

A Comparative Survival Study between Familial and Sporadic Breast Cancer in Iranian Women

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Abstract

Background: Breast cancer (BC) is the most common cancer in Iranian women, with 13400 new cases annually. A few studies have reported that BC patients with a positive familial history had different prognoses and outcomes.

Objectives: The aim of the present study was to evaluate and compare survival between familial breast cancer (FBC) patients and sporadic breast cancer (SBC) patients in Iranian women.

Methods: In a longitudinal study, 1710 patients with complete medical records from the Cancer Research Center, database were extracted and divided into two groups: the FBC group (n=311) and the SBC group (n=1399). Then, five-year overall survival (OS) and five-year disease-free survival (DFS) for these two groups were evaluated and compared.

Results: The FBC group and SBC group represented 18.22% and 81.8% of all cases, with mean ages of 44.2 years and 47.7 years, respectively (p=0.0024). There were more advanced stage and positive lymph nodes, higher grade of tumor, more positive lymphovascular invasion and P53 status and higher degrees of negative progesterone receptor status in the FBC group than in the SBC group (p=0.0200, p=0.0001, p=0.0001, p=0.0386, p=0.0182 and p=0.0003, respectively). In the FBC group and SBC group, the five-year DFS was 81% and 86.5%, (p=0.0121), and the five-year OS was 71.1% and 76.5%, respectively (p=0.0401).

Conclusions: The findings of this study showed that better five-year OS, five-year DFS and favorable prognostic factors in the SBT group than in the FBC group. The initial results might be helpful as better treatment modalities and careful follow-up in the FBC group.

Introduction

Breast cancer (BC) is the most common visceral cancer among women around the world. In Iranian women, BC is the most frequently diagnosed cancer with a second cause of death due to cancer based on the Cancer Registry System (1).

There are 13400 new cases of BC annually, with an incidence rate of 32 in 100000 in Iranian women. In Iran, BC is diagnosed with a mean age of 49 ± 12 years and occurs one decade earlier than most developed countries; therefore, we have had major health and treatment problems of burden of this disease (2).

BC is a heterogeneous cancer, and the outcome and prognosis of the disease depends on the clinical and pathological characteristics, such as age at diagnosis, tumor histology, positive or negative familial history (FH) of BC, marital status, parity status, breast feeding history, benign breast disease, menopausal status, diabetes status, smoking history, alcohol consumption, fatty food regimen, oral contraceptive use,

high density of breast tissue, stage of tumor, tumor size, nodal status, lymphovascular invasion, P53 status, tumor grade, estrogen receptor (ER) status, progesterone receptor (PR) status and human epidermal receptor 2 (HER2) expression. (3-6).

Based on various studies, 10-30% of BC cases had a positive FH of BC in their first or second degree relatives, and the clinical and pathological characteristics, outcome and survival of this group are significantly influenced by this risk factor and might differ among familial breast cancer (FBC) and sporadic breast cancer (SBC) patients (7-10).

Some studies have reported that FBC patients had an earlier age, more positive pathologic lymph node involvement, larger tumor size, more advanced stage, negative hormone receptors and unfavorable prognosis than SBC patients. On the other hand, some other studies showed no significant differences between the two groups as these factors (11-14).

There is no study in Iran that compared the clinical, pathological features, prognosis and survival between the FBC group and SBC group.

2. Objectives

In this longitudinal study, clinical and pathological characteristics, local recurrence, distant recurrence, 5-year disease-free survival (DFS) and 5-year overall survival (OS) in FBC and SBC patients were compared at the Cancer Research Center (CRC) of the Shahid Beheshti University of Medical Sciences (SBUMS) between September 2002 and December 2017.

Materials And Methods

In this longitudinal study, a consecutive series of patients with BC (3010 patients) from the database at CRC of SBUMS, a referral breast clinic in Tehran, Iran, was extracted.

In the database, between September 2002 and December 2017, only 1710 patients were considered with complete medical records and pathologic diagnosis of primary or metastatic breast cancer, and 1300 breast cancer patients with incomplete medical records were omitted.

The inclusion criteria were as follows: BC patients with acceptable follow-up after initial diagnosis who had all 23 baseline variables (positive or negative FH of BC, age at diagnosis, marital status, parity status, breast feeding history, menopausal status, diabetes status, smoking history, fatty food regimen, type of surgery (breast conserving surgery (BCS) or modified radical mastectomy (MRM)), tumor histology, stage of tumor, tumor size, nodal status, lymphovascular invasion, P53 status, tumor grade, ER, PR, HER2 status, local recurrence (if present), distant recurrence (if present), and death (if present)).

The exclusion criteria were BC patients who did not have acceptable follow-up after initial diagnosis and who did not have all 23 baseline variables as mentioned before.

All included patients were divided into two groups: group A or FBC group (breast cancer patients who had one or more first or second degrees or both within three generations) with 311 patients and group B or SBC group (breast cancer patients without any positive FH of BC with 1399 patients). Then, OS, DFS and prognostic factors for the two groups were evaluated and compared.

After all treatments were over, every BC patient was visited and examined every 3 to 6 months for five years and yearly afterwards. The patients underwent annual mammography. In case of clinical symptoms or signs of any recurrences, patients underwent imaging or biopsy to identify any recurrences.

Until December 2017, all 1710 BC patients were followed. As the time interval between initial diagnosis and local or distant recurrence (if present) was defined as DFS and the time interval between initial diagnosis and death (if present) was defined as OS.

In the act provided by SBUMS, the ethical regulations dictated were approved to review the medical records for the purposes of our study (ethical code: IR.SBMU.MSP.REC.1396.358).

Differences in all 23 variables evaluated and compared by the log-rank test between two groups. A P value < 0.05 was considered significant. All statistical analyses were performed using IBM SPSS 22.0.

Results

In this longitudinal study, 1710 BC patients in two groups (FBC group (group A) with 311 patients) and (SBC group (group B) with 1399 patients) were divided. In the FBC group (group A), 121 BC patients (38.9%) had an affected first-degree relative, 161 breast cancer patients (51.8%) had an affected second-degree relative and 29 BC patients (9.3%) had both first- and second-degree relatives (Table 1).

In the FBC group (group A) and SBC group (group B), the mean age was 44.2 years (SD=9.4 years) and 47.7 years (SD=10.9 years), respectively. The age of onset seemed to be earlier in group A than in group B ($p=0.0024$).

In the FBC group, 130 cases (41.8%) were postmenopausal, and 181 cases (58.2%) were premenopausal. In the SBC group, 794 cases (56.8%) were postmenopausal, and 605 cases (43.2%) were premenopausal. These differences were statistically significant (RR=1.63, 95% CI= 1.33-2.00, $p<0.0001$). Then, the FBC group was more likely to be premenopausal.

Diabetes, smoking and fatty food regimens were seen in 13.8%, 6.8% and 47.9% of the FBC group and 15%, 6.5% and 48.3% of the SBC group, respectively, without significant differences (RR=0.92, 95% CI= 0.68 -1.23, $p=0.5970$, RR=1.03, 95% CI= 0.69 -1.54, $p=0.8727$ and RR=0.98, 95% CI= 0.80 -1.20, $p=0.9139$).

There were 195 patients (62.7%) with BCS and 116 patients (37.3%) with MRM in group A, 868 patients (62%) with BCS, and 531 patients (38%) with MRM without significant differences (RR=0.98, 95% CI=0.79 -1.20, $p=0.8291$) in group B. Table 2 summarizes the baseline clinical and surgical features of 1710 adult patients with BC.

In situ carcinoma, invasive ductal carcinoma, invasive lobular carcinoma and other pathology were seen in 0%, 93.3%, 4.8% and 1.9% of the FBC group and 0.6%, 90.9%, 4.4% and 4.1% of the SBC group, respectively, without significant differences (RR=3.71, 95% CI= 0.24-55.47, p=0.3414, RR=4.07, 95% CI= 0.26-63.04, p=0.3142 and RR=2.03, 95% CI= 0.12 -33.34, p=0.6196).

Based on tumor stage, in group A, 51 cases (16.4%) had stage I, 161 cases (51.8%) had stage II, 95 cases (30.5%) had stage III, and 4 patients (1.3%) had stage IV. In group B, 311 cases (22.2%) had stage I, 650 cases (46.5%) had stage II, 371 cases (26.5%) had stage III, and 67 patients (4.8%) had stage IV. There were statistically significant differences between groups A and B as stage II and stage III (RR=1.40, 95% CI=1.05-1.88, p=0.0203 and RR=1.44, 95% CI=1.06-1.97, p=0.0200), but there were no statistically significant differences between groups A and B as stage I and stage IV. The FBC group had more stage II and stage III disease than the SBC group.

T1, T2, T3 and T4 were seen in 19.1%, 47.6%, 15.2% and 18.1% of the FBC group and 20.4%, 47.2%, 14.6% and 17.8% of the SBC group, respectively, without significant differences (RR=1.07, 95% CI= 0.81-1.41, p=0.6173, RR=1.11, 95% CI= 0.79-1.57, p=0.5399 and RR=1.07, 95% CI= 0.77-1.49, p=0.6888).

Node positivity was observed in 72.4% of the FBC group and 58.9% of the SBC group, with a statistically significant difference (RR=1.57, 95% CI= 1.25 -1.97, p=0.0001). Then, the FBC group was more likely to have node positivity.

Positive lymphovascular invasion was seen in group A (46.6%) and group B (58.9%), with a statistically significant difference (RR=1.24, 95% CI= 1.01 -1.51, p=0.0001). Group A had less positive lymphovascular invasion than group B.

Positive P53 was observed in 42.1% of the FBC group and 35.1% of the SBC group, with a statistically significant difference (RR=1.27, 95% CI= 1.04 -1.56, p=0.0182). Then, the FBC group was more likely to have node positivity. Then, the FBC group had more positive P53 than the SBC group.

Twenty-one patients (6.7%) had well-differentiated grades, 154 patients (49.5%) had moderately differentiated grades, 136 patients (43.8%) had poorly differentiated grades in group A, 168 patients (12.04%) had well-differentiated grades, 857 patients (39.8%) had moderately differentiated grades, and 374 patients (26.7%) had poorly differentiated grades in group B. There was a statistically significant difference between groups A and B as poorly differentiated grades (RR=2.40, 95% CI=1.56-3.68, p=0.0001), but there were no statistically significant differences between groups A and B as well-differentiated grades and moderately differentiated grades.

Positive ER was seen in group A with 59% and in group B with 61.3%, without a significant difference statistically (RR=1.07, 95% CI= 0.87-1.31, p=0.4931). However, positive PR was observed in group A (46.7%) and in group B (57.8%), with a statistically significant difference (RR=1.44, 95% CI= 1.18-1.77, p=0.0003). Then, group A had less PR positivity than group B.

HER2 positivity was observed in 31.9% of the FBC group and 26.9% of the SBC group, without a statistically significant difference (RR=0.82, 95% CI= 0.66-1.02, p=0.0798). Table 3 summarizes the association between FH and the pathological characteristics of BC patients in CRC.

As of December 2017, 10 cases (3.2%) of local recurrence were shown in the FBC group, and 49 patients (3.5%) of local recurrence were shown during the five years of follow-up in the SBC group. Thus, the 5-year local recurrence-free survival (LRFS) was 96.8% in the FBC group and 96.5% in the SBC group. There were no significant local recurrence differences between the FBC group and SBC group (p= 0.8022, RR=0.91, 95% CI=0.47-1.89) (table 4). Patients in the FBC group did not show more local recurrence than those in the SBC group.

In the FBC group, 49 cases (15.8%) were diagnosed with distant metastasis during the five years of follow-up, and 140 breast cancer patients (10.1%) had distant recurrence in the SBC group. Thus, the 5-year distant recurrence-free survival (DRFS) rates were 84.2% in the FBC group and 89.9% in the SBC group. This study found a significant difference between the two groups in distant recurrence-free survival (p=0.0031, RR=1.57, 95% CI=1.16-2.12) (table 4).

The five-year DFS rates were 81% and 86.5% in the FBC and SBC groups, respectively. The study observed a significant difference between the two groups in the five-year DFS (p=0.0121, RR=1.40, 95% CI=1.07-1.83) (Table 4). Patients in the SBC group showed better five-year DFS than those in the FBC group.

In the FBC and SBC groups, the five-year OS rates were 71.1% and 76.5%, respectively. This study showed a significant difference between the two groups in terms of the five-year OS (p=0.0401, RR=1.23, 95% CI=1.01-1.50) (table 4). Patients in the SBC group showed better five-year OS than those in the FBC group.

Discussion

The aim of this study was to show better 5-year DFS and 5-year OS rates in the SBC group than in the FBC group. In the current study, with CRC of SBUMS, clinical and pathological characteristics, local recurrence, distant recurrence, 5-year DFS, and 5-year OS in 1710 breast cancer patients in the FBC and SBC groups were compared, and to the best of our knowledge, this is the greatest series in Iran.

There are 52 epidemiological studies including 58209 women with breast cancer and 101986 without BC that showed a positive FH of BC in first or second degrees was an important risk factor for the disease. Based on these studies, 10-30% of BC cases had a positive FH of BC in their first or second degree relatives. In the current study, 18.2% of the cases had a positive FH of BC in their first- or second-degree relatives, which is consistent with these 52 epidemiological studies (15).

In group A and group B, the mean age at diagnosis was 44.2 years and 47.7 years, respectively (p=0.0024). The age of onset seems to be earlier in the FBC group than in the SBC group. This result was consistent with Pharoah et al. and Molino et al who found that breast cancer patients with a positive FH

were younger than patients with a negative FH (16-17). For these reasons, women with a positive FH could benefit more often through mammography and ultrasonography screening since younger age.

Fukutomi et al reported that among patients with a positive FH, premenopausal women were more prevalent than patients with a negative FH (18). These findings were consistent with this study, which observed that premenopausal patients were more prevalent in the FBC group than in the SBC group ($p < 0.0001$).

BC is also an environmentally dependent disease, and the influence of some of these environmental risk factors, such as diabetes, smoking and fatty food regimen consumption of this cancer, has been widely studied (19-20). These findings were inconsistent with the current study, which found that there were no statistically significant differences between group A and group B in diabetes, smoking and fatty food regimen consumption ($p = 0.5970$, $p = 0.8727$ and $p = 0.9139$, respectively).

Gaffield et al showed that oral contraceptive consumption can increase the risk of BC in patients with a positive FH (21). These findings were inconsistent with this study, which found that there were no statistically significant differences between the FBC group and SBC group in oral contraceptive consumption ($p = 0.9525$).

The study found that there were no significant differences between group A and group B in marital status, parity status, or breast feeding history ($p = 0.5642$, $p = 0.8848$ and $p = 0.8146$, respectively). However, Olsson et al. showed that the FBC group with a parity history and/or breast feeding had a protective effect compared to the SBC group (22).

Regarding the histological type of tumor, the current study findings did not vary between the two groups. Allen-Brady et al. observed that invasive lobular carcinoma was more common in the FBC group than in the SBC group (23), although this study did not find a statistically significant difference between the two groups in relation to invasive lobular carcinoma (0.3142).

In agreement with Fukutomi et al.'s study (24), this study did not find a significant difference in tumor size between the two groups, but in disagreement with Colditz et al.'s study, which showed a higher proportion of T1 tumors in group A than in group B (25).

Gavrilov et al. reported that patients with a positive history of FBC had a more advanced stage than patients with a negative history of FBC (26). These results were consistent with the current study, which showed that there were more advanced stages in the FBC group than in the SBC group.

In agreement with Marcus et al. and Mohammed et al. (27-28), who showed FBC patients had more tumors with positive lymph node metastasis, positive lymphovascular invasion, positive P53 and higher grade of tumor, this study observed the same results ($p = 0.0001$, $p = 0.0386$, $p = 0.0182$ and $p = 0.0001$, respectively).

Molino et al. (29) reported that the FBC group had more ER-positive tumors than the SBC group. These findings were inconsistent with this study, which found that there were no statistically significant differences between the FBC group and SBC group as ER-positive tumors ($p=0.4931$) but were similar to the findings of Yamashita et al. (30), who reported that ER-positive tumors were the same in the two groups.

D'Eredita et al (31) found that the FBC group had more PR-negative tumors than the SBC group, which is in agreement with the results of this study ($p=0.0003$). D'Eredita et al. also indicated that HER2 negativity was the same in these two groups, similar to the results of this study ($p=0.0798$).

However, Govindan et al. (32) reported that the PR gene polymorphism had an important role in the development of breast cancer.

Russo et al. (33) showed that the 5-year OS was 78.6 (95% CI 70.0–88.0) in the FBC group and was lower than that in the SBC group, with a 5-year OS of 79.8 (95% CI 77.0–83.0), but they did not differ significantly (log-rank test, $X^2=0.02$, $p=1.0$). In agreement with this study, which found that the 5-year OS was 71.1 in the FBC group and 76.5 (RR=1.23, 95% CI=1.01-1.50, $p=0.0401$), but unlike the study by Russo et al., the difference was statistically significant.

Verkooijen et al. (34) found that the risk of BC mortality was the same in BC with or without a positive FH. Their findings were inconsistent with those of the current study, and the FBC group had more BC mortality and less 5-year OS than the SBC group ($P=0.0401$). They could not show any comparison, as 5-year LRFS, 5-year DRFS and 5-year DFS between the two groups, but we showed that 5-year DRFS and 5-year DFS were 84.2% and 81% in group A and 89.9% and 86.5% in group B, respectively ($p=0.0031$ and $p=0.0121$).

The limitations of this study included the missing data of some patients' information and the short follow-up period.

Conclusion

The initial findings of this study showed poorer survival for familial breast cancer patients in Iran. The results of the study indicated that the FBC group was younger and more premenopausal than the SBC group, and they had a more advanced stage, more lymph node involvement, a higher rate of negative PR and a higher grade of tumor than the SBC group. Because of the short follow-up period, this study cannot prove that the SBC group had a better prognosis than the FBC group. A longer follow-up time of the patients to compare 10-year DFS and 10-year OS or even 20-year OS between the two groups is recommended.

Declarations

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Conflict of Interest

There is no conflict of interest to be declared.

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Tables

Table 1: Distribution of breast cancer patients according to family history in the cancer research center

Group	Family History	Number	%
Group A, FBC^a(n=311)	Yes	311	18.2
	1st degree	121	38.9
	2nd degree	161	51.8
	1st and 2nd degree	29	9.3
Group B, SBC^b(n=1399)	No	1399	81.8

^aFBC: Familial breast cancer, ^bSBC: Sporadic breast cancer

Table 2. Baseline clinical and surgical features of 1710 adult patients with breast cancer.

VARIABLES	Group A	Group B	RR^c (95%CI^d)	p value
	FBC^a(n=311)	SBC^b(n=1399)		
Mean age at diagnosis (years)	44.2 (SD=9.4)	47.7 (SD=10.9)	—	0.0024
Marital status, n (%)				
Married	295 (94.9)	1315 (94)	1	
Single	16 (5.1)	84 (6)	0.87 (0.55-1.38)	0.5642
Parity status, n (%)				
Nulliparous	45 (14.5)	198 (14.1)	1	
Parous	266 (85.5)	1201 (85.9)	0.98 (0.73-1.30)	0.8848
Breast feeding history				
No	82 (26.4)	378 (27)	1	
Yes	229 (73.6)	1021 (73)	1.02 (0.81-1.29)	0.8146
Menopausal status, n (%)				
Postmenopausal	130(41.8 %)	794 (56.8 %)	1	
Premenopausal	181 (58.2 %)	605 (43.2%)	1.63 (1.33 -2.00)	<0.0001
Hormone consumption, n (%)				
No	222 (71.4)	1001 (71.6)	1	
Yes	89 (28.6)	398 (28.4)	1.00 (0.80-1.25)	0.9525
Diabetes status				
No	268 (86.2)	1189 (85)	1	
Yes	43 (13.8)	210 (15)	0.92 (0.68-1.23)	0.5970
Smoking history				
No	290 (93.2)	1308 (93.5)	1	
Yes	21 (6.8)	91 (6.5)	1.03 (0.69-1.54)	0.8727
Fatty food regimen				

No	162 (52.1)	724 (51.7)	1	
Yes	149 (47.9)	675 (48.3)	0.98 (0.80-1.20)	0.9139
Type of surgery				
BCS ^e	195 (62.7)	868 (62)	1	
MRM ^f	116 (37.3)	531 (38)	0.98 (0.79-1.20)	0.8291

^aFBC: Familial breast cancer, ^bSBC: Sporadic breast cancer, ^cRR: relative risk, ^dCI: confidence interval, BCS^e: breast conserving surgery, MRM^f: modified radical mastectomy

Table3. Association between family history and pathological characteristics of breast cancer patients in cancer research center

VARIABLES	Group A	Group B	RR ^c (95%CI ^d)	p value
	FBC ^a (n=311)	SBC ^b (n=1399)		
Histological type n (%)				
In situ carcinoma	0 (0%)	9 (0.6%)	1	
Invasive ductal carcinoma	290 (93.3%)	1273 (90.9%)	3.71 (0.24 -55.47)	0.3414
Invasive lobular carcinoma	15 (4.8%)	60 (4.4 %)	4.07 (0.26 -63.04)	0.3142
Others	6 (1.9%)	57 (4.1%)	2.03 (0.12 -33.34)	0.6196
Tumor Stage, n (%)				
I	51 (16.4)	311(22.2)	1	
II	161 (51.8)	650 (46.5)	1.40 (1.05-1.88)	0.0203
III	95 (30.5)	371(26.5)	1.44 (1.06-1.97)	0.0200
IV	4 (1.3)	67 (4.8)	0.40 (0.15-1.07)	0.0683
Tumor size n (%)				
T1	59 (19.1 %)	286 (20.4%)	1	
T2	148 (47.6%)	659 (47.2 %)	1.07 (0.81 -1.41)	0.6173
T3	48 (15.2%)	204 (14.6%)	1.11 (0.79-1.57)	0.5399
T4	56 (18.1%)	250 (17.8%)	1.07 (0.77 -1.49)	0.6888
Nodal status, n (%)				
Node-negative	86 (27.6%)	555 (39.7%)	1	
Node-positive	225 (72.4%)	844 (60.3%)	1.57 (1.25 -1.97)	0.0001
Lymphovascular invasion				
Negative	166 (53.4)	836 (59.7)	1	
Positive	145 (46.6)	563 (40.3)	1.24 (1.01-1.51)	0.0386
P53 Status				
Negative	180 (57.9)	909 (64.9)	1	
Positive	131 (42.1)	490 (35.1)	1.27 (1.04-1.56)	0.0182

Tumor grade, n (%)				
Well diff	21 (6.7%)	168 (12.04%)	1	
Moderately diff	154 (49.5%)	857 (39.8%)	1.37 (0.89 -2.10)	0.1492
Poorly diff	136 (43.8%)	374 (26.7%)	2.40 (1.56 -3.68)	0.1492
				0.0001
Receptor status, n (%)				
ER positive	184 (59.0%)	857 (61.3%)	1	
ER negative	127 (41.0%)	542 (38.7%)	1.07 (0.87 -1.31)	0.4931
PR positive		809 (57.8%)		0.0003
PR negative	145 (46.7%)	590 (42.2%)	1	
	166 (53.3%)		1.44 (1.18 -1.77)	0.0798
HER2 positive		377 (26.9)		
HER2 negative	99 (31.9)	1022 (73.1)	1	
	212 (68.1)		0.82 (0.66-1.02)	

^aFBC : Familial breast cancer, ^bSBC: Sporadic breast cancer, ^cRR: relative risk, ^dCI: confidence interval

Table 4. Comparison of local recurrence, distant recurrence over 5 years, the five-year disease-free survival (DFS) rate and the five-year overall survival rate (OS) between Group A and Group B Breast Cancer.

Group	Included patients, n	5-years local recurrence-free survival, n (%)	RR ^c (95%CI ^d)	P-value
Group A FBC ^a	311	301 (96.8)	1	0.8022
Group B SBC ^b	1399	1350 (96.5)	0.91 (0.47-1.89)	
5-years distant recurrence-free survival, n (%)				
Group A FBC	311	262 (84.2)	1	0.0031
Group B SBC	1399	1259 (89.9)	1.57 (1.16-2.12)	
5-year DFS^e Rate, n (%)				
Group A FBC	311	252 (81)	1	0.0121
Group B SBC	1399	1210 (86.5)	1.40 (1.07-1.83)	
5-year OS^f Rate, n (%)				
Group A FBC	311	221 (71.1)	1	0.0401
Group B SBC	1399	1070 (76.5)	1.23 (1.01-1.50)	

^aFBC: Familial breast cancer, ^bSBC: Sporadic breast cancer, ^cRR: relative risk, ^dCI: confidence interval, ^eDFS: Disease-free survival, ^fOS: Overall survival