Journal of BUON **17:** 649-657, 2012

ORIGINAL ARTICLE

Association between family history and clinicopathologic characteristics in 1987 breast cancer patients: single institution experience from Turkey

F.P. Turkoz[1], M. Solak[1], S. Aksoy[1], I. Petekkaya[1], O. Keskin[1], N. Kertmen[1], F. Sarici[1], Z. Arik[1], T. Babacan[1], E. Simsek[2], Y. Ozisik[1], K. Altundag[1]

[1]Department of Medical Oncology, Hacettepe University Institute of Oncology, Ankara; [2]Department of Medical Biology, Yildirim Beyazit University Faculty of Medicine, Ankara, Turkey

Summary

Purpose: *To evaluate the clinicopathologic characteristics and survival of patients with family history of breast/ovarian cancer (FHBOC).*

Methods: *In this study with 1987 breast cancer patients, we analyzed their tumor characteristics and outcomes, as well as the total number, degree and age of affected relatives, and their type of cancer. Results were assessed using Pearson chi-square test, Kaplan-Meier method and Cox regression analysis.*

Results: *24.1% (n=479) of the patients had FHBOC. Patients with FHBOC were younger (47.7 vs. 49.1 years; p=0.03) and tended to have node-negative breast cancer (45.4 vs. 39.8%; p=0.006). The median overall survival (OS) was shorter in patients with FHBOC with a borderline p value (p=0.063), compared to patients with no family history. The median OS was shorter in patients who had ≥ 2 relatives with breast cancer (p=0.014), in those having first degree relatives with breast cancer, presenting with metastatic disease (p= 0.020). FHBOC patients with triple negative breast cancer had the highest risk of death (p<0.0001) and recurrence (p<0.0001). Patients who had at least one relative with breast cancer aged ≤ 50 years were also at increased risk of recurrence (p=0.006).*

Conclusion: *Our results suggest that patients with FHBOC are younger, tend to have small tumor size, node-negative disease and their survival is shorter compared to patients without family history. This is the first study evaluating the clinicopathologic differences of patients with and without FHBOC in Turkish population.*

Key words: breast cancer, clinicopathologic characteristics, family history, Turkish population

Introduction

Breast cancer is the most commonly diagnosed cancer in women worldwide and the second leading cause of cancer death [1]. It is also noted to be the most common type of cancer in women with an increasing trend in the report of Turkish Ministry of Health, Department of Cancer Control [2]. According to the GLOBOCAN 2008, the crude as well as age-standardized incidence and mortality rates of breast cancer in Turkey per 100 000 were 25.6; 28.3 and 17.6; 12.4 (10 065 new cases and 4 311 deaths) respectively [1].

Breast cancer is characterized by its complex etiology with an interaction of hormonal, genetic and environmental factors. Family history of breast cancer is one of the well-established risk factors for the disease development. The familial relative risk for breast/ovarian cancer varies with the age of the patient and the age of the relative, and increases with the number of affected relatives [3,4]. In a meta-analysis of 52 case-control and 22 cohort studies, the overall risk of developing breast cancer was found to be 2.1-fold (95% CI 2.0-2.2) in women with a first-degree family history and 1.5-fold (95% CI 1.4-1.6) in women with a second-degree family history compared to women with no family history of breast cancer [3]. A study with 58 209 women with breast cancer and of 101 986 controls reported that the risk ratios were 1.80 (95% CI 1.69-1.91), 2.93 (95% CI

Correspondence to: Kadri Altundag, MD. Department of Medical Oncology, Hacettepe University Institute of Oncology, Sihhiye Ankara 06100, Turkey. Tel: +90 312 3052954, Fax: +90 324 2009, E-mail: altundag66@yahoo.com

Received 05-03-2012; Accepted 27-03-2012

2.36-3.64), and 3.90 (95% CI 2.03-7.49), respectively, for 1, 2, and 3 or more affected first-degree relatives compared with women who had no affected relative [4].

The Breast Cancer Linkage Consortium indicates that most families with both breast and ovarian cancer or early-onset breast cancers are largely attributable to mutations in BRCA-1 and BRCA-2 genes. However, only about 5-10% of breast cancer patients carry a genetic predisposition due to a highly penetrant germline mutation [5]. Women carrying a BRCA-1 or BRCA-2 mutation have a substantially elevated risk of developing breast/ovarian cancer with a lifetime risk for breast cancer of up to 85%, and for ovarian cancer between 40- 60% for BRCA-1 carriers and between 20- 30% for BRCA-2 carriers [6]. The breast cancer cases arising in BRCA-1 and BRCA-2 positive women differ from sporadic breast cancers in terms of clinical and pathological features, response to treatment and survival outcomes [7,8]. Risk-reducing operations including mastectomy or bilateral salpingo-oophorectomy are options to decrease the risk and to lower the mortality [9]. Mutations in the PTEN gene, p53 gene and CHEK-2 gene are also known or suspected to be associated with an increased risk of breast cancer, but none of these genes are likely to explain an important fraction of familial aggregation of the disease [5].

To date, the spectrum of BRCA-1 and BRCA-2 mutations in Turkish breast/ovarian cancer patients were reported only in a few small sample size studies. Yazici et al. identified BRCA mutations in 33% of the families with 3 or more breast cancer cases in a first- or second-degree relationship of 53 individuals with personal and family history [10]. Aydin et al. detected large genomic rearrangements in BRCA-1 in 4 (1.9%) of 211 breast cancer patients, however, no BRCA-2 rearrangements were found [11]. Manguoglu et al. revealed no large genomic rearrangements in both genes, and, no 1100del variant in CHEK-2 gene in 50 high risk Turkish women [12]. In the largest study, Aktas et al. evaluated 667 ovarian cancer patients and observed BRCA-1 point mutations (5382insC) in 9.8% and large genomic rearrangements (E1A-1B-2) in 40.9% of familial breast/ovarian cancer cases [13]. Analyses of family-based studies may lead to inflated risk estimates, however, we have no population-based data yet about BRCA-1/2 status in breast cancer patients in Turkey.

A positive family history is responsible for 6-19% of all new breast cancer cases. Although the importance of family history as a risk factor for breast cancer is well-recognized, its prognostic value has not been clearly elucidated yet. Only a few studies have investigated the characteristics of breast cancer in women with a family history, however, the results are conflicting [7,14-16]. To ascertain the differences, we analyzed several demographic, clinical and pathological characteristics including tumor subtypes, as well as survival outcomes of the patients who had breast/ovarian cancer in first-, second- or third-degree relatives, in our cohort. This is the first study evaluating clinicopathological differences between patients with and without family history of breast/ovarian cancer (FHBOC) in Turkish population.

Methods

This retrospective cohort study consisted of 2004 cases of breast cancer between 1981 and 2011 who have been followed up in Department of Medical Oncology at Hacettepe University, Institute of Oncology. A positive family history of breast cancer was defined as having one or more close blood relatives with breast/ovarian cancer. Cases with missing data of family history (n=17) were excluded because we were unable to classify these cases as familial or non-familial breast cancer. After exclusion, 1987 cases were eligible for analysis.

All breast cancer cases were interviewed upon admission at the medical oncology department. The data of personal, maternal and paternal family history, type of cancer, the total number and degree of affected relatives over 3 generations, the age of the case and the age of their affected relative(s) were recorded. All data regarding family history were based on interviews with the patients; medical records of relatives with malignancy were not checked.

FHBOC was classified into 4 categories: i) patients with no FHBOC; ii) breast/ovarian cancer in first-degree relatives (parents, children and siblings; iii) breast/ovarian cancer in second-degree relatives (aunts/uncles, grandparents); iv) breast/ovarian cancer in third-degree relatives (cousins). Women with FHBOC in both first- and second-degree or both first- and third-degree relatives were considered as belonging to the first-degree FHBOC category. Similarly, women with a positive FHBOC in both second- and third-degree relatives were considered as belonging to the second-degree FHBOC category.

Tumor characteristics, including size, grade, lymphovascular invasion, estrogen receptor (ER) and progesterone receptor (PR), HER-2 status and number of involved axillary nodes were obtained from diagnostic pathology reports. Distant or locoregional metastasis were abstracted from medical reviews. ER and PR status were assessed by immunohistochemistry. Nuclear staining in more than 5% of tumor cells was considered as positive. Expression of HER-2 was also determined immunohistochemically. HER-2 positivity (a score of 3+) was defined as strong complete membrane staining in more than 10% of tumor cells; scores of 0 and 1 were considered negative, and fluorescence *in situ* hybridization was done for all 2+ tumors.

Cases diagnosed within 3 months of diagnosis of the first breast cancer were classified as synchronous and those diagnosed more than 3 months apart were classified as metachronous. OS was measured from the date of diagnosis to the date of last information/death. The interval from the date of diagnosis to the date of locoregional or distant recurrence was defined as disease free survival (DFS) for non-metastatic breast cancer cases and time to progression (TTP) for metastatic cases.

Before statistical analysis, risk factors defined by National Comprehensive Cancer Network (NCCN) Guidelines were classified as follows: age at diagnosis ≤50 years (no, yes), triple negative

breast cancer (no, yes), bilateral breast cancer (no, synchronous, metachronous), at least one relative with breast cancer ≤ 50 years (no, yes), at least one relative with ovarian cancer at any age (no, yes), ≥ 2 relatives with breast cancer and/or pancreatic cancer at any age (no, yes), male breast cancer (no, yes), breast and ovarian cancer (no, yes), a combination of breast cancer with one or more the following: thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumors, diffuse gastric cancer, leukemia/lymphoma on the same side of family (no, yes) [17].

Statistical analysis

Differences in demographic and clinicopathologic characteristics of the patients with or without FHBOC were examined using one-way ANOVA for continuous variables and Pearson chi-square test for the categorical variables. OS, DFS and TTP were estimated using the Kaplan-Meier method. Differences in terms of survival by FHBOC within groups characterized by clinical and pathologic features were tested using the log-rank test. Cox proportional hazards models were also performed to assess the relative excess risk of breast cancer mortality and recurrence among patients with and without FHBOC and to adjust for confounding factors. To select those factors with independent significant influence on recurrence and mortality, multivariate analyses were carried out in a stepwise Cox regression model. Prior to this application, univariate analyses were performed for a preliminary exploration of marked associations.

All data was entered and analyzed using Statistical Package for Social Sciences version 15.0 (SPSS, Inc., Chicago, IL, USA). Appropriate statistical analysis was carried out with a two-sided level of 0.05 and/or 95% confidence interval (CI).

Results

Of 1987 breast cancer patients, 1140 (57.4%) had family history of cancer and 479 (24.1%) had FHBOC. Patients with FHBOC were younger (47.7±11.4 vs. 49.1±11.8 years; p=0.03) and more frequently premenopausal (59 vs. 53.2%; p=0.026) than patients with no family history at the time of diagnosis. Table 1 shows the comparison of the risk factors between the patients who reported first-, second- and third-degree relatives with breast/ovarian cancer.

Of the patients, 186 had affected first-degree, 172 second-degree and 121 third-degree relative with breast/ovarian cancer. Of the patients with FHBOC 60.5% reported maternal and 49.3% paternal history of cancer; 20.7% had mother with breast or ovarian cancer and 3.9% of these had both; 33.8% had a history of cancer in siblings or children. Only 2.9% of the patients with FHBOC reported no affected relative with breast cancer. On the other hand, 27% had 2 or more affected relatives with breast cancer.

Family history of prostate cancer was more frequent in patients with FHBOC (6.7 vs. 2.8%; p=0.001). Moreover, patients with FHBOC more frequently had relatives with multiple primary cancers (6.1 vs. 0.8%; p<0.0001). The percentages of relatives with pancreatic cancer history did not differ among patients with or without FHBOC (2.9 vs. 2.5%; p=0.216). In our cohort there were only 13 (0.7%) male breast cancer patients and 12 out of 13 had no family history.

Synchronous bilateral breast cancers were more frequent in patients with FHBOC (40.9 vs. 32%); on the contrary, metachronous breast cancers were more frequent in patients without family history (68 vs. 59.1%). However the difference was not statistically significant (p=0.420).

Table 2 shows the comparison of tumor characteristics of the patients who reported breast/ovarian cancer in first-, second-, and third-degree relatives and the patients with no family history. The most common histopathology was invasive ductal carcinoma, followed by mixed carcinoma (invasive ductal + lobular carcinoma). Invasive lobular carcinoma (6.1 vs. 5.3%; p=0.022) and lobular carcinoma *in situ* (1.4 vs. 0.1%; p=0.018) were slightly higher in patients with FHBOC.

Patients with breast/ovarian cancer in first-degree relatives more often had disease in the right breast than those with no family history (54.6 vs. 45.5%; p=0.691). The majority of the patients had T1-T2 tumors both with

Table 1. Comparison of patients with and without risk factors of breast and/or ovarian cancer

*Risk factors**	*Breast/ovarian cancer in relatives*			
	First-degree N (%)	*Second-degree N (%)*	*Third-degree N (%)*	*p-value*
Breast cancer ≤ 50 years	99 (54.1)	120 (71.0)	88 (73.9)	<0.0001
Breast cancer ≤ 40 years	34 (18.6)	63 (37.3)	38 (31.9)	<0.0001
Bilateral breast cancer	9 (4.8)	9 (4.8)	8 (6.5)	0.816
≥1 relatives with breast cancer at any age	174 (93.5)	169 (96,6)	119 (96)	0.359
≥1 relatives with breast cancer ≤ 50 years	109 (58.6)	73 (41.7)	70 (56.5)	0.003
≥1 relatives with ovarian cancer at any age	16 (8.6)	8 (4.6)	1 (0.8)	0.009
≥2 relatives with breast cancer and/or pancreas cancer at any age	50 (26.9)	54 (30.9)	37 (29.8)	0.691
A combination of breast cancer with other malignancies on the same side of the family**	184 (98.9)	100 (100)	124 (99.2%)	0.408

*NCCN Guidelines Version 1.2011. Breast and/or Ovarian Cancer Genetic Assessment, **Thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumors, diffuse gastric cancer, leukemia/lymphoma on the same side of family

Table 2. Comparison of tumor characteristics of patients with and without FHBOC

Tumor characteristics	*No family history (%)*	*Breast/ovarian cancer in relatives (%)*			*p-value*
		First-degree	*Second-degree*	*Third-degree*	
Histology					0.022
Invasive ductal carcinoma	75.9	75.0	79.9	72.3	
Invasive lobular carcinoma	5.3	6.0	5.9	6.7	
Ductal carcinoma in situ	2.6	2.7	2.4	3.4	
Lobular carcinoma in situ	0.1	0.5	1.2	2.5	
Others	7.6	7.6	4.1	5.9	
Localization					0.691
Right breast	45.5	54.6	48.0	45.0	
Left breast	52.9	43.8	50.3	53.3	
Tumor size					0.097
T0 / Tis	5.1	2.7	4.1	5.0	
T1	24.2	32.6	29.4	24.2	
T2	49.0	42.4	45.9	45.8	
T3	16.3	20.1	19.4	17.5	
T4	5.4	2.2	1.2	7.5	
Lymph node involvement					0.006
Yes	53.3	40.8	57.6	53.3	
No	46.7	59.2	42.4	46.7	
Local / distant metastasis					0.165
Yes	9.4	5.4	8.3	12.6	
No	90.6	94.6	91.7	87.4	
Grade					0.817
1	11.9	14.5	11.6	13.2	
2	45.6	46.7	41.8	41.5	
3	42.5	38.8	46.6	45.3	
Ki-67					0.661
Yes	81.0	81.8	87.5	70.6	
No	19	18.2	12.5	29.4	
Lymphovascular invasion					0.141
Yes	61.2	51.3	65.5	69.6	
No	38.8	48.7	34.5	30.4	
Estrogen receptor					0.944
Positive	67.4	66.5	70.8	71.7	
Negative	26.9	26.5	24.6	25.0	
Progesterone receptor					0.639
Positive	66.0	66.5	68.4	75.0	
Negative	27.4	25.9	26.9	21.7	
HER-2 status					0.136
Positive	24.0	16.3	20.5	21.1	
Negative	76.0	83.8	79.5	78.9	
Subtype					0.553
TNBC	11.6	15.1	13.3	11.9	
HER-2 overexpressing	9.5	6.1	6.0	7.6	
Luminal A	58.0	61.4	60.4	61.0	
Luminal B	12.5	9.1	12.8	11.9	

FHBOC: family history of breast/ovarian cancer, TNBC: triple negative breast cancer

and without family history. T4 tumors were observed in 5.4% of the patients with no family history and 3.4% of the patients with FHBOC (p=0.027). Of the patients with FHBOC 45.4% had node-negative disease vs. 39.8% of the patients with no family history (p=0.006), while the frequency of metastatic breast cancer at the time of diagnosis was similar in both groups (8.5 and 9.4%; p=0.809). We found no significant associations between grade, lymphovascular invasion, Ki-67 index and FHBOC (p=0.711, p=0.506 and p=0.839, respectively).

The hormone receptor status was known in 1894 patients and HER-2 status was known in 1767 patients. There were no significant differences in hormone receptor status among the two groups (p=0.865, p=0.467,

respectively). Luminal A cancer had 58.7% of the patients, luminal B 12.1%, 8.8% had HER-2 overexpression and 12.1% had triple negative breast cancer (TNBC). Luminal breast cancer was the most common subtype in all groups. TNBC was observed in 11.6% of the patients with no family history and in 13.5% of the patients with FHBOC (p=0.274). HER-2 overexpressing breast cancer was significantly higher in the patients with no family history (9.5 vs. 6.4%; p=0.039).

We observed no differences in treatment administration. Adjuvant, neoadjuvant and palliative chemotherapy was administered to 80.9, 8.2 and 7.3% of the patients with no FHBOC and in 83.1, 6.3 and 7.4% of the patients with FHBOC (p=0.277). Hormone therapy was prescribed in 73.5% of the patients with no family history and in 75.6% of the patients with FHBOC (p=0.359). The proportion of cases who underwent risk-reducing surgery was 3.8% and of those who used tamoxifen for prevention 1.4%. All of these cases were alive with no evidence of disease (median 14 months, range 2-14).

The median follow-up period after breast cancer diagnosis was 27 months (range 1-400). The median OS was longer in patients with no family history (185 months; 95% CI 156.5-213.5) than in patients with FHBOC (161 months; 95% CI 138.4-183.6) (p=0.063). The median DFS was 85 months (95% CI 68.9-97.0) for patients with no family history and 83 months (95% CI 41.2-128.8) for patients with FHBOC (p=0.436). OS and DFS of the patients with no family history and of those with breast/ovarian cancer in first-, second- and third-degree relative are shown in Figures 1 and 2.

The median OS was significantly shorter in patients who had at least 2 relatives with breast cancer (104 months; 95% CI 32.5-175.5) than patients who had 1 relative with breast cancer (178 months; 95% CI 149.4-205.6) and patients with no family history (179 months; 95%CI 150.4-208.6) (p =0.014). No significant differences were found in DFS. The association between OS and number of affected relative is shown in Figure 3. We also analyzed the association between OS and DFS of patients with maternal or paternal family history. Median survival was similar in both patient groups.

The median OS was 38 months (95% CI 32.3-43.7) and the median TTP 21 months (95% CI 9.3-32.7) in metastatic breast cancer patients with FHBOC. There were no significant differences in OS and TTP between patients with and without FHBOC (p=0.131 and p=0.126, respectively). However, TTP was significantly shorter in patients who had breast/ovarian cancer in first-degree relative (6.8 months; 95% CI 4.4-9.2) compared to patients with no family history (43 months; 95% CI 30.2-55.9; p= 0.020).

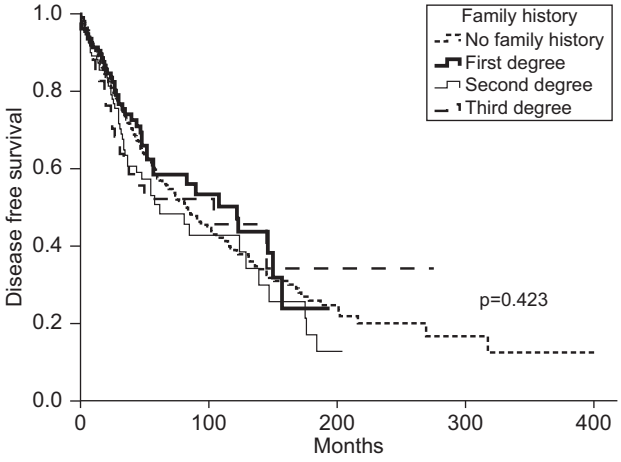

Figure 2. Disease free survival of patients with and without family history.

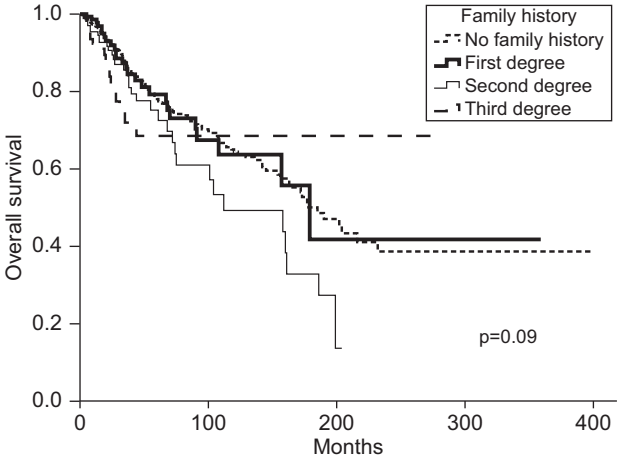

Figure 1. Overall survival of patients with and without family history.

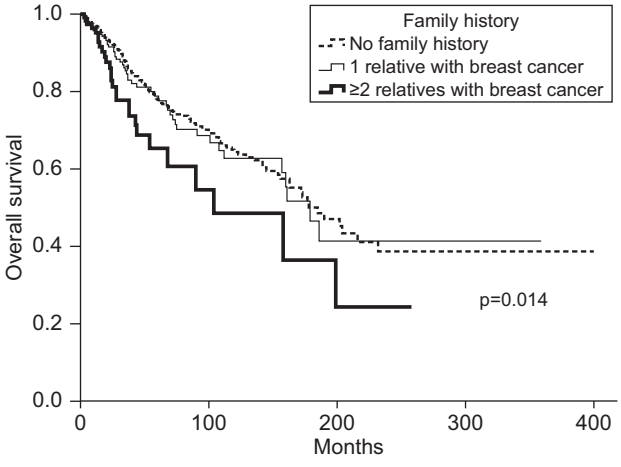

Figure 3. The association between overall survival and the number of affected relatives.

Of 1987 patients, 291 (14.6%) died and 544 (27.1%) had a breast cancer recurrence. Patients with FHBOC had an increased risk of breast cancer mortality, however without reaching statistical significance (HR 1.27; 95% CI 0.99-1.65; p=0.064). We analyzed the impact of risk factors on OS and DFS using Cox regression analysis (Tables 3 and 4). After adjustment for age, tumor size and nodal involvement, we found that the patients with FHBOC who had TNBC had the highest risk of breast cancer recurrence (HR 1.82; 95% CI 1.44-2.29; p<0.0001) and death (HR 2.55; 95% CI 1.86-3.37; p<0.0001). Patients with FHBOC having at least one relative with breast cancer aged ≤50 years were also at increased risk of recurrence (HR 1.62; 95% CI 1.15-2.27; p=0.006) and death (HR 1.55; 95% CI 1.00-2.40; p=0.050) with a borderline p value. Male breast cancer patients had high breast cancer mortality, yet without statistical significance (HR 2.49; 95% CI 0.94-15.31; p=0.062). There was no significant impact of the number of relatives with breast/ovarian or any type of cancer on risk of breast cancer mortality. However, all HR were >1. Patients with FHBOC who had bilateral breast cancer (HR 1.70; 95% CI 1.25-2.30; p = 0.001) were found to be at increased risk of recurrence.

Discussion

Family history

In our cohort, 24.1% (n=479) of the patients had FHBOC and 38.8% of those had first-degree, 35.9% had second-degree and 25.3% had third-degree relatives with breast/ovarian cancer. The prevalence of family history varies in studies, ranging from 15 to 30% and the rate of positive family history in women with breast cancer ranges from 10 to 35% in the literature [4,15,18-21]. A significant proportion (20.7%) of the patients had mother affected with breast or ovarian cancer and 3.9% had mother affected with both. In a pooled analysis of 38 studies, it was estimated that the relative risk of developing breast cancer in women who had a mother affected with breast cancer was 2.0 (95% CI 1.8-2.1) [3].

In this study patients with FHBOC were younger than patients with no family history at the time of diagnosis, consistent with several studies [3, 18, 19,22], but inconsistent with others [14,15,21]. Previous studies suggest that breast cancer risk is greater among women with first- or second-degree relatives who have a younger age at diagnosis [3,4]. In the present study, we found

Table 3. Univariate and multivariate analysis of the risk factors affecting mortality

*Risk factors**	*Univariate analysis OR (95% CI)*	*p-value*	*Multivariate analysis OR (95%CI)*	*p-value*
Breast cancer ≤ 50 years	1.27 (0.98-1.65)	0.068	1.24 (0.96-1.61)	0.100
Triple negative breast cancer	2.49 (1.85-3.35)	<0.0001	2.55 (1.86-3.37)	<0.0001
Bilateral breast cancer	1.01 (0.60-1.70)	0.979	1.16 (0.69-1.95)	0.580
≥1 relatives with breast cancer ≤ 50 years	1.62 (1.17-2.23)	0.004	1.55 (1.00-2.40)	0.050
≥1 relatives with ovarian cancer at any age	1.49 (0.48-4.65)	0.494	0.68 (0.20-2.29)	0.529
≥2 relatives with breast and/or pancreatic cancer at any age	1.41 (0.95-2.08)	0.085	1.22 (0.78-1.89)	0.382
Male breast cancer at any age	2.89 (0.96-13.67)	0.056	2.49 (0.94-15.31)	0.062
Combination of breast cancer with other malignancies on the same side of the family**	1.23 (0.98-1.55)	0.077	1.11 (0.85-1.46)	0.436

OR: odds ratio, CI: confidence interval. *NCCN Guidelines Version 1.2011. Breast and/or Ovarian Cancer Genetic Assessment, **Thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumors, diffuse gastric cancer, leukemia/lymphoma on the same side of the family

Table 4. Univariate and multivariate analysis of the risk factors affecting recurrence

*Risk factors**	*Univariate analysis OR (95% CI)*	*p-value*	*Multivariate analysis OR (95%CI)*	*p-value*
Breast cancer ≤ 50 years	1.01 (0.85-1.21)	889	1.00 (0.83-1.19)	964
Triple negative breast cancer	1.81 (1.43-2.29)	<0.0001	1.82 (1.44-2.29)	<0.0001
Bilateral breast cancer	1.76 (1.27-2.44)	1	1.70 (1.25-2.30)	1
≥1 relatives with breast cancer ≤ 50 years	1.62 (1.15-2.27)	6	1.37 (1.02-1.83)	36
≥1 relatives with ovarian cancer at any age	1.13 (0.47-2.72)	793	0.71 (0.29-1.76)	460
≥2 relatives with breast and/or pancreatic cancer at any age	1.17 (0.87-1.59)	302	1.04 (0.74-1.47)	808
Male breast cancer at any age	2.26 (0.73-7.04)	160	2.88 (0.92-9.20)	74
Combination of breast cancer with other malignancies on the same side of the family**	1.14 (0.96-1.35)	146	1.05 (0.86-1.27)	662

For abbreviations see footnote of Table 3. *NCCN Guidelines Version 1.2011. Breast and/or Ovarian Cancer Genetic Assessment, **Thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumors, diffuse gastric cancer, leukemia/lymphoma on the same side of the family

that patients who had at least one relative with breast cancer ≤50 years were at increased risk of breast cancer recurrence (HR 1.62; 95% CI 1.15-2.27; p=0.006) and mortality (HR 1.55; 95% CI 1.00-2.40; p=0.050). In guidelines the prerequisite for starting breast cancer surveillance before the age of 50 is having at least one first-degree relative with breast cancer aged ≤50 years. Women aged 25 years or older with a strong family history should start annual breast examination and mammography 5-10 years prior to the youngest breast cancer case in the family [23].

In our study, bilateral breast cancer was observed in 6.2% of the patients and those with FHBOC were at increased risk of breast cancer recurrence (HR 1.70; 95% CI 1.25-2.30; p=0.001). It is suggested that bilateral cases are mostly associated with FHBOC [14,15,21,22]. In a study with 102 176 breast cancer patients, the relative risk for contralateral breast cancer was remarkably high in women with FHBOC (OR 5.48; 95% CI 4.38-6.84) compared to women with no family history [24].

Family history of breast cancer has been associated with increased ovarian cancer risk. A study of 49 975 breast cancer patients with family history reported that women with a personal history of breast cancer (RR 3.7; 95% CI 1.8-7.7), with 2 or more first-degree relatives with breast cancer (RR 1.8; 95% CI 1.1-2.8), and at least one affected relative diagnosed before the age of 50 (RR 2.6; 95% CI 1.4-4.8) were all at high risk of ovarian cancer development [25]. Ovarian cancer was significantly associated with FHBOC and the degree of relatives in our study (p<0.0001).

It has been shown that male breast cancer is an important covariate in predicting early-onset breast cancer [5]. We found that male breast cancer patients had high breast cancer mortality (HR 2.49; 95% CI 0.94-15.31), with a borderline p value (p=0.062). The results of a recent study showed that the relative risk for breast cancer was increased around 10 times in women with both parents affected and HR 2.48 when a brother was affected, thus suggesting a higher genetic basis of male breast cancer vs. female breast cancer [26]. The authors of another recent, hospital-based case-control study of 86 men with breast cancer reported a significantly greater proportion of cases with a positive family history of cancer (p=0.002) compared to controls [27]. There was a low frequency of male breast cancer (n=13) in our cohort, therefore, we could not confirm these associations.

Tumor characteristics

In the present study T1 tumors were more likely to be observed in women who had breast/ovarian cancer in first-degree relative (32.6 vs. 24.2%; p=0.09) compared with patients with no family history. Most of the studies reported no significant difference in tumor size of patients with and without FHBOC [14-16,19,20,22], whereas others observed smaller tumor size in women with family history [18,28]. On the other hand, Gavrilov et al. found that women with family history presented with more advanced disease stages [29].

Although clear histopathological differences have been observed between sporadic and BRCA-1 related breast cancers (high proliferation rate, ER/PR negativity and high expression of epidermal growth factor receptor), these features have not been demonstrated for familial cases of breast cancer [5]. Our results suggested that there were no statistically significant differences in grade, Ki-67 index and lymphovascular invasion, which show the aggressiveness of tumors, in agreement with previous studies [14-16,22]. In some studies, family history was associated with high grade tumors [28,29]. However, we observed a trend towards a low grade in our patients who had breast/ovarian cancer in first-degree relative compared with patients who had no family history.

Axillary lymph node involvement at presentation (53.3 vs. 40.8%; p=0.022) was less likely to be observed in patients with FHBOC, particularly in those who had first-degree relative with breast/ovarian cancer, consistent with previous studies [16,21,28]. Some studies reported that patients with family history were more likely to have tumors with nodal metastasis [20,28], however, most of other authors found no significant difference [14,15,18,22].

Invasive lobular carcinoma (6.1 vs. 5.3%) and lobular carcinoma *in situ* (1.4 vs. 0.1%) were slightly higher in patients with FHBOC compared to patients without family history. Previous epidemiological studies have suggested that lobular carcinoma *in situ* and invasive lobular breast cancers are associated with somewhat higher familial risks than other subtypes, consistent with our findings [20,21].

Although no statistically significant difference was observed, the lowest percentages of patients with ER/PR positivity and the highest percentage of patients with TNBC were observed in the group of FHBOC who had in first-degree relative with disease. Some studies found that tumors of patients with family history are more likely to be ER/PR negative [29], particularly in BRCA-related tumors [7,8,30], but most of the studies found no significant difference, consistent with our results [2,14-16]. HER-2 overexpressing breast cancer was found to be slightly higher in patients with no family history (9.5 vs. 6.4%; p=0.039). Previous studies found no association between family history and HER-2 status [16,18] whereas others showed a lower

percentage of HER-2/neu positivity, in agreement with our data [7,8].

Survival

We found a shorter median OS in the patients with FHBOC, with a borderline p value (p=0.063). Moreover, the median OS was significantly shorter in patients who had at least 2 relatives with breast cancer compared to patients with no family history (p=0.014). Most of the studies found no association between family history and survival [14,15,21,22]. However, some previous studies demonstrated that family history was associated with a significantly longer [16,28] or shorter survival [7] compared to patients with no family history. The conflicting data on the impact of family history on breast cancer survival could be explained with the different definitions of family history and the heterogeneity of patients. In our study the median DFS was similar for both patients with and without FHBOC, in agreement with previous studies [14,15,22]. The TTP was shortest in patients who had breast/ovarian cancer in first-degree relative (6.8 months; 95% CI 4.4-9.2; p=0.020). To our knowledge, there is no study in the literature evaluating the impact of family history on metastatic breast cancer outcomes.

We found that patients with FHBOC who had TNBC had the highest risk of mortality (HR 2.55; 95% CI 1.86-3.37; p<0.0001) and recurrence (HR 1.82; 95% CI 1.44-2.29; p<0.0001) after adjustment for tumor size and nodal status. A possible interpretation of these findings could be the increased likelihood of this group of BRCA-1/2 mutations. Individuals with ER-negative tumors, or with ER-negative tumors diagnosed in their family members, are predicted to have a higher BRCA1 mutation carrier probability [7,8,30]. The published literature suggests a worse prognosis for BRCA mutation carriers than for sporadic cases [7].

Study limitations

Our data of family history relying on interviews with patients and their relatives may cause some bias. However, previous studies have shown patient-reported family history of breast cancer in first- and second-degree relatives to be accurate and valid for cancer risk assessment [31]. The lack of genetic analysis is another limitation of our study which would be helpful in identifying the role of FHBOC in breast cancer patients. As mentioned before, we have no population-based data on the prevalence of BRCA-1/2 mutations. Genetic variation in susceptibility across ethnic populations is plausible, though similar frequencies of BRCA-1/2 mutations are assumed within countries [5].

In summary, patients with FHBOC are younger and tend to have small and node-negative breast cancer. Invasive lobular carcinoma and lobular carcinoma *in situ* are more common than in patients with no family history. There is no significant association between FHBOC and ER/PR status, however, HER-2 positivity is low. Our results suggest a decreased survival in patients with FHBOC, particularly in patients who had at least 2 relatives with breast cancer. Patients with FHBOC who had TNBC or at least 1 relative with breast cancer aged ≤50 years are at increased risk of breast cancer recurrence and mortality. Synchronous bilateral breast cancers are more frequent and associated with increased risk of recurrence. Furthermore, women who had a breast/ovarian cancer in first-degree relative and presented with metastatic breast cancer, showed the poorest prognosis.

Age ≤ 50 years, TNBC, bilateral breast cancer, at least 1 relative with breast cancer aged ≤ 50 years, at least 1 relative with ovarian cancer are the factors that suggest a family history. While the number of affected individuals are increasing worldwide, it is important to identify high-risk women for primary and secondary prevention of breast cancer. Informing the public on the risk of family history of breast cancer and the importance of breast self examination and screening will provide survival benefit for high-risk women. Additionally, further molecular and genetic analyses of familial breast cancer will clarify the mechanisms of cancer accumulation within families.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008. Globocan 2008. Int J Cancer 2010; 127: 2893-2917.
2. Yilmaz HH, Yazihan N, Tunca D et al. Cancer trends and incidence and mortality patterns in Turkey. Jpn J Clin Oncol 2011; 4110-4116.
3. Pharoah PDP, Day NE, Duffy S, Easton DF, Ponder BA. Family history and the risk of breast cancer: a systematic review and meta-analysis. Int J Cancer 1997; 71: 800-809.
4. Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. Lancet 2001; 358: 1389-1399.
5. Ford D, Easton DF, Stratton M et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet 1998; 62: 676-689.
6. King MC, Marks JH, Mandell JB. New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in BRCA-1 and BRCA-2. Science 2003; 302: 643-646.
7. Chappuis PO, Nethercot V, Foulkes WD. Clinico-pathological

characteristics of BRCA-1 and BRCA-2 related breast cancer. Semin Surg Oncol 2000; 18: 287-295.
8. Lakhani SR, Van De Vijver MJ, Jacquemier J et al. The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2. J Clin Oncol 2002; 20: 2310-2318.
9. Domchek SM, Friebel TM, Singer CF et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA 2010; 304: 967-975.
10. Yazici H, Bitisik O, Akisik E et al. BRCA1 and BRCA2 mutations in Turkish breast/ovarian families and young breast cancer patients. Br J Cancer 2000; 83: 737-742.
11. Aydin F, Akagun T, Yildiz B, Fidan E, Ozdemir F, Kavgaci H. Clinicopathologic characteristics and BRCA-1/BRCA-2 mutations of Turkish patients with breast cancer. Bratisl Lek Listy 2011; 112: 521-523.
12. Manguoglu E, Guran S, Yamac D et al. Genomic large rearrangement screening of BRCA1 and BRCA2 genes in high-risk Turkish breast/ovarian cancer patients by using multiplex ligation-dependent probe amplification assay. Cancer Invest 2011; 29: 73-77.
13. Aktas D, Gultekin M, Kabacam S et al. Identification of point mutations and large rearrangements in the BRCA1 gene in 667 Turkish unselected ovarian cancer patients. Gynecol Oncol 2010; 119: 131-135.
14. Tsuchiya A, Kanno M, Nomizu T, Hatakeyama Y, Kimijima I, Abe R. Clinical characteristics of breast cancer patients with family history. Fukushima J Med Sci 1998; 44: 35- 41.
15. Russo A, Herd-Smith A, Gestri D et al. Does family history influence survival in breast cancer cases? Int J Cancer 2002; 99: 427-430.
16. Fukutomi T, Kobayashi Y, Nanasawa T, Yamamoto H, Tsuda H. A clinicopathological analysis of breast cancer in patients with a family history. Surg Today 1993; 23: 849-854.
17. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™). Genetic/ Familial High-Risk Assessment: Breast and Ovarian. Version 1.2011. www.nccn.org.
18. Molino A, Giovannini M, Pedersini R et al. Correlations between family history and cancer characteristics in 2256 breast cancer patients. Br J Cancer 2004; 91: 96-98.
19. Yip CH, Mohd Taib AN, Lau PC. Does a positive family history influence the presentation of breast cancer? Asian Pacific J Cancer Prev 2008; 9: 63-65.
20. Saxena S, Rekhi B, Bansal A, Bagga A, Chintamani, Murthy NS. Clinico-morphological patterns of breast cancer including family history in a New Delhi hospital, India--A cross-sectional study. World J Surg Oncol 2005; 3: 67.
21. Margolin S, Johansson H, Rutqvist LE, Lindblom A, Fornander T. Family history and impact on clinical presentation and prognosis in a population-based breast cancer cohort from the Stockholm County. Fam Cancer 2006; 5: 309-321.
22. Israeli D, Tartter PI, Brower ST, Mizrachy B, Bratton J. The significance of family history for patients with carcinoma of the breast. J Am Coll Surg 1994; 179: 29-32.
23. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™). Breast Cancer Screening and Diagnosis. Version 1.2011. www.nccn.org.
24. Hemminki K, Ji J, Forsti A. Risks for familial and contralateral breast cancer interact multiplicatively and cause a high risk. Cancer Res 2007; 67: 868-870.
25. Kazerouni N, Greene MH, Lacey JV Jr, Mink PJ, Schairer C. Family history of breast cancer as a risk factor for ovarian cancer in a prospective study. Cancer 2006; 107: 1075-1083.
26. Bevier M, Sundquist K, Hemminki K. Risk of breast cancer in families of multiple affected women and men. Breast Cancer Res Treat 2011; [Epub ahead of print].
27. Satram-Hoang S, Moran EM, Anton-Culver H et al. A pilot study of male breast cancer in the Veterans Affairs healthcare system. J Environ Pathol Toxicol Oncol 2010; 29: 235-244.
28. Mohammed SN, Smith P, Hodgson SV et al. Family history and survival in premenopausal breast cancer. Br J Cancer 1998; 77: 2252-2256.
29. Gavrilov I, Nacheva M, Tzingilev D. Familial breast cancer. Part II: Relationships with histology, staging, steroid receptors and serum tumor markers. J BUON 2002; 7: 61-65.
30. Mavaddat N, Pharoah PD, Blows F et al. Familial relative risks for breast cancer by pathological subtype: a population-based cohort study. Breast Cancer Res 2010; 12: R10.
31. Murff HJ, Spiegel DR, Syngal S. Does this patient have a family history of cancer? An evidence-based analysis of the accuracy of family cancer history. JAMA 2004; 292: 1480-1489.