recurrence or recurrence in the skin (Table 6). Before discussing the role of microscopic margin involvement we should first mention several limitations of the retrospective assessment of resection margins in our study. Only part of the tumour specimens had been routinely inked and only a limited number of tumour slides were available for review for most patients. Therefore, underreporting of positive margins due to sampling error could have underestimated the effect. Microscopic margin involvement as a risk indicator for local recurrence has been reported by others [11, 21, 23, 24]. Further evidence for the significance of margin involvement has been provided by studies in which the risk of recurrence was found to be inversely related to the amount of breast tissue resected [40, 41]. Although it is now generally accepted that margins should be routinely assessed, the different techniques of margin evaluation and the clinical implications of microscopically involved margins are still widely debated [42, 43].

Vascular invasion, which appeared to be associated with diffuse local recurrence and recurrence in the skin in the univariate analysis (Table 6), has been reported as a risk indicator by others [21, 22]. Vascular invasion was seen in 65% of the patients with margin involvement, which supports its role as a potentially significant mechanism of local tumour growth in the breast [44]. It would also explain why recurrences evolving from incomplete excision of tumours with vascular invasion tend to have a diffuse growth pattern or skin involvement.

It seems likely that risk indicators for recurrences that occur at sites distant from the original tumour will be similar to those associated with cancer in the opposite breast, such as young age and lobular histology [45]. The limited number of cases with recurrence elsewhere in the breast did not allow us to confirm this hypothesis.

In summary, this case-control study indicates that different risk patterns can be distinguished, according to the type and site of local recurrence and taking menopausal status into account. To prevent local recurrence at or near the site of the primary tumour, local excision with a 1–2 cm margin of healthy tissue and a 15 Gy boost seem adequate local treatment for patients with well differentiated EIC. A wider surgical margin, a higher boost dose or mastectomy should be considered for patients with poorly differentiated EIC. The difficulty of obtaining tumour-free margins in the presence of vascular invasion indicates that wider excision may have less effect on the risk of diffuse recurrence or recurrence in the skin. The increased risk of recurrence found for patients <35 years was confirmed and merits further study.

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APPENDIX

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