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ORIGINAL ARTICLE

Familial breast cancer. Part IV: survival of familial breast cancer in Bulgarian patients

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Summary

Purpose: *The aim of part IV of this study was to register and compare the survival rates of sporadic and familial breast cancer, and to estimate the prognostic value of familial predisposition of the disease as a risk factor.*

Patients and methods: *We investigated retrospectively 504 patients belonging to families with accumulation of the disease (study group, group I) and 300 patients with the sporadic form of breast cancer (control group, group II). All patients were diagnosed, treated, and followed-up at the Clinic of Thoracic Surgery, National Oncological Centre. For determination of the familial predisposition we used the Anderson's classification.*

The statistical significance of the difference between two groups and subgroups was evaluated by the x^2 Pearson's test and Student's paired t-test.

Results: *Women with familial breast cancer were characterized by worse survival rates compared to the sporadic cases. Of the patients in group I 20.79% survived more than 5 years versus 76.74% in group II ($p < 0.0000$). Group I patients with first degree of kinship had the lowest survival rates. Highly significant differences were found in survival, depending on stage: in group I stage IIA patients the survival was 42.86% versus 97.73% for group II; in IIB it was 14.17% versus 89.41%; and in IIIA it was 4.76% versus 75.00%, respectively. Tumor size, lymph nodes status, metastases and steroid receptors also showed a high statistical difference in survival between the 2 groups. Five-year survival in group I patients without metastases was 22.34%, while it was 80.71% in group II. In patients with metastases 4-year survival rates were 2.94% and 22.22%, respectively. Estrogen receptor (ER)-negative patients in groups I and II had 5-year survival of 17.41% and 72.06%, respectively. Progesterone receptor (PR)-negative patients in groups I and II had 5-year survival of 17.50% and 83.67%, respectively. Invasive lobular and invasive ductal carcinoma showed very poor survival in both groups (18.75% and 17.73% in group I versus 53.33% and 77.48% in group II, respectively).*

Conclusion: *Familial breast cancer displays particular clinical characteristics that differ from the sporadic form of the disease in terms of clinical, histological and biochemical features. Our results show that patients with familial breast cancer have significantly lower survival rates in comparison with women with the sporadic form of the disease. The need for surveillance and diagnosis of the disease at an earlier stage is crucial for women with familial predisposition for breast cancer.*

Key words: hereditary breast cancer, familial predisposition, prognostic factors, survival

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Introduction

Family history is a well-recognized risk factor for breast cancer, but its impact in terms of breast cancer survival is less known. Some authors have demonstrated statistically significant higher survival rates in breast cancer patients with family history of breast cancer [1-3], while others have shown a significantly worse prognosis [4-6]. A number of investigators have found no influence on survival in famil-

ial breast cancer patients compared with cases of the sporadic form of this disease [7-8]. Ansquer et al. showed that when early-onset breast cancer patients with BRCA1 mutations were selected as the cases, a worse 5-year overall survival was observed in the germline mutation carrier group [9].

These conflicting literature data about breast cancer survival were a reason for undertaking this investigation concerning the survival of women with breast cancer with familial predisposition and with the sporadic form of the disease.

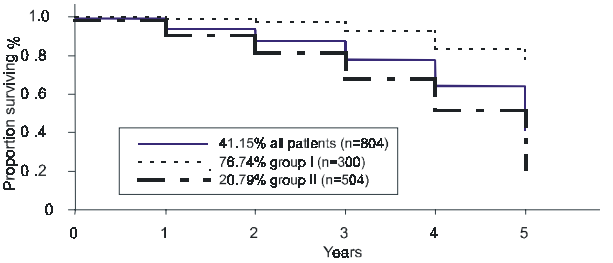

Figure 1. 5-year overall survival of all 804 investigated patients and of the 2 groups (group I *versus* group II, p <0.0000).

Patients and methods

The records of 504 patients belonging to families with accumulation of the disease (group I) and 300 patients with the sporadic form of the disease (group II) were retrospectively analyzed. All patients were diagnosed, treated, and followed in the Clinic of Thoracic Surgery, National Oncological Centre from 1982-1994. For determination of the familial predisposition we used the Anderson's classification modified by Skolnic and Cunnon-Albright (Table 1) [10-11].

Tumor size, nodal status and the presence of metastasis were recorded and evaluated according to the TNM staging system. The histological type and grading of the tumor were also examined. For estimating the grade of malignancy we used 3 morphological features: tubule formation, degree of nuclear pleomorphism, and mitotic count in a defined field area.

For the statistical processing of the results the SPSS applied computer programs (Base System Syntax Reference Guide, Release 5, Copy Right, USA) was used. The statistical significance of the difference between two groups and subgroups was evaluated by the x^2 Pearson's test and Student's paired t-test.

Table 1. Familial predisposition for breast cancer [10,11]

1. Diagnosis of breast cancer at the age of 36 years or earlier.
2. Bilateral breast cancer at the age of 50 years or earlier.
3. Breast cancer at the age of 50 years or earlier and first-degree relative having breast cancer diagnosis at the age of 50 years or earlier.
4. Ovarian cancer and first-degree relative having ovarian cancer (at any age) or breast cancer diagnosed at the age of 60 years or less.
5. Ovarian or breast cancer (any age) with at least two first-degree relatives with ovarian cancer (any age) or breast cancer diagnosed at the age of 50 years or earlier.
6. Males with breast cancer at any age.

Results

The 5-year overall survival rate of all 804 investigated women with breast cancer was 41.15%, with highly statistical significance between the 2 groups (group I 20.79% *versus* group II 76.46%, p <0.0000; Figure 1).

Table 2 and Figure 2 show the 5-year overall survival rates in the two groups according to kinship. The results show lower 5-year survival for patients of first degree of kinship (20.15% ± 3.38) in comparison with patients of second degree of kinship (23.00% ± 6.80) and third degree of kinship (20.27% ± 4.92), without reaching statistical significance (p <0.243).

The survival in relation to TNM stage, histological subtypes, grade and steroid receptors status of both groups is analysed in Table 3. Highly statistical

Table 2. 5-year overall survival of patients with familial breast cancer according to kinship

Year *Degree of kinship*	*1*	*2*	*3*	*4*	*5+*	*p-value*	*Median survival (days)*
1st degree (%)	87.48±1.98	76.80±2.60	62.47±3.11	47.56± 3.38	20.15±3.38	< 0.243	1765
2nd degree (%)	94.87±2.50	86.80±3.89	76.04±5.11	57.50±6.40	23.00±6.80		1979
3rd degree (%)	93.08±2.36	87.71±3.08	73.33±4.26	55.95±5.0	20.27±4.92		1979

±: standard deviation

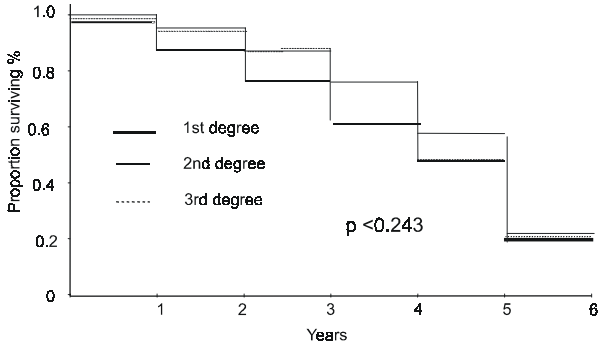

Figure 2. Comparison of 5-year overall survival rates of the patients with familial breast cancer according to kinship.

significance (p <0.0000) in the 5-year survival rate was shown for all disease stages, favoring group II patients.

The tumor size and axillary node status displayed great differences in 5-year survival. For patients without metastases the 5-year survival was 22.34% for group I and 80.71% for group II (p <0.0000) (Table 3). For patients with metastases the 4-year survival rates were 2.94% and 22.22%, respectively (p <0.0000, Table 3).

Both invasive and noninvasive carcinomas showed significantly lower 5-year survival rates in group I compared to group II: 18.75% and 53.33% with invasive lobular carcinoma; 57.14% and 100.00% with intraductal carcinoma; 17.73% and 77.48% with invasive ductal carcinoma (p <0.00001). The results for other histological types retained these differences (Table 3).

Pertaining to the grade of malignancy, we found that well-differentiated (G1) tumors showed the highest survival rate (81.69%), while for cancers with poor differentiation (G3) this percent was 4.31% (p <0.00001; Table 3).

Group I ER-positive patients showed 5-year survival in 22.19% of the cases *versus* 78.41% for group II (p <0.00001). The rates for ER-negative patients in cases and controls were 17.41% and 72.06%, respectively. In a similar pattern, the corresponding rates for patients with positive PR were 23.64% and 73.09% and for PR-negative they were 17.50% and 83.67% for group I and II, respectively (p <0.0001; Table 3).

Table 4 describes 5-year survival in relation to the treatment modalities applied. According to the performed surgical technique we found highest survival rates when conservative surgical procedures were carried out (76.92% and 100% for group I and II, respectively). In contrast, the survival rate was

Table 3. 5-year overall survival in the two groups of patients according to several tumor factors

Tumor (T)	*Group I (n=504) n surviving / total n (%)*	*Group II (n=300) n surviving / total n (%)*	*p-value*
T1a	7/8 (87.50)	4/4 (100.00)	0.0376
T1b	9/13 (69.23)	29/32 (90.62)	0.1358
T1c	45/74 (60.81)	50/54 (92.59)	0.0180
T2	175/286 (61.19)	142/163 (87.12)	0.0000
T3	0/95 (0.00)	7/25 (28.00)	0.0900
T4b	0/28 (0.00)	3/22 (13.64)	0.0032
Axillary lymph nodes (N)			
0	97/194 (50.00)	152/158 (96.20)	0.0000
1	3/28 (10.71)	0/0 (0.00)	—
2-3	18/163 (11.04)	58/106 (54.71)	0.0000
> 3	0/95 (0.00)	3/29 (10.34)	0.0000
in packet	2/10 (20.00)	0/4 (0.00)	0.0166
parasternal +	0/14 (0.00)	3/3 (100.00)	0.1266
Metastases (M)			
M(–)	105/470 (22.34)	234/291 (80.71)	0.0000
M(+)	0/34 (0.00)*	0/9 (0.00)*	—
Stage			
I	48/56 (85.71)	62/62 (100.00)	0.0002
IIA	63/147 (42.86)	86/88 (97.73)	0.0000
IIB	18/127 (14.17)	76/85 (89.41)	0.0000
IIIA	1/21 (4.76)	6/8 (75.00)	0.0029
IIIB	0/122 (0.00)	7/48 (14.58)	0.0000
IV	0/31 (0.00)**	0/0 (0.00)**	0.0000
Grade (G)			
G1	58/71 (81.69)	88/91 (96.70)	0.0000
G2	4/201 (24.37)	112/120 (93.33)	0.0000
G3	10/232 (4.31)	24/89 (26.97)	0.0000
Steroid receptors			
ER (+)	71/320 (22.19)	178/227 (78.41)	0.0000
ER (–)	31/178 (17.41)	49/68 (72.06)	0.0000
PR (+)	61/258 (23.64)	144/197 (73.09)	0.0000
PR (–)	42/240 (17.50)	8/98 (83.67)	0.0000
Unknown	6	5	
Histology			
Lobular *in situ*	4/11 (36.36)	0/0 (0.00)	—
Invasive lobular	30/160 (18.75)	8/15 (53.33)	0.0000
Intraductal	16/28 (57.14)	15/15 (100.00)	0.0019
Invasive ductal	47/265 (17.73)	148/191 (77.48)	0.0001
Mucinous (colloid)	3/30 (10.00)	22/22 (100.00)	0.0001
Medullary	6/10 (60.00)	5/5 (100.00)	0.1233

*for 4 years 2.94% *versus* 22.22%; p=0.0000
**for 4 years 12.90% *versus* 22.22%; p <0.0001

reduced in both groups with more radical operations. The differences were significant for all special techniques ($p < 0.0000$, Table 4).

Regarding pre- and postoperative treatment the results showed lower 5-year survival rate for patients of group I in comparison with group II. For pre- and postoperative radiotherapy this rate was 6.66% and 57.14% for group I and II, respectively. For chemotherapy the respective rates were 5.19% and 62.50% ($p < 0.0000$; Table 4).

Discussion

Familial breast cancer displays particular clinical characteristics that differ from the sporadic form of the disease. In the literature there are many reports about differences in clinical stage, histological type, grade of malignancy or biochemical characteristics between these two forms of the disease [12-14]. The results of our previous studies confirmed this [15-19]. We established that familial breast cancer is more often bilateral and is diagnosed in a more advanced stage. The histological type is more of invasive carcinomas and with poor differentiation (G3) [1,9,12]. Predisposed patients develop the disease predominantly in younger age and are premenopausal [13,15].

It is less clear whether survival of breast cancer is influenced by the family history of disease. Some authors report that family history has been associated with increased, as well as decreased survival rates [3,4,6,20], or has been found to have no influence [9]. In this study we compared the survival rates of patients with familial predisposition (group I) and with the sporadic form of the disease (group II).

The 5-year survival rate for all 804 investigated patients was 41.15%. Yet the survival of group I patients was very poor compared with the one of group II patients (20.79% *versus* 76.74%, $p < 0.0001$). The same trend for worse survival is also reported by other authors [20,21].

It has been reported that about 20% of the patients with breast cancer have relatives with the same disease [22-25]. These are patients with genetic predisposition inherited from their parents. We found significant differences depending on the degree of kinship. The results show that patients of first degree of kinship have the lowest survival rates (20.15% ± 3.38). The survival rates increase in second degree of kinship (23.00% ± 6.80, Table 2).

Our results show significant differences in survival by stage, which are remarkably worse for group I. As the TNM stage progresses, the survival of patients decreases, as in IIIB and IV it is 0.00%. The survival for group I in stage IIA was 42.86% *versus* 97.73% for group II; in IIB 14.17% *versus* 89.41%; in IIIA 4.76% *versus* 75.00%; and in IIIB and IV no group II patient survived for 5 years.

In our study survival showed strong dependence on tumor size, histological type, grade of malignancy and presence of metastases. In our previous studies we found that the familial breast cancer cases were often associated with a higher incidence of invasive carcinomas with poor differentiation (G3) [12,16,23]. Advanced stage of disease and poor differentiation indicate an unfavorable prognosis. This is also supported by the statistically significant differences regarding the survival rates of the two groups. In invasive lobular carcinoma the 5-year survival rate in group I was 18.75% *versus* 53.33% for group II. We found the same differences in invasive ductal carcinoma: 17.73% for patients with familial predisposition and 77.48% for controls.

In the literature medullary carcinoma accounts for only 5% of all cases of breast cancer. It is a poorly differentiated tumor with high frequency of p53 mutations (almost 100%) and a paradoxically favorable prognosis in comparison with the poorly differentiated common invasive cancer [27,28]. This is not entirely sup-

Table 4. 5-year overall survival in both groups of patients according to treatment

Treatment	*Group I (n=504) n surviving / total n (%)*	*Group II (n=300) n surviving / total n (%)*	*p-value*
Surgery			
Quadrantectomy with lymph node dissection	30/39 (76.92)	20/20 (100.00)	0.0741
Patay-Pirogov	9/13 (69.23)	0/0 (0.00)	–
Patay	54/260 (20.77)	159/201 (79.10)	0.0000
Patay with parasternal nodal biopsy	21/118 (17.79)	39/57 (68.42)	0.0000
Halsted	6/74 (8.11)	13/22 (59.10)	0.0000
Radiotherapy			
Preoperative	1/7 (14.28)	1/1(100.00)	0.0000
Postoperative	82/333 (24.62)	116/184 (63.04)	0.0000
Pre-and postoperative	1/15 (6.66)	4/7 (57.14)	0.0231
Chemotherapy			
Preoperative	0/4 (0.00)	0/0 (0.00)	–
Postoperative	4/64 (6.25)	8/13 (61.54)	0.225
Pre-and postoperative	4/77 (5.19)	30/48 (62.50)	0.0000
Antioestrogen therapy			
Antioestrogen therapy alone	74/167 (44.31)	124/133 (93.23)	0.0000
Postoperative chemotherapy with antiestrogen therapy	10/149 (6.71)	42/71 (59.15)	0.0000

ported by our entire study with a 12 year follow-up period. We found 10 (1.98%) medullary carcinomas in family predisposed patients and 7 (2.33%) in sporadic cases [10]. The 5-year survival in group II was 100.0%, while in group I it was 60.00%, ($p < 0.0001$).

Steroids hormones are a most important prognostic factor. They are involved, especially estrogens, in the development and progression of breast carcinoma. Breast carcinomas with low levels of ER and PR very often carry germline mutations of BRCA1 or BRCA2 genes and are associated with bad prognosis [29-31]. Our results are in agreement with the findings of these authors. We found significant differences in survival between the two groups: 22.19% (group I) and 78.41% (group II) for ER-positive carcinomas. For PR-positive tumors the results were 23.64% (group I) and 73.09% (group II). For ER-negative tumors the corresponding results were 17.41% and 72.06, and for PR-negative tumors they were 17.50% and 83.67%, respectively. Depending on the disease progression, the patients received in addition radiotherapy, chemotherapy or antiestrogen therapy.

The postoperative radio-, chemo- and antioestrogen therapy is a sign for locally advanced disease concerning T and N, that has been detected intraoperatively. In our previous studies [15, 17] we found that postoperative radiotherapy is almost equally applied in both groups, while postoperative chemotherapy is more frequent in the group of the patients with a family history. This is a proof for primarily determined aggressiveness in patients belonging to group I. Antiestrogen therapy, which is more common in group II confirms this fact, as there is an established hormonal susceptibility of the primary tumor, in contrast with the lower hormonal sensitivity of group I, which is a negative prognostic sign. Regardless of the applied complex of radio-, chemo- and antiestrogen therapy, the survival rates for familially predisposed patients was considerably lower: 24.62% *versus* 63.04%, 6.25% *versus* 61.54% and 6.71% *versus* 59.15%, respectively ($p < 0.0000$).

In conclusion, our results indicate a more aggressive course of the disease for patients with familial predisposition, which makes the prognosis worse and affects adversely patients' survival.

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