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# Ipsilateral breast tumour recurrence in hereditary breast cancer following breast-conserving therapy

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**Abstract**

The overall rate of an ipsilateral breast tumour recurrence (IBTR) after breast-conserving therapy (BCT) ranges from 1% to 2% per year. Risk factors include young age but data on the impact of BRCA1/2 mutations or a definite positive family history for breast cancer are scarce. We investigated IBTR after BCT in patients with hereditary breast cancer (HBC). Through our family cancer clinic we identified 87 HBC patients, including 26 BRCA1/2 carriers, who underwent BCT between 1980 and 1995 (cases). They were compared to 174 patients with sporadic breast cancer (controls) also treated with BCT, matched for age and year of diagnosis. Median follow up was 6.1 years for the cases and 6.0 years for controls. Patient and tumour characteristics were similar in both groups. An IBTR was observed in 19 (21.8%) hereditary and 21 (12.1%) sporadic patients. In the hereditary patients more recurrences occurred elsewhere in the breast (21% versus 9.5%), suggestive of new primaries. Overall, the actuarial IBTR rate was similar at 2 years, but higher in hereditary as compared to sporadic patients at 5 years (14% versus 7%) and at 10 years (30% versus 16%) ($P = 0.05$). Post-relapse and overall survival was not different between hereditary and sporadic cases. Hereditary breast cancer was therefore associated with a higher frequency of early (2–5 years) and late (>5 years) local recurrences following BCT. These data suggest an indication for long-term follow up in HBC and should be taken into account when additional 'risk-reducing' surgery after primary BCT is eventually considered.



*Keywords:* Breast cancer; Ipsilateral breast tumour recurrence; Breast-conserving therapy; Hereditary breast cancer; *BRCA1*; *BRCA2*; Historical cohort study

## 1. Introduction

Breast-conserving surgery with subsequent radiation therapy (breast-conserving therapy; BCT) has become the treatment of choice in women with early-stage breast cancer (BC). It was found to be equivalent to mastectomy for distant disease-free and overall survival [1–4]. However, following BCT, recurrences in the preserved ipsilateral breast occur at an average rate of 1–2% per year, accumulating to approximately 15% after 10 years [1,2,5,6]. While early recurrences most probably represent outgrowth of residual disease, therefore occurring in the vicinity of the original tumour, late recurrences are suggestive of a new primary tumour. Accordingly, the latter are found more often in an area distinct from the site of the primary breast tumour [7,8].

Patients with breast cancer who develop an ipsilateral recurrence (IBTR) have an increased risk of developing distant metastatic disease, indicative of the prognostic

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value of this event [1,9–11]. Subanalyses show that early rather than late recurrences are especially associated with a worse outcome [7–9]. Recurrences in the skin are probably a separate entity and are also associated with a worse outcome [12,13]. Finally, although scientifically difficult to assess, besides the adverse outlook, breast cancer patients face intense emotional turmoil and psychological distress at the time of a recurrence.

A number of risk factors for IBTR following BCT have been reported, including the presence of extensive ductal carcinoma-*in-situ* and vascular invasion, multifocality of the primary tumour, large tumour size, microscopically involved excision margins and young age of the patient [10,14,15]. Whether or not a positive family history for breast cancer or proven genetic susceptibility is also a risk factor has already been the subject of a number of studies [16–27]. However, many of these studies are hampered by incomplete data on the family pedigree, selection of populations (resulting in specific *BRCA1/2* mutations) and short follow up. Therefore we have compared the incidence and localisation of IBTR in the short and long term between a well-defined group of patients with hereditary and sporadic breast cancer treated with BCT.

## 2. Patients and methods

### 2.1. Patient cohorts

From the cancer registry of our institute we selected retrospectively participants fulfilling the following criteria:

1. women with early-stage infiltrating breast cancer being treated by BCT;
2. breast cancer diagnosis between 1980 and 1995;
3. treatment performed at the Erasmus MC-Daniel den Hoed Cancer Centre either from diagnosis onward or within 3 months after diagnosis at referral for radiation therapy.

The Daniel den Hoed cancer registry includes data from more than 15 000 breast cancer patients treated in the hospital since 1980. Within this group, 87 patients with hereditary breast cancer (HBC) were identified who were also known at our institute's family cancer clinic. HBC patients were selected that belonged either to families with *BRCA1/2* mutations or families with hereditary breast (ovarian) cancer (HB(O)C) (defined as having $\geqslant$three first-degree relatives with breast and/or ovarian cancer). This hereditary group consisted of 26 carriers of *BRCA1/2* mutations (21 *BRCA1*; 5 *BRCA2*), and 61 patients from HB(O)C families in which the diagnosis was based upon pedigree data since as yet no mutations have been identified (unspecified HBC). *BRCA1/2*-mutation analysis is described elsewhere [28,29].

From the initial population, eligible patients with 'sporadic' breast cancer were then selected and frequency matched in a 1:2 ratio, for age at onset and period of diagnosis (5-year periods), with the hereditary cases, totalling 174 patients with sporadic breast cancer. As the registry contains information on malignancies in family members, patients with a positive family history for breast cancer were excluded from the sporadic group.

### 2.2. Primary therapy for breast cancer

BCT generally consisted of wide local excision of the tumour with an attempted margin of healthy tissue of at least 1 cm after fixation, axillary lymph-node dissection, followed by radiation therapy. All patients received whole-breast irradiation to a total dose of 45–50 Gy, given in fractions of 1.8 or 2 Gy, five times a week. A boost dose of 16–20 Gy was delivered to the tumour bed using either photons or electrons. Radiation therapy of the axillary and supraclavicular lymph nodes (46 Gy) was considered as indicated in patients with extensive axillary involvement, defined as four or more metastatic lymph nodes with either involvement of the highest level, extracapsular extension and/or loose tumour deposits in the fat.

Adjuvant systemic therapy was given in lymph node-positive patients. In general, premenopausal women were treated with six cycles of CMF or four cycles of (F)AC chemotherapy, without subsequent tamoxifen. Postmenopausal patients received tamoxifen, 40 mg daily, for a period of 2–5 years, initially irrespective of the hormonal receptor status. Follow-up consisted of 3-monthly evaluation the first 2 years, 6-monthly during years 3 to 5, and yearly thereafter. At each visit a history was taken and a physical examination was carried out. Mammography was performed once a year. Other tests were performed as needed.

### 2.3. Data collection

Detailed data were abstracted from the hospital records onto standardised forms. Information was collected on age at onset of breast cancer, menopausal status, tumour characteristics (location and extent of the tumour, histological type, differentiation grade, presence and extent of ductal carcinoma-*in-situ*, microscopic tumour margin involvement, hormonal receptor status), TNM status, and local and systemic therapy. Central review of histology of the primary and recurrent tumour was not possible because material from the primary breast cancer was not always available or was no longer retrievable.

The main endpoint of this analysis was the occurrence of IBTR as a first failure or simultaneously (within 3 months) with distant recurrence of the disease. IBTR

was defined as recurrence of tumour within the initially treated breast tissue or overlying skin. The time interval from initial surgery to IBTR and its exact location were recorded as follows: at or near the scar (in the vicinity of the original tumour), elsewhere in the breast (quadrant distinct from the site of the primary tumour), or diffuse in the breast/skin.

### 2.4. Statistical analysis

$\chi^2$ tests were used to compare personal and tumour characteristics of hereditary and sporadic patients. In addition, characteristics of the 21 identified carriers of *BRCA1* mutations and 61 other hereditary patients were analysed separately. Kaplan–Meier survival probabilities were calculated and differences between curves tested by the log-rank test. The simultaneous effect of several characteristics on the IBTR and other endpoints was investigated by Cox's proportional-hazards method. This was done separately for *BRCA1* and unspecified HBC versus sporadic cases. Covariates were added to the model if a change of more than 10% in the hazard ratio of either *BRCA1* or unspecified HBC patients versus sporadic cases was seen. All analyses were performed with *STATA* and *SPSS for Windows* software.

## 3. Results

### 3.1. Patient and tumour characteristics

The characteristics of the cases are summarised in Table 1. There were no clear differences between the hereditary and sporadic groups in TNM status, histology type, differentiation grade, microscopic margin involvement, extent of *in situ* component, radiation and systemic therapy. Subgroup analysis of the 21 *BRCA1*-mutation carriers and the 61 as yet unspecified HBC patients showed a different age at onset of the disease, with a mean age of 38.7 years for *BRCA1*-mutation carriers in contrast with 48.9 years for the unspecified hereditary patients ($P=0.003$). Furthermore, there was a trend for smaller tumour size ($P=0.07$) and more oestrogen receptor-positive tumours ($P=0.07$) in the unspecified hereditary patient group as compared to *BRCA1*-mutation carriers.

### 3.2. Ipsilateral breast tumour recurrence

An IBTR occurring as first event was observed in 40 cases, 21 times in sporadic (12.1%) and 19 times in HBC patients (21.8%). Four recurrences (4/26; 15%) occurred in *BRCA1/2*-mutation carriers and 15 (15/61; 24%) in unspecified HBC patients. As is shown in Table 1, more recurrences at/near the site of the primary tumour were found in the hereditary group (12.6 versus 6.9%), especially in unspecified hereditary patients (14.7%). Furthermore, a recurrence in a quadrant distinct from the site of the primary tumour (defined as 'elsewhere'), suggestive of a new primary, occurred more often in the hereditary group (4.5 versus 1.1%). More IBTRs presented as diffuse/skin locations in the sporadic group. Overall, however, the differences were not statistically significant. There was no association between the location of a local recurrence and both the microscopic margin involvement and the extent of an *in situ* component (data not shown).

The histological subtype of the primary and the recurrent tumour mainly was a ductal (adeno)carcinoma, but was clearly different in two cases (10.5%) in the hereditary group and in one (4.8%) in the sporadic group.

The recurrence rate as a function of time, i.e. period elapsing between initial therapy and IBTR, is demonstrated in Table 2 and Figs. 1 and 2. At 2 years after primary therapy the rate of IBTR was identical in both groups. At 5 years, however, it was twice as high in the hereditary as in the sporadic cohort (14% versus 7%, respectively). This was mainly due to recurrences in the vicinity of the primary tumour, with a rate of 10% versus 4%, respectively. The IBTR rate at 10 and 15 years in the hereditary group remained twice as high (30% and 49%) as in the sporadic group (16% and 20%). Now, in the hereditary group there were mainly recurrences elsewhere in the breast ($P=0.08$). Overall, the difference in recurrence rate was borderline statistically significant ($P=0.05$; Fig. 2).

### 3.3. Contralateral breast cancer (CBC)

The incidence of CBC was increased in the hereditary as compared to the sporadic group (13.8% versus 6.3%, respectively; $P=0.06$). This was most pronounced in *BRCA1/2*-mutation carriers with synchronous bilateral breast cancer occurring in two cases (7.7%), and metachronous CBC in four (15.4%) (Table 1). The time span to CBC occurrence was variable, ranging between 2 and 7 years for sporadic and between 1 and 12 years for HBC patients (mean 5 and 3.7 years. respectively).

### 3.4. Outcome after IBTR

At 2 years, the survival after local relapse was not different between the groups: 75% (confidence interval (CI) 50–89%) for hereditary, and 74.6% (CI 52–88%) for sporadic patients ($P=0.91$). Overall survival (OS) at 2 and 5 years was 96% (CI 90–99%) and 78% (CI 68–85%) for hereditary patients, and 98% (CI 94–99%) and 82% (CI 76–87%) for sporadic breast cancer patients, respectively. However, the OS at 10 and 15 years was lower in the hereditary group, being 59% and 42%, respectively, compared to 73% and 60%, respectively, for the sporadic group ($P=0.08$).

Table 1
Distribution of patient and tumour characteristics for *BRCA1/2*-associated, unspecified hereditary and sporadic breast cancers

| | Hereditary breast cancer (HBC) | | | Sporadic breast cancer | |
|---|---|---|---|---|---|
| | BRCA1/2 ($n=26$) | Unspecified HBC ($n=61$) | Total ($n=87$) | ($n=174$) | $P^*$ |
| Age at diagnosis (years) | | | | | |
| Mean | 38.7 | 48.9 | **45.9** | **46.1** | 0.87 |
| Range | 27–54 | 28–78 | **27–78** | **23–76** | |
| Follow up (years) | | | | | |
| Median | 5.7 | 6.4 | **6.1** | **6.0** | 0.78 |
| Range | 1.5–14.9 | 1.6–14.9 | **1.5–14.9** | **0.4–16.3** | |
| | *n* (%) | *n* (%) | *n* (%) | *n* (%) | |
| Menopausal status | | | | | |
| Pre- | 21 (80.8) | 29 (47.5) | **50 (57.5)** | **105 (60.0)** | 0.85 |
| Peri- | 1 (3.8) | 5 (8.2) | **6 (7.0)** | **10 (5.8)** | |
| Post- | 3 (11.5) | 25 (41.0) | **28 (32.2)** | **50 (28.7)** | |
| Unknown | 1 (3.8) | 2 (3.3) | **3 (3.5)** | **9 (5.2)** | |
| Tumour size | | | **t** | | |
| $\leqslant 2$ cm | 14 (53.8) | 38 (62.3) | **52 (60.0)** | **121 (69.5)** | 0.09 |
| 2–5 cm | 8 (30.8) | 9 (14.7) | **17 (19.5)** | **35 (20.1)** | |
| $>5$ cm | 0 (0.0) | 0 (0.0) | **0 (0.0)** | **1 (0.6)** | |
| Unknown | 4 (15.4) | 14 (22.9) | **18 (21.0)** | **17 (9.8)** | |
| Lymph node involvement | | | | | |
| Yes | 20 (76.9) | 41 (67.2) | **61 (70.0)** | **117 (67.0)** | 0.54 |
| No | 4 (15.4) | 16 (26.2) | **20 (23.0)** | **49 (28.0)** | |
| Unknown | 2 (7.7) | 4 (6.6) | **6 (7.0)** | **8 (5.0)** | |
| Histological type of tumour | | | | | |
| Ductal | 25 (96.0) | 49 (80.0) | **74 (85.0)** | **147 (84.5)** | 0.92 |
| Lobular±ductal | 0 (0.0) | 2 (3.3) | **2 (2.3)** | **6 (3.4)** | |
| Medullary | 1 (3.8) | 1 (1.6) | **2 (2.3)** | **7 (4.0)** | |
| Mucinous | 0 (0.0) | 3 (4.9) | **3 (3.4)** | **4 (2.3)** | |
| Other | 0 (0.0) | 4 (6.6) | **4 (4.6)** | **5 (2.9)** | |
| Unknown | 0 (0.0) | 2 (3.3) | **2 (2.3)** | **5 (2.9)** | |
| Differentiation grade | | | | | |
| I | 0 (0.0) | 4 (6.6) | **4 (4.6)** | **3 (1.7)** | 0.47 |
| II | 4 (15.4) | 12 (19.7) | **16 (18.4)** | **29 (16.7)** | |
| III | 15 (57.7) | 32 (52.5) | **47 (54.0)** | **92 (52.9)** | |
| Unknown | 7 (26.9) | 13 (21.3) | **20 (23.0)** | **50 (28.7)** | |
| Microscopic margin | | | | | |
| Free | 15 (57.7) | 28 (45.9) | **43 (49.4)** | **97 (55.8)** | 0.32 |
| Involved | 1 (3.8) | 6 (9.8) | **7 (8.1)** | **10 (5.8)** | |
| Doubtful | 1 (3.8) | 13 (21.3) | **14 (16.1)** | **16 (9.2)** | |
| Unknown | 9 (34.6) | 14 (22.9) | **23 (26.4)** | **51 (29.3)** | |
| *In situ* component | | | | | |
| No | 15 (57.7) | 26 (42.6) | **41 (47.1)** | **62 (35.6)** | 0.18 |
| Moderate | 5 (19.2) | 13 (21.3) | **18 (20.7)** | **36 (20.7)** | |
| Extensive | 2 (7.7) | 10 (16.4) | **12 (13.8)** | **24 (13.8)** | |
| Unknown | 4 (15.4) | 12 (19.7) | **16 (18.4)** | **52 (29.9)** | |
| Radiotherapy | | | | | |
| Axillary nodes | 2 (7.7) | 9 (14.7) | **11 (12.6)** | **13 (7.5)** | 0.26 |
| Regional nodes | 1 (3.2) | 8 (13.1) | **9 (10.3)** | **25 (14.4)** | 0.34 |
| Systemic treatment | | | | | |
| Chemotherapy | 5 (19.2) | 10 (16.4) | **15 (17.2)** | **33 (19.4)** | 0.23 |
| Tamoxifen | 1 (3.8) | 2 (2.7) | **3 (3.4)** | **4 (2.3)** | 0.36 |

(*continued on next page*)

Table 1 (*continued*)

| | Hereditary breast cancer (HBC) | | | Sporadic breast cancer | |
|---|---|---|---|---|---|
| | BRCA1/2 ($n=26$) | Unspecified HBC ($n=61$) | Total ($n=87$) | ($n=174$) | $P$* |
| Breast tumour recurrence | | | | | |
| At/near scar | 2 (7.7) | 9 (14.7) | **11 (12.6)** | **12 (6.9)** | 0.14 |
| Elsewhere | 1 (3.8) | 3 (4.9) | **4 (4.5)** | **2 (1.1)** | |
| Diffuse/skin | 1 (3.2) | 1 (1.6) | **2 (2.3)** | **7 (4.0)** | |
| Unknown | 0 (0.0) | 2 (3.3) | **2 (2.3)** | **0 (0.0)** | |
| Total | 4 (15.4) | 15 (24.6) | **19 (21.8)** | **21 (12.1)** | |
| Contralateral breast cancer | | | | | |
| No | 20 (76.9) | 55 (90.2) | **75 (86.2)** | **163 (93.7)** | 0.06 |
| Synchronous | 2 (7.7) | 1 (1.6) | **3 (3.5)** | **4 (2.3)** | |
| Metachronous | 4 (15.4) | 5 (8.2) | **9 (10.3)** | **7 (4.0)** | |

*$P$-value for the difference between the total group of HBC versus the sporadic group.

Table 2
Ipsilateral breast tumour recurrence rates for HBC ($n=87$) versus sporadic BC patients ($n=174$) in relation to site of the recurrence

| | Hereditary breast cancer | | | | Sporadic breast cancer | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 2 year | 5 year | 10 year | 15 year | 2 year | 5 year | 10 year | 15 year | $P$ |
| Overall ipsilateral recurrence rate (%) | 0.03 | 0.14 | 0.30 | 0.49 | 0.04 | 0.07 | 0.16 | 0.20 | 0.05 |
| Recurrence rate at/near the scar (%) | 0.02 | 0.10 | 0.16 | 0.23 | 0.02 | 0.04 | 0.10 | 0.14 | 0.12 |
| Recurrence rate elsewhere in the ipsilateral breast (%) | 0 | 0 | 0.08 | 0.24 | 0 | 0.01 | 0.03 | 0.03 | 0.08 |

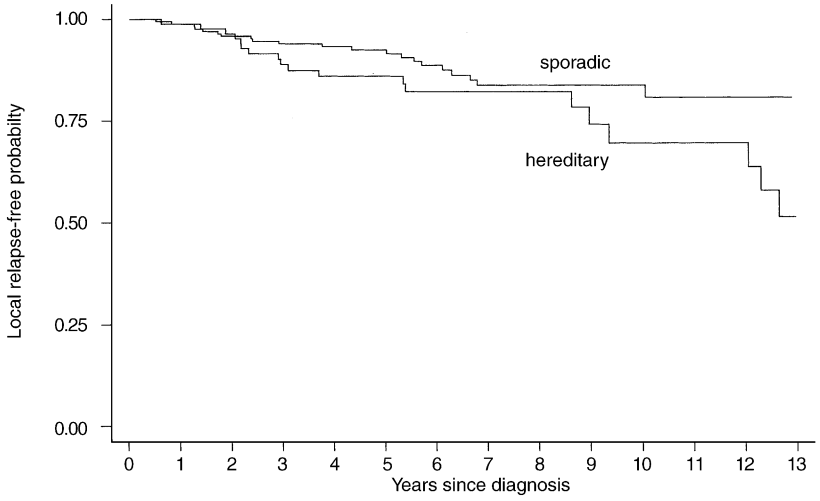


Fig. 1. Ipsilateral breast tumour recurrence by group: total group of hereditary and sporadic breast cancer patients.

### 3.5. Subgroup analysis for various endpoints

In Table 3, multivariate hazard ratios (HR) for ipsilateral recurrence and other endpoints are presented separately for *BRCA1* carriers and unspecified HBC patients versus sporadic cases. After correction for age at onset and tumour size, no increased risk of ipsilateral recurrence was found for mutation carriers, whereas a significantly increased risk for unspecified HBC patients was found (HR 2.31; $P=0.02$).

OS did not differ between unspecified HBC patients and sporadic patients; for *BRCA1*-mutation carriers a non-significantly worse OS was found (HR 1.76; $P=0.22$). The CBC risk was significantly increased for *BRCA1* carriers (HR 5.17; $P=0.01$) and non-significantly for unspecified HBC versus sporadic cases (HR 2.01; $P=0.24$).

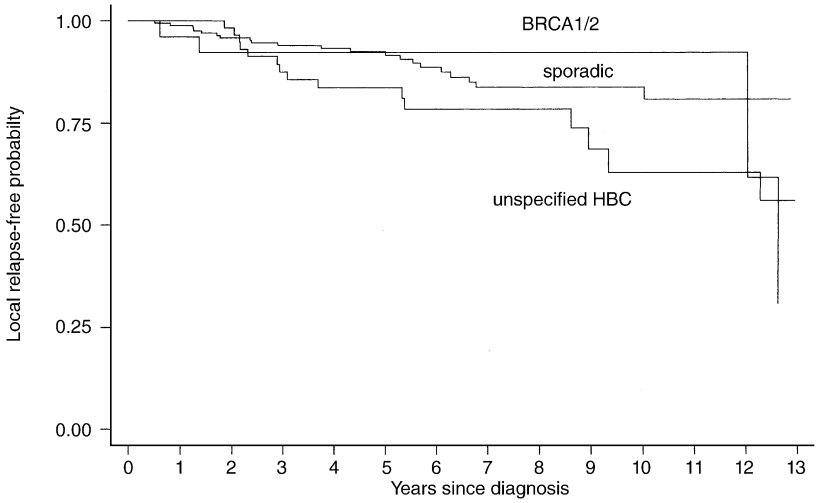


Fig. 2. Ipsilateral breast tumour recurrence by group: unspecified hereditary, *BRCA1/2*-associated and sporadic breast cancer patients.

Table 3
Hazard ratios (HR) adjusted for age at diagnosis and tumour size with 95% confidence intervals (CI) for *BRCA1*-associated and unspecified hereditary breast cancer (HBC) patients as compared to sporadic patients

| | BRCA1-associated breast cancer | | Unspecified HBC | |
|---|---|---|---|---|
| Event | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Ipsilateral recurrence | 0.69 (0.16–2.95) | 0.61 | 2.31 (1.18–4.52) | 0.02 |
| Death of all causes | 1.76 (0.72–4.30) | 0.22 | 0.88 (0.42–1.87) | 0.74 |
| Contralateral breast cancer | 5.17 (1.48–18.1) | 0.01 | 2.01 (0.63–6.44) | 0.24 |

## 4. Discussion

This study was prompted by the question asked both by clinicians and patients whether BCT is appropriate for HBC. On the one hand, a potentially higher risk of ipsilateral recurrence might be expected in HBC because (1) the residual ipsilateral (as well as the contralateral) breast tissue is genetically predisposed to develop cancer; (2) both *BRCA1* and *BRCA2* are involved in the repair of damaged DNA while radiation therapy causes breaks in double-stranded DNA, therefore possibly inducing secondary malignancies more readily in *BRCA1/2*-mutation carriers. The latter could apply to the treated breast as well as the contralateral breast, due to scattered radiation [30]. On the other hand, the tumour characteristics of hereditary patients, such as the less frequent presence of an extensive intraductal component and more frequent pushing borders in *BRCA1*-associated breast cancer [31], might lead to a surgical excision with free margins and thus a decreased risk of subsequent ipsilateral recurrence. Finally, instead of inducing new primary tumours, radiation therapy could possibly prevent the development of these tumours by 'sterilising' the remaining breast tissue or tumour residues, due to an increased radiosensitivity of tumour cells [25].

In our study a higher frequency of IBTR after BCT was observed in the hereditary group than in the sporadic group, becoming evident between 2–5 years after the primary diagnosis. Although non-significant, when subdivided into ipsilateral recurrences at or near the site of the original tumour and recurrences elsewhere in the breast, the latter appeared to develop after a longer follow-up period (10 years and more). A different histological subtype, suggesting a new primary tumour, was seen in two recurrences in the hereditary group and in one of the sporadic cases. From the original pathology reports it was not possible to differentiate more definitely between a true recurrence or a new primary tumour. As it was not possible to retrieve all the tumour material, no pathological review was performed. This is certainly warranted for future similar studies.

Furthermore, in our study the higher incidence of CBC was confirmed, especially in *BRCA1/2*-mutation carriers. Survival after local relapse and overall survival were not significantly different, but there was a trend for a worse 10- and 15-year overall survival in the hereditary group. Cautious interpretation of these results is necessary in view of the relative short median follow up (6.1 and 6.0 years for hereditary and sporadic patients, respectively).

In the light of a higher risk for IBTR, the trend toward a worse survival in the hereditary group is not

surprising because, as mentioned before, this is a predictor of a worse distant disease-free survival. However, the long time interval to ipsilateral recurrence as observed in the hereditary group is an indicator of a relative favourable outcome [7]. A recent study by Huang and colleagues attempted to classify ipsilateral recurrences as either true recurrence or new primary tumour by comparing the site of the IBTR and the histology [32]. They showed an improved 10-year overall survival for the group of patients with an IBTR that was assumed to be a new primary. Interestingly, the mean time until the (assumed) new primary was 7.3 years, in contrast to 5.2 years in the case of a true recurrence, whereas patients with a new primary were more likely to develop CBC.

Several groups have studied the relation between ipsilateral recurrence and genetic susceptibility, yielding inconsistent results. The reasons may be different ways of selecting comparison groups and defining the family history for inherited breast cancer. Most studies fail to find an association between a 'positive family history of breast cancer and an increased risk for ipsilateral recurrence [16–19,21,27], underscoring the importance of studying patients with a well-defined family history. Because the medical registration at our institute is set up in such a way that cases with a positive family history can be distinguished, we definitely selected patients with sporadic breast cancer. Our definition of HB(O)C families is in agreement with what is generally accepted as indicative of a predominant genetic susceptibility. Though the number of patients we studied was large enough to make separate analyses for *BRCA1/2*-associated cases and unspecified HBC, we are aware that the latter group is heterogeneous with respect to the underlying susceptibility genes.

Regarding proven *BRCA1/2*-mutation carriers, data are scarcer (Table 4). In a first analysis of Ashkenazi Jewish patients with breast cancer (diagnosis before 42 years; BCT in 9 *BRCA1/2*-mutation carriers versus 25 sporadic cases, short follow up), Robson and colleagues did not find an increased rate of ipsilateral recurrence [20]. By extending the group of patients and prolonging the follow-up period, however, they found an increased rate of IBTR and CBC at 5 and 10 years in the *BRCA1/2*-mutation group [22], which is in accordance with our findings.

Haffty and colleagues report a case-control study on the outcome after BCT in 22 *BRCA1/2*-mutation carriers and 105 sporadic cases with a diagnosis of breast cancer at the age 42 years or younger [26]. The median follow up in this study was 12.7 years. The rate of IBTR at 5 and 10 years was increased in the genetic group as compared to the sporadic group, which became evident after 5 years of follow up. The distinctly different location and histological features of nine out of 11 ipsilateral recurrences were suggestive of new primary breast tumours. Likewise, the rate of CBC was increased in the genetic group. These data are well in accordance with our findings.

The data of Pierce and colleagues on the results of BCT in 71 *BRCA1/2*-mutation carriers versus 213 sporadic patients are in a way different, but not contradictory [25]. With a median follow up of 5.3 and 4.6 years, the 5-year local control rates were 98% and 96% for the hereditary and sporadic groups respectively, while the actuarial survival at 5 years was 86% and 91%, respectively. We believe that data on ipsilateral recurrence after more than 5 years are of special relevance in this matter. Interestingly, in their study, the median time to local recurrence of the 3 patients in the genetic group was 8.2 years compared to 3.1 years in the sporadic group. No difference was seen in the site of recurrence within the breast between the two groups.

Following a different approach, but again well in line with the present findings, Turner and colleagues genetically tested 52 breast cancer patients with ipsilateral recurrence following BCT [33]. Eight *BRCA1/2* mutations were detected (15%), and six of these were encountered in the 15 patients with breast cancer diagnosed under the age of 40 years (40%). In the 15 matched control patients, also with breast cancer diagnosis under the age of 40 but without an ipsilateral recurrence, only one mutation was found (6.6%). Moreover, median time to IBTR in the group of mutation carriers was 7.8 years compared to

Table 4
Ipsilateral breast tumour recurrence (IBTR) rate following breast-conserving therapy in hereditary breast cancer (HBC) patients

| First author | Year | No of patients | | 5 year IBTR[a] (%) | | 10 year IBTR[a] (%) | | *P* | Median follow up (years) |
|---|---|---|---|---|---|---|---|---|---|
| | | Unspecified HBC[b] | BRCA1/2 | HBC[c] | Controls | HBC[c] | Controls | | |
| Robson [22] | 1999 | – | 28 | 14.9 | 4.5 | 22.0 | 6.9 | 0.25 | 10.3 |
| Pierce [25] | 2000 | – | 71 | 2 | 4 | – | – | 0.8 | 7.5 |
| Eccles [24] | 2001 | 36 | 36 | – | – | 18 | 21 | 0.4 | 7.0 |
| Haffty [26] | 2002 | – | 22 | 22 | 18 | 41 | 19 | 0.007 | 12.7 |
| Present study | | 61 | 26 | 14 | 7 | 30 | 16 | 0.05 | 6.1 |

[a] Ipsilateral breast tumour recurrence rate.
[b] Unspecified HBC: patients with a significant family history of breast (and/or ovarian) cancer; as yet no *BRCA1/2* mutations identified.
[c] Total group of *BRCA1/2*-mutation carriers and unspecified HBC patients.

4.7 years for the patients with no *BRCA1/2* mutation. From clinical and histological criteria the investigators concluded that the ipsilateral recurrences in *BRCA1/2*-mutation carriers were 'new' primary tumours that had developed in the conservatively treated breast.

Eccles's group did not find an increased rate of IBTR in hereditary cases as compared to controls, although their population is rather similar to ours [24]. Strikingly, their results show an ipsilateral recurrence frequency of 24% in the control cases, much higher than the rate in controls in the studies by Robson, Haffty and ourselves and that reported in the literature, being approximately 15% or less. It might be possible that in the Eccles study (no genetic testing for *BRCA2* performed; patients with a borderline family history and a calculated heterozygote risk of $<20\%$ were classified as having a negative family history), some hereditary cases were assigned to the control group, confounding their results.

As we selected the hereditary cases from high-risk families ($\geqslant$three family members with either breast and/or ovarian cancer) by means of a complete pedigree (up to third-degree relatives, and verification of the pathology reports in persons with a malignancy) we assume that a genetic predisposition is present in the unspecified HBC group, but not identified or as yet unidentifiable. It is likely that some of these unspecified hereditary cases might in fact be unidentified *BRCA1/2*-mutation carriers, because not all the hereditary cases in our study have been genetically tested. However, even with complete sequencing of the *BRCA* genes, approximately 20% of the mutations are missed. Further, since at present *BRCA* mutations are identified in only 20% of the families with aggregation of breast cancer, most of the remaining familial breast cancer is believed to be the result of (combinations of) other breast cancer-susceptibility genes, resulting in a heterogeneous group. Even so, our results suggest that the separation in *BRCA1/2*-mutation carriers and unspecified HBC patients defines different groups, in view of the different rates of IBTR (RR 0.69 and 2.31, respectively) and CBC (RR 5.17 and 2.01).

Our results, in line with those of others, show again that the residual breast tissue in HBC patients remains at risk for developing new primary tumours, i.e. both the ipsilateral and contralateral breast. This is essential information to discuss with these patients, especially *BRCA*-mutation carriers, at the moment of diagnosis of a primary breast tumour. These women (generally participating in screening programmes) and their attending physicians have to choose between uni- or bilateral mastectomy (i.e. contralateral prophylactic mastectomy) or the 'standard' BCT. The fact that an IBTR more often manifests itself after longer follow up indicates that decisions concerning additional 'risk-reducing' surgery in a breast cancer patient with a *BRCA1/2* mutation should not be taken hastily. Careful monitoring of the remaining breast tissue is indicated, which may provide time for both physicians and patients to make a well-considered decision, taking into account the stage and prognostic factors of the primary breast cancer. Further, in time it may become possible to identify other breast cancer-susceptibility genes, allowing for more exact risk estimation in patients of the 'unspecified HBC' group. These patients, however, also remain at increased risk of developing a new primary breast cancer, as our data show, and therefore are eligible for continuing and long-term follow up after breast cancer. This is the more important since at present the value of long-term follow up after breast cancer therapy is being widely discussed.

The data from this study must also be seen in the light of other preventative or therapeutic measures possibly affecting the remaining breast cancer risk. Prophylactic oophorectomy has been shown to reduce the risk of breast cancer by about 50% in carriers of *BRCA1/2* mutations [34,35]. Presumably this will also apply to CBC and the ipsilateral recurrences that are new primary tumours. Knowledge about the effects of tamoxifen on ipsilateral recurrence and CBC are growing [36], but may differ in HBC patients. Tamoxifen only decreases the risk of oestrogen receptor-positive contralateral breast tumours [37], while the majority of CBCs in *BRCA1* carriers are expected to be oestrogen receptor-negative. Further, it has been reported that adjuvant chemotherapy also reduces the risk of CBC [38], which presumably may also affect the risk of IBTR. Separate analyses for the effects of these variables in our study were not possible because of small numbers.

From the above it may be clear that decision-making on the optimal therapy and follow up of HBC patients ultimately gains from a multidisciplinary approach involving both geneticists and oncologists.

In conclusion, we found an increased risk of IBTR after BCT in HBC, consisting both of early recurrences in the vicinity of the primary tumour (2–5 years after initial therapy), and late, presumably new, primary tumours ($>5$ years after initial therapy). Furthermore, the increased risk of developing CBC, both in *BRCA1/2*-associated and in unspecified HBC, was confirmed. These data are valuable for facilitating clinical decisions in these patients, specifically when additional 'risk-reducing' surgery is eventually considered. Finally, our finding that IBTR is frequently a late event should mean that a careful monitoring schedule, also beyond 5 years after diagnosis and treatment, remains indicated in HBC.

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