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ORIGINAL ARTICLE

Family history in breast cancer is not a prognostic factor?

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S U M M A R Y. The aim of this study is to determine if breast conservative treatment is justified for patients with a positive family history of breast cancer and to investigate whether they have a worse prognosis.

We performed a prospective cohort study of breast cancer patients, treated with breast conservative treatment with radiotherapy at the Radiotherapy Department of the Medisch Spectrum Twente. Between 1984 and 1996, 1204 patients with T1 and T2 ≤3cm were treated. Family history (FH) was recorded according to first degree relative (FDR). Treatment consisted of lumpectomy with axillary dissection followed by radiotherapy to the whole breast with a boost to the primary area. Adjuvant systemic therapy was given to patients with positive nodes.

A positive FH was noted in 243 (20.5%) patients, of whom 208 (17.6%) had one FDR, and 35 (3.0%) ≥2 FDRs. The local recurrence rate was 4.1%, with similar rates for all groups. In young patients, ≤40 years, a significant relation between local recurrence and FH was found. The distant metastasis rate was 15.5%, with the lowest rate (5.7%) among patients with ≥2 FDRs. Patients with a positive FH had significantly more contralateral tumours. The 5-year corrected survival was 91.3%. Among patients with a positive FH, a 5-year corrected survival of 91% was observed and the survival 100% among patients with one and ≥2 FDR.

Family history is not a contraindication for breast conservative treatment and is not associated with a worse prognosis. Family history is not a prognostic factor for local recurrence rate in patients older than 40 years. © 2000 Harcourt Publishers Ltd

INTRODUCTION

It has been estimated that 5–10% of breast cancer patients have a major inherited component.[1] The question has risen whether breast conservative treatment for patients with a family history (FH) of breast cancer is justified and if these patients have a worse prognosis. To address these questions we performed a prospective cohort study of breast cancer patients, treated with breast conservative treatment only, and radiotherapy at the Radiotherapy Department of the Medisch Spectrum Twente (MST). Our research question was, whether a positive FH of breast cancer is a risk factor for increased rates of contralateral breast cancer, local recurrence and distant metastasis, and a decreased 5-year survival in patients receiving breast conservative treatment.

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MATERIALS AND METHODS

Between 1984 and 1996, 1204 patients with early breast cancer, T1 and T2 ≤3 cm, were treated with breast conservative treatment in the Twente-Achterhoek region. All patients have undergone close follow-up and details of family history, local recurrence, regional recurrence, distant metastasis and survival were available. To get the most reliable family history (FH) we only recorded the history of the first-degree relatives. The (FH) was recorded according to first degree relative (FDR): none, or one or more (≥1) FDRs. We also made a subdivision with a positive FH of one, or more than one (≥2) FDRs. Patients were divided into three age categories: 40 years or less, 41 to 50 years, and over 50 years. For the purpose of this study the cut-off for analysis was July 1999. Patients were followed-up for local and regional recurrence, distant metastasis, second breast tumour contralateral, time to local recurrence and distant metastasis, and for survival. Because local recurrence and new primaries in the treated breast are often

difficult to differentiate, they were classified as local recurrences. Recurrences in the axilla, parasternal, or a combination were classified as regional recurrence. Clinical, histological, demographic and follow-up information was regularly collected and entered in our data base on all breast cancer patients treated with breast conservative treatment. The specific features recorded for each patient included tumour size, presence and number of positive lymph nodes (subdivided by number of nodes), TNM classification, histologic subtype, presence of an intraductal component (CIS), presence of microscopically involved margin of the lumpectomy specimen, radiotherapy with or without regional or parasternal radiotherapy and treatment with systemic adjuvant therapy. These data are displayed in Table 1.

Treatment

The standard treatment for breast conservative treatment consisted of lumpectomy with axillary dissection, clearance level I-III, followed by radiotherapy to the whole breast with a boost to the primary tumour area. Twelve patients did not have an axillary dissection. According to FDR 11 of those 12 patients had none and 1 patient had one FDR.

Radiotherapy consisted of 50 Gy to the whole breast delivered by tangential technique in 2 Gy fraction 5 times a week. This was followed by a boost to the primary tumour bed of 14 Gy in 2 Gy fraction 5 times a week delivered by external photon or electron beam therapy. In the early years a boost of 15 Gy, 2.5 Gy per fraction was delivered to 172 patients. Twenty-eight patients were treated by iridium implantation peroperatively with a dose of 15 Gy low dose rate.

Adjuvant therapy consisted of regional or parasternal radiotherapy and of hormonal and/or chemotherapy. The regional or parasternal radiotherapy was 50 Gy in 2 Gy fraction 5 times a week. The indication was the presence of and number of positive lymph nodes and/or extranodal (EN) disease.

Table 1 Comparison of the distribution of clinical, histological and treatment features of patients with no family history (FH) to a positive FH, ≥1 FDR, and the subdivision of first degree relative (FDR)

	None (*n*=941) number (%)	≥1 FDR (*n*=243) number (%)	*P* value	one FDR (*n*=208) number (%)	>2 FDR (*n*=35) number (%)	*P* value
Age, mean	56	56.3	ns	56.3	56.3	ns
Age cat						
≤40	76 (8.1)	23 (9.5)		20 (9.6)	3 (8.6)	
41–50	251 (26.7)	59 (24.3)	ns	49 (23.6)	10 (28.6)	ns
>50	614 (65.3)	161 (66.3)		139 (66.8)	22 (62.9)	
TNMclass						
pT_1N_0	558 (59.3)	151 (62.1)		129 (62.1)	22 (62.9)	
pT_1N_1	182 (19.3)	46 (18.9)	ns	40 (19.2)	6 (17.1)	ns
pT_2N_0	95 (10.1)	24 (9.9)		18 (8.6)	6 (17.1)	
pT_2N_1	91 (9.7)	17 (7)		16 (7.7)	1 (2.9)	
Histology						
ductal carc	744 (79.1)	190 78.2)		163 (78.4)	27 (77.1)	
lobular carc	92 (9.8)	25 (10.3)		22 (10.6)	3 (8.6)	
tubular carc	53 (5.6)	14 (5.8)	ns	12 (5.8)	2 (5.7)	ns
medullary carc	24 (2.6)	6 (2.5)		3 (1.9)	2 (5.7)	
rest	28 (3)	8 (3.3)		7 (3.4)	1 (2.9)	
CIS						
none	648 (68.9)	165 (67.9)		142 (68.3)	23 (65.7)	
DCIS	239 (25.4)	58 (23.9)	ns	50 (24)	8 (22.9)	ns
lob.CIS	42 (4.5)	15 (6.2)		13 (6.3)	2 (5.7)	
NO. pos. lymph node						
None	653 (69.4)	178 (73.3)		150 (72.1)	28 (80)	
1–3	199 (21.2)	49 (20.2)	ns	45 (21.6)	4 (11.4)	ns
>3	78 (8.3)	14 (5.8)		11 (5.3)	3 (8.6)	
Margin lumpectomy						
Positive	84 (8.9)	28 (11.5)	ns	22 (10.6)	6 (17.5)	ns
Negative	854 (90.6)	214 (88.1)		185 (88.9)	29 (82.9)	
Radiotherapy						
Mamma	666 (70.8)	179 (73.7)		154 (74)	25 (71.4)	
Mamma+regional	155 (16.5)	37 (15.2)	ns	33 (15.9)	4 (11.4)	ns
Mamma+parast.	120 (12.8)	27 (11.1)		21 (10.1)	6 (17.1)	
Adjuvant syst.ther.						
none	688 (73.1)	193 (79.4)		164 (78.8)	29 (82.7)	
Horm or chemo	253 (26.9)	50 (20.6)	p=0.044	44 (21.6)	6 (17.1)	ns

CIS: carcinoma in situ, DCIS: ductal carcinoma in situ, lob.CIS: lobular carcinoma in situ.

For premenopausal patients chemotherapy was related to the number of positive lymph nodes in the early years of the treatment period. Nowadays all premenopausal patients with positive lymph nodes have chemotherapy.

For postmenopausal patients adjuvant hormonal therapy was given when positive lymph nodes were present.

Statistical methods

Time to recurrence and follow-up was calculated from the start of the treatment. To test between-group differences for categorical data, α^2-tests were used, while differences in continuous variables were analysed by Student-*t*-test. Survival statistics were calculated by the method of Kaplan and Meier. The overall survival, due to all causes and corrected survival, corrected for intercurrent death, were calculated. This means that data on patients who died of other causes were regarded as censored data. For comparing survival distributions we used the logrank test. Multivariate survival analysis was done with Cox regression, while for the categorical data logistic regression was used.

RESULTS

For 20 of the 1204 patients FH was unknown, leaving 1184 patients for analysis. A positive FH of carcinoma of the breast was noted in 243 (20.5%) patients, of which 208 (17.6% of total) had one FDR, and 35 (3% of total) ≥2 FDRs. The mean age was 56 years (range 20–89) and when separated according to FH there was no significant difference in age (Table 1). Comparisons in terms of clinical, histological, and demographic characteristics, between patients without and with a positive FH, and among the groups with one FDR and ≥2 FDRs are presented in Table 1. The only significant difference between patients with and without a positive FH was found regarding adjuvant systemic therapy. Patients with a positive FH more often did not receive adjuvant systemic therapy (P=0.042).

The distribution of adjuvant treatments is presented in Table 2.

The follow-up ranged from 2 to 175 months, with a median of 65 months and a mean of 70 months.

Recurrence rates (Table 3)

The local recurrence rate was 4.1%, with similar rates and localisations of the recurrence for all groups. The relationship between local recurrence and FH was significant (P=0.005) for patients of ≤40 years (Table 4). In 11 (1%) patients a regional recurrence was observed, of which 7 were in the axilla, 2 parasternal and 2 both together.

Table 2 Distribution of the adjuvant treatment of systemic and radiotherapy with 1184 patients

Radiotherapy	Hormonal	Chemother.	Horm.+chemo	Trial	None	Unknown
Breast only (71.4%)	54 (4.6%)	33 (2.8%)		1	756 (63.9%)	1
Breast + regional node (16.2%)	100 (8.5%)	47 (4%)	2 (0.2%)	7 (0.6%)	36 (3%)	
Breast + parasternal node (12.4%)	28 (2.4%)	31 (2.6%)			86 (7.3%)	2
Total (100%)	182 (15.4%)	111 (9.4%)	2 (0.2%)	8 (0.7%)	878 (74.2%)	3 (0.2%)

Table 3 Univariate analysis of results in breast conservative treatment for 1184 patients with a family history according to first degree relative (FDR)

	None 941 pat. (%)	≥1 243 pat. (%)	*P* value	One 208 pat. (%)	≥2 35 pat. (%)	*P* value
Contralat. tumour						
yes	69 (7.4)	32 (13.2)	P=0.004	29 (14)	3 (8.6)	P=0.009
no	866	210		178	32	
Local recur.						
yes	39 (4.2)	10 (4.1)	ns	9 (4.3)	1 (2.9)	ns
no	901	233		199	34	
Regional rec.						
yes	6 (0.6)	5 (2.1)	P=0.040	4 (1.9)	1 (2.9)	ns
no	935	238		204	34	
Metastasis						
yes	152 (16.2)	31 (12.8)	ns	29 (13.9)	2 (5.7)	ns
no	789	212		179	33	

Table 4 Univariate analysis of the relation of family history and local recurrence according to age category

Age category	Family history	Local recurrence		*P* value
≤40 years		Positive	Negative	
n=99	≥ 1 FDR	7 (30.4%)	16 (69.6%)	*P*=0.005
	None	6 (7.9%)	70 (92.1%)	
41–50 years				
n=310	≥ 1 FDR	1 (1.7)	58 (98.3%)	ns
	none	15 (6%)	236 (94%)	
> 50 years				
n=774	≥ 1 FDR	2 (1.2%)	159 (98.8%)	ns
	none	18 (2.9%)	595 (97.1%)	

Univariate analysis showed a significant relationship between regional recurrence and a positive FH ($P=0.04$). Distant metastases were found in 183 patients (15.5%), with the lowest rate (5.7%) among the patients with ≥2 FDRs. No significant relation between metastasis and FH for the three different age categories was found. Contralateral carcinoma of the breast was diagnosed in 69 (7.4%) of the 935 patients without a positive FH, and in 32 (13.2%) of those with a positive FH ($P=0.004$).

In a multivariate logistic regression we analysed the relative risk of getting local and regional recurrence, distant metastasis and contralateral tumour in relation to FH. A significant increased risk was seen for regional recurrence (OR=4.8; 95% Confidence Interval 1.4-16.7; $P=0.014$) and contralateral carcinoma of the breast (OR=2.0; 95% Confidence Interval 1.3-3.1; $P=0.003$) for patients with a FH.

The 5-year overall survival was 88% with a corrected survival of 91.3% and it was similar for patients with or without a positive FH. Also stratified for the different age categories there was no significance difference. Among the 243 patients with a positive FH, a 5-year survival of 91% and 100% was observed among patients with one and ≥2 FDR, respectively (Fig. 1). In a multivariate Cox regression, with FH and other clinical and histological factors family history was not a significant factor.

DISCUSSION

One of the main reasons to look at the influence of family history, is the fact that women with a FH and a tumour in the breast were and still are often advised not to have a breast conservative treatment in our region. This is because of the so-called high rate of local recurrence and in consequence a less good prognosis.

Except for retrospective and case control sutdies, no prospective randomised trial is known to us, that could scientifically confirm this hypothesis.

In order to obtain a reliable family history from every patient we chose to ask only for first degree relatives. We are aware of the fact that by doing so we might miss patients with positive second-degree relatives. Despite that, it is our opinion that in this way we have obtained a reliable family history. Data from the literature with regard to local recurrence are not consistent.[6–11] Chabner et al. and others did not

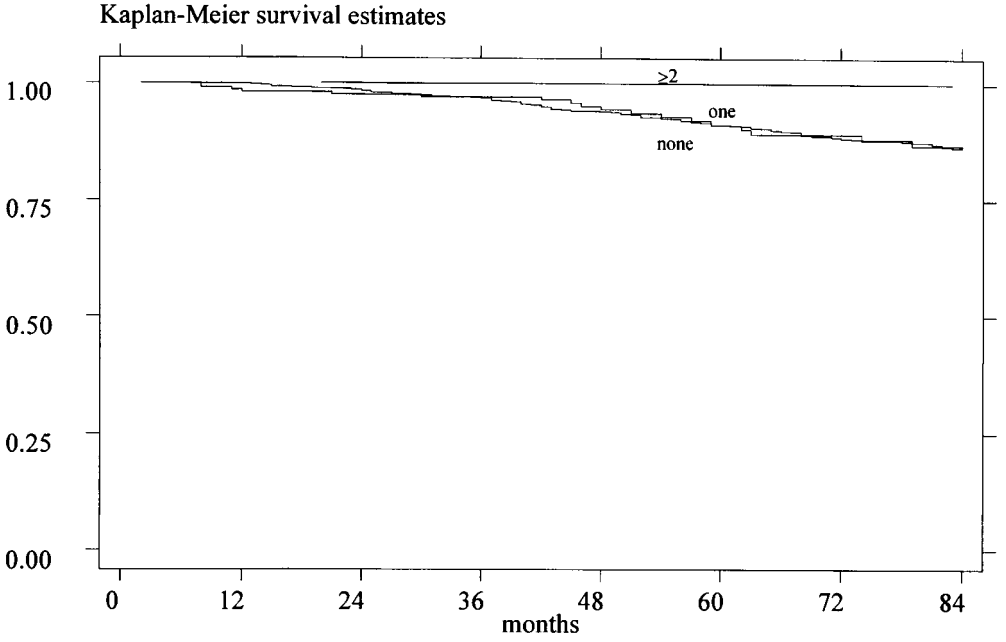

Fig. 1 Corrected survival of 1184 patients by FDR.

find a higher rate of local recurrence after breast conservative threatment, this in contrast to Ravaioli et al. and others who did find a higher local recurrence rate. In our large study we did not find a higher rate of local recurrence for patients with a FH.

Looking at the local recurrence rate in relation to FH in different age categories we found a very high rate for patients of ≤40 years (Table 4). In the multivariate logistic analysis we did not find a significant relation between age category and FH. Also the multivariate survival analysis did not show any significance in this respect. This indicates that FH might not be the dominant factor in the relation to local recurrence for patients ≤40 years.

While for all patients a positive FH did not result in a higher local recurrence rate and as a consequence FH is not a contra indication for breast conservative treatment, it might be contraindicated for young patients, ≤40 years, and a positive FH. On the other hand we do no know if mastectomy will give better results in this respect.

In our analysis we found a significant relation between the incidence of regional recurrence and FH. When analysing the relevance of this in relation to other clinical, histological and demographic factors we find could not any significant relation. This makes the importance of the significance questionable, which is supported by the wide 95% confidence interval in the multivariate analysis.

Also the prognosis for patients with a FH is not consistent.[15–17]

Looking at the incidence of metastasis for the different groups, a positive FH of breast cancer did not have any influence on the incidence of distant metastasis on univariate analysis. Also in the multivariate logistic regression metastasis did not have a significant relation with FH. This is not consistent with Marcus et al. who found a lower rate, but is consistent with data of Israeli and of Chabner.[4,6,7] It suggests that the prognosis is not influenced by a positive FH according to FDR. Marcus et al. found in hereditary breast cancer patients a lower recurrence rate.[4] We could not confirm his results with our small series of 35 patients with ≥2 FDRs and who possibly had hereditary breast cancer.

Looking at the survival our results are consistent with the literature.[2,3,5,7,8,14,15] There is no survival difference between patients with or without a FH. Only if we look in particular to the small group of patients with ≥2 FDRs (Fig. 1) we see a 100% survival, which is supported by data of Marcus et al. and Malone et al.[4,12,16] We must be do aware that this group of 35 patients with possibly hereditary breast cancer is rather small, which means that we have to interpret this with caution. The results with regard to the incidence of contralateral tumour are consistent with other data.[6,7,16] However, in those 35 patients with ≥2 FDRs we observed a similar rate as in patients with no FH.

In conclusion, patients with a positive family history have no worse prognosis. A positive family history is no contraindication for breast conservative treatment for patients older than 40 years. A positive family history and an age of ≤40 years might be a contra indication to breast conservative treatment. Larger prospective cohort studies are necessary to evaluate further the influence of a positive FH on the treatment results and prognosis of women with breast carcinoma.

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