

RESEARCH ARTICLE

Incidence and Survival in Breast Cancer Patients and Stressful Life Events

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Abstract

Due to increasing incidence of breast cancer, recognition of risk factors has become increasingly important. Over the past few decades, among risk factors of this disease, stressful life events have attracted particular attention, but their relationship with breast cancer incidence and survival remains a mystery. This study aimed to examine the relationship between severe stressful life events and incidence and survival of women with breast cancer. In this case-control study, using a structured telephone interview with 355 women with breast cancer and also with 516 women with benign breast diseases who were matched in demographic characteristics, necessary information about the experience of major stressful events in the years before the diagnosis were collected. Data were analyzed using statistical methods of χ^2 , t, and Kaplan-Meier with a significance level of <0.05 . Generally, in the case and control groups, there were no significant association between experience of stressful life events and incidence of breast cancer. Regarding associations between each of the events and incidence of breast cancer only "severe interpersonal problems with spouse" was significant. In the breast cancer group, even after controlling confounding variables, there was no significant association between major stressful events and disease-free survival, or overall 5-and 10-year survival. In this study, only "severe interpersonal problems with spouse" was confirmed as a risk factor. This result can be useful in developing preventive policies. More research regarding the interactive effects of psycho-social factors in the incidence and survival of breast cancer with stressful life events is recommended.

Keywords: Major stressful life events - breast cancer – incidence - survival

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Introduction

Due to advances in diagnosis and treatment of breast cancer, its mortality rate has declined in recent decades in Iran. Its incidence, like many other countries in the world is growing, though (Movahedi et al., 2012; Akbari et al., 2008). Thus, the study of risk factors associated with this disease has found great importance (Santos et al., 2009). Today, estimates from various studies indicate that well-known breast cancer risk factors such as age, genetics, use of hormones (Richie and Swanson, 2003), reproductive history, breast feeding (Akbari et al., 2011), abortion and fatty diets (Raza et al., 2011), age at menopause (Eskelinen and Ollonen, 2009), smoking (Nagata et al., 2006) and alcohol (Longnecker and Tseng, 1998) can only partially explain 40% to 50% causes of this disease in women (Bleiker and Ploeg, 1999; Duijts et al., 2003), and other causes still remain unclear (Ollonen et al., 2005).

Since early 1950s that the effect of psycho-social factors in etiology of cancer attracted attention in the academic and research circles, the concept of stress and stressful events were more seriously considered in relation to its etiology (Bleiker and Ploeg, 1999). Since then, many studies with different characteristics in terms of sample size, methods and tools, have explored this issue in various types of cancer, particularly breast cancer. But with varied spectrum of results obtained from those studies indicating non-significant to completely significant association between stressful life events and cancer (Lillberg et al., 2003; Wise et al., 2011; Surtees et al., 2010; Schraub et al., 2009), still the problem of whether such events can affect breast cancer remains unresolved (Maunsell et al., 2001; Sood and Lutgendorf, 2011).

Alongside the studies that examined the impact of stress and stressful life events on incidence of cancer, another group of researchers emphasize the hypotheses that stress is more likely to affect progress and recurrence

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of cancer than to cause its initiation (Cohen et al., 2007). Some of them have identified activation of sympathetic nervous system caused by stress as a new neural regulator for metastasis in breast cancer in animal studies (Sloan et al., 2010). Molecular studies on the biological effects of stress have achieved some particular signaling pathways that can affect cancer growth. Accordingly, stress-related hormones that can have significant impact on prevention of anoikis form of programmed death of (cancer) cells and consequently providing a mechanism for metastasis are emphasized (Sood and Lutgendorf, 2011). Of course, despite such convincing biological mechanisms, just as before, findings in this area remain paradoxical and the outcome is not yet certain (Falagas et al., 2007; Graham et al., 2002; Saito-Nakaya et al., 2012; Palesh et al., 2007).

Complexity of the relationship between stressful life events and the etiology of breast cancer incidence and survival is of vital importance to survivors, and many regard stress as a factor in the development and relapse of their disease (Stewart et al., 2001; Dhabhar et al., 2012). This attribution can affect their coping with the disease and their quality of life (Oba et al., 2009; Ferrucci et al., 2011). Besides, gaining better understanding of the relationship between stress and cancer and knowledge of its psychological mechanisms, can prepare the grounds for clinical and research programs to reduce the incidence of this disease in people and also provide increased survival rates in afflicted patients. Therefore, more research is still required. Accordingly, the present study was designed and implemented. In this study, report of major stressful life events experienced in the life span was considered as a criterion to estimate the amount of stress suffered by the individual in the years before the cancer diagnosis and its relationship with breast cancer incidence and survival was investigated. What is meant by major stressful life events is negative events which are extremely uncomfortable for the person and require re-adjustment by the person (Maunsell et al., 2001). This study was carried out to examine the hypothesis that there is a significant association between lifetime major stressful events and breast cancer incidence and survival.

Materials and Methods

Women with breast cancer participated in this case-control study which was carried out in two stages. The case group consisted of women with breast cancer aged between 25 and 70 years. Cancer diagnosis was confirmed in them in years between 2001 and 2011 in specialty clinics affiliated with Cancer Research Center at Shahid Beheshti University of Medical Sciences. Those who showed evidence of metastasis in their first visit were excluded from the study. The control group consisted of women with benign breast diseases who were referred to the same clinic the same time as the case group and had no previous history of any type of cancer and matched the case group in terms of demographics. In this study, 410 women with breast cancer in the case group and 640 women with benign breast diseases in the control group participated.

In the first stage of collecting data, a questionnaire that

included demographic details, reproductive status, and lifestyle (consumption of fatty foods/ alcohol/ tobacco/ psychiatric drugs) was completed for both groups. Then another questionnaire which included clinical and pathological prognostic factors related to tumor mass in the case group was completed using existing information in their medical records. This study was approved by the ethics committee of the research deputy at Shahid Beheshti University of Medical Sciences.

In the next stage, these patients were contacted on the phone and the project was explained to them, and if they were ready to participate, the second stage of data collection began. At this stage, patients were required to attend a structured telephone interview consisting of an 11-item questionnaire with a close-end (yes/no) responses on major stressful and negative life events in their life span. This extended span in the case group included intense events experienced from childhood to the time of cancer diagnosis, and in the control group, included major events from childhood to the first time they visited the clinic. The reason for selecting this long period was because of the results of studies that estimate the average length of time from the start of formation of malignant mass and its clinical diagnosability approximately between 5 to 15 years (Kronke et al., 2004) and also oncology findings that have shown breast cancer causing agents occur and develop over a 20-year period (Jacobs and Bovasso, 2000).

The interview was based on 3 sources: 1). Major negative stressful events based on the social re-adjustment scale of Holmes and Rahe. 2). The 50-item questionnaire of stressful events that was the modified Holmes and Rahe questionnaire and was used in a study in Tabriz, Iran (Malek et al., 2008) and 3). A list of intense life events reported by 40 women with breast cancer in a survey conducted earlier for this purpose. In the end, the items of structured interview included the following events: Death of a loved one, major own health problems, major health problems of loved ones, major problems communicating with a spouse, divorce, major problems related to children, serious communicating problems with family or friends, major career problems, severe financial problems, legal problems and unexpected life changing events. During the interview the participants were also required to express how many years before their diagnosis or first visits each event had occurred. The investigation into stressful life events of those who had passed away because of cancer before conducting the study was done through their main family caregiver. The reliability of this questionnaire was found to be 0.91 in a pilot study on 90 women using a one month test- re-test method. Average duration of each interview was 7 minutes and was conducted by a trained MSc psychology graduate. During the interview, 9 patients in the case group and 15 in the control refused to participate in the study. Also despite trying 3 times to contact these patients, due to change of phone number, 46 women in the case group and 109 in the control group were not reachable.

The analysis of the results was done using SPSS16. In the first phase, to compare each of the stressful life events in both groups of case and control, the chi-square test

Table 1. Characteristics of the Study Participants

Characteristics	Cases (N=355)	Controls (N=516)	P-values
Age			0.18
25-29	1.0 (%0.3)	1.0 (%0.2)	
30-39	61.0 (%17.2)	42.0 (%8.1)	
40-49	137.0 (%38.6)	208.0 (%40.3)	
50-59	125.0 (%35.2)	214.0 (%41.5)	
60-70	31.0 (%8.7)	51.0 (%9.9)	
Marital status			0.03
Married	311.0 (%87.6)	456.0 (%88.4)	
Single	23.0 (%6.5)	15.0 (%2.9)	
Divorced	9.0 (%2.5)	21.0 (%4.1)	
Widowed	12.0 (%3.4)	24.0 (%4.7)	
Number of pregnancies			0.2
0	43.0 (%12.1)	36.0 (%7.0)	
1,2,3	197.0 (%55.5)	313.0 (%60.6)	
>3	115.0 (%32.4)	167.0 (%32.4)	
Abortion status			0.32
0	230.0 (%64.7)	315.0 (%61.0)	
≥ 1	125.0 (%35.3)	201.0 (%39.0)	
Duration of Breast feeding			0.57
0	64.0 (%18)	76.0 (%14.7)	
1-3 years	152.0 (%42.8)	258.0 (%50.0)	
>3 years	139.0 (%39.2)	182.0 (%35.3)	
Menopause status			0.82
(yes/no)	229.0(%64.5)/ 126.0(%35.5)	329.0(%63.8)/ 187.0(%36.2)	
Hormone use			0.92
(yes/no)	124.0(%34.9)/ 231.0(%65.1)	182.0(%35.3)/ 334.0(%64.7)	
Alcohol/Cigarette use			0.19
(yes/no)	47.0(%13.2)/ 308.0(%86.8)	55.0(%10.7)/ 461.0(%89.3)	
Fatty foods			0.43
(yes/no)	258.0(%72.2)/ 97.0(%27.3)	372.0(%72.0)/ 144.0(%27.9)	
Psychiatric drugs use			<0.01
(yes/no)	143.0(%40.6)/ 209.0(%59.4)	276.0(%53.5)/ 240.0(%46.5)	
Residence			0.46
Tehran	208.0(%58.6)	301.0(%58.3)	
Large provinces	92.0(%25.9)	148.0(%28.7)	
Small provinces	55.0(%15.5)	67.0(%13.0)	
Occupation status			0.22
Housewife	210.0(%59.2)	299.0(%57.9)	
Occupied	82.0(%23.1)	142.0(%27.5)	
Retired	63.0(%17.7)	75.0(%14.5)	
Education			0.73
Elementary school	79.0(%22.2)	96.0(%18.6)	
High school	157.0(%44.3)	233.0(%45.2)	
Academic education (university)	119.0(%33.5)	187.0(%36.2)	

was used. Then, t-test was used to analyze the difference between case and control groups in terms of mean number of experienced major life events. Logistic regression was applied to analyze the multi-variable risk factors.

In the second phase, statistical analysis of data related to the relationship between major stressful life events and disease-free survival, and overall survival (5 and 10 years), in patients with breast cancer was conducted

for two scenarios: in the first scenario, all women with breast cancer were divided into the following two groups (based on experiencing or not experiencing life events); at this stage, 40 women with no experiences of any major life events before diagnosis were compared with 315 women with at least experience of one major life event in their lives. The Kaplan-Meier method was used for comparison of differences in survival of these two groups. The differences between the two groups in terms of tumor prognostic characteristics were tested using appropriate parametric and non-parametric statistical methods. In the latter case, the group that had not reported any severe life events were matched with the group with experiences of some important stressful life events in terms of age, marital status in order to control confounding factors. The significance level of $p < 0.05$ was considered for all tests.

Results

The demographic characteristics of participating women in both groups of case and control are presented in table 1. It can be seen that in terms of age, number of pregnancies, deliveries and abortion, breast feeding duration, menopausal status, use of hormone, use of alcohol/smoking, fatty foods, lodging, education, and occupational status, both groups were similar.

Table 2 shows mean number of cumulative major stressful events in the life span, and also percentage of experience of each of these stressful events in both groups. According to this table, women in the control group compared to the case group women generally had had more stressful events in their lives. But of course this difference was not significant. Univariate analysis of life events and their relationship with incidence of breast cancer did not show a significant difference confirming the relationship between experiencing major events and incidence of breast cancer. Major problems in relation to spouse was the only event that, among breast cancer women was more compared to women with benign breast diseases and led to a significant difference between the

two groups. It must be mentioned that the mean interval between diagnosis and interview in the case group was three years and two months with a range between 1 to 12 years, and the mean interval between first visit and interview in the control group was two years and nine months with a range between 1 to 10 years.

In table 3 that contains information related to survival of women with breast cancer, the demographic characteristics and histology of the tumor are presented. In this Table, women with breast cancer are compared in three sub-groups. The first sub-group is women with breast cancer that had not reported any major events in their lives. The second sub-group is women with breast cancer that had at least one major event in their lives, and the third sub-group is women with breast cancer that had experienced more events (3 or more) in their lives. To begin with, the first and second sub-groups were compared in respect of demographic and histological variables, which showed significant difference in terms of age ($P=0.01$), marital status ($p=0.05$), menopause ($P=0.03$) and childbirth ($P=0.03$). In the second stage through the logistic regression test, only variables of age and marital status were identified as risk factors. So, the third sub-group was formed with elimination of these confounding factors.

Comparative analysis of relationship between stressful events in life span and survival rate between the first sub-group (no event) and second sub-group (at least one event) made it clear that disease-free survival ($P < 0.01$) and overall survival of 5 ($P=0.02$) and 10 years ($p=0.03$) in women in second sub-group was significantly higher than women in the first sub-group.

Also, survival was higher in the third sub-group (multiple events) as compared with the first sub-group (after eliminating confounding variables) although it was not statistically significant (Figure 1). Comparing the two groups did not show any significant relationship between experiencing events and the prognostic factors related to survival in breast cancer, including, tumor size, number of affected axillaries lymph nodes, type and pathological

Table 2. Nature and Frequency of Life Span Major Stressful Events Reported by the Study Participants

Life events	Cases(N=355)	Controls(N=516)	P- values
Death of a loved one	172.0(%48.5)	305.0(%59.1)	<0.01
Personal major health difficulties	55.0(%15.5)	102.0(%19.8)	0.1
Loved ones major health difficulties	93.0(%26.2)	175.0(%33.9)	0.01
Major difficulties in interpersonal relationship with husband	118.0(%33.2)	93.0(%18)	<0.01
Divorce	9.0(%2.5)	19.0(%3.7)	0.34
Problems related to children	36.0(%10.1)	55.0(%10.7)	0.80
Major discords with others	23.0(%6.2)	52.0(%10.1)	0.06
Major problems in occupation	46.0(%13)	50.0(%9.7)	0.13
Major negative changes in financial status	87.0(%24.5)	129.0(%25)	0.86
Trouble with the law	37.0(%10.4)	81.0(%15.7)	0.02
Unforeseen events	34.0(%9.6)	53.0(%10.3)	0.73

Table 3. Demographic and Tumor Prognostic Characteristics of Breast Cancer Patients for Three Sub-Groups

Characteristics	No event	At least 1 event	Multiple events	P-values(sub groups 1&2)	P-values(sub groups 1&3)
Age(mean±Sd)	45.4±9.12	49.3±8.5	48.1±7.3	0.01	0.11
Marital status				0.05	0.11
Married	34.0(85.0%)	277.0(87.9%)	78.0(82.1%)		
Single	6.0(15.0%)	17.0(5.4%)	7.0(7.4%)		
Divorced		9.0(2.9%)	6.0(6.3%)		
Widowed		12.0(3.8%)	4.0(4.2%)		
Histological variables					
Tumor size (mean±Sd)	2.9±1.5	3.0±2.0	3.2±2.0	0.59	0.31
≤2	13.0(32.5%)	123.0(39.0%)	32.0(33.7%)	0.52	<0.01
>2	27.0(67.5%)	191.0(60.8%)	63.0(66.3%)		
Invaded axillary lymph nodes	3.1±5.6	2.2±3.4	2.2±3.2	0.30	0.35
Examined axillary lymph nodes	11.1±5.7	9.7±5.0	10.2±4.4	0.15	0.39
Type of tumor				0.46	0.36
IDCA	24.0(60.0%)	222.0(70.4%)	61.0(64.2%)		
ILC A(ILCA & IDCA)	10.0(25.0%)	56.0(14.5%)	18.0(19.0%)		
DCIS(DCIS&IDCA)	5.0(12.5%)	46.0(14.8%)	16.0(16.8%)		
LCIS	1.0(2.5%)	1.0(0.3%)			
Grade				0.5	0.81
1 & 2	27.0(67.5%)	202.0(64.1%)	58.0(61.2%)		
3	9.0(22.5%)	87.0(27.6%)	25.0(26.3%)		
Mixed	4.0(10.0%)	22.0(7.0%)	11.0(11.6%)		
Stage				0.74	0.3
1	8.0(20.0%)	78.0(24.8%)	26.0(27.4%)		
2	21.0(52.5%)	147.0(46.7%)	36.0(37.9%)		
3	11.0(27.5)	87.0(27.6%)	32.0(33.7%)		
LV1(positive/negative)	20.0(50.0%)/18.0(45.0%)	128.0(40.6%)/135.0(42.9%)	37.0(38.9%)/44.0(46.3%)	0.82	0.47
ERPR(positive/negative)	30.0(75.0%)/10.0(25.0%)	221.0(70.2%)/89.0(28.3%)	70.0(73.7%)/24.0(25.3%)	0.62	0.94
Her-2(positive/negative)	11.0(27.5%)/29.0(72.5)	80.0(25.4%)/228(72.4%)	28.0(29.5%)/66.0(69.5%)	0.83	0.79

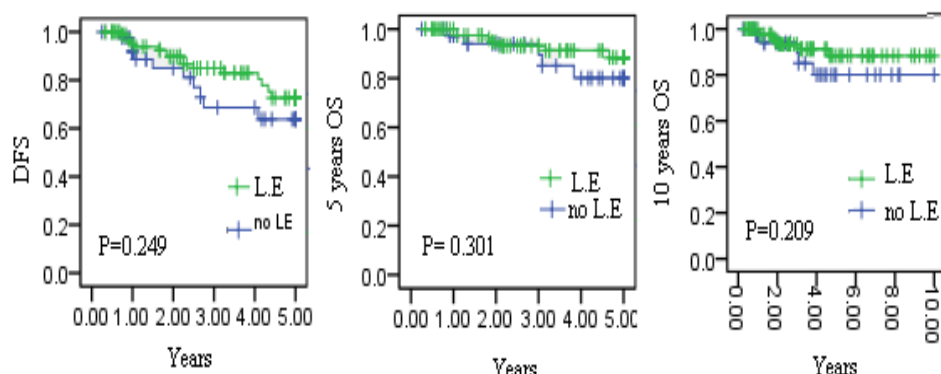


Figure 1. Duration of DFS and OS(5&10 Years) for Women in First and Third Sub-Groups after Controlling Age and ManualStatus

grade of tumor, clinical stage of tumor, status of ERPR, LVI, and Her-2 (Table 3).

Discussions

Generally, cumulative stressful life events in the case and control groups showed no significant relationship with incidence of breast cancer. In the univariate study of each event with incidence of this disease, other than one event (major problems in interpersonal relationship with spouse), no other significant correlation was observed. Of course, relationship between independent events and breast cancer incidence has been reported in many studies. For example, results of a meta-analysis could be mentioned that did not support association between stressful life events and risk of breast cancer, and only showed relatively small association between a major event (death of spouse) and risk of breast cancer (Duijts et al., 2003). Fang et al. in a nationwide study in Sweden over 15 years on the association between death of a child and incidence of breast cancer in the parents reached the conclusion that parents who have lost a child compared to parents who did not were more at risk of cancer. This association was stronger in the first 5 years of the child loss, particularly in case of cancers associated with HPV infection (Fang et al., 2011). Another 5-year prospective study on 10,808 women showed that, independently of total life events, divorce/separation, death of spouse, death of relative or close friend, are related to risk of breast cancer (Lillberg et al., 2003). Jacobs in his prospective study reached the conclusion that, mother's death, 20 years prior to hospitalization of patient for breast cancer, could be effective in the disease etiology (Jacobs and Bovasso, 2000). The mechanism that has been defined for the effects of stress on incidence of cancer is a neuro-psycho-immunological (Jakovljevic et al., 2012). It has been proven that stress reduces immune function of cells in the body through the axis of hypothalamic-pituitary-adrenal (HPA) and increased cortisol and consequently increases cancer incidence. There is also this hypothesis that, as the immune system is effective in deletion of mutant cells, reduced immunity could accelerate incidence of cancer or result in increased likelihood of cancer recurrence. Also, stress can increase the risk of cancer through damaging DNA, partial repair of DNA, prevention of cell death (apoptosis), effects on endocrine parameters or other biological changes (Graham et al., 2002; Kronke et al., 2004).

What seems interesting here is the superiority of patients with benign breast diseases both in the investigation of correlation between cumulative life events and incidence of breast cancer, and in the correlation between individual events and incidence of this disease, which of course only in the latter case, in three events, that is, death of loved ones, health problems of loved ones, and legal problems, have shown significance. This finding has caused a peculiar complexity in the present study. That is, it can be assumed that more experience of some events is related to less risk of breast cancer. In this regard, some researchers also have supported of reports of more stressful events in patients with benign breast diseases

compared to patients with cancer (Lopez et al., 2010). In addition, compilation of results has shown that not only there is no association between stress and increased risk of breast cancer, but also, a reduction in this respect has been observed (Kronke et al., 2004; Nielsen et al., 2007; Nielsen et al., 2005). The explanation for this phenomenon is that the high endogenous concentration of estrogen has been identified as risk factor for breast cancer, therefore, defects in the synthesis that is caused due to chronic stress can contribute to a lower incidence of this disease in women (Nielsen et al., 2005).

Of course, care must be taken in applying this interpretation because numerous studies have shown that the interaction between some psychological factors and life events can ultimately determine the association between experiencing these events and increased or decreased risk of breast cancer.

Various theoretical models that have taken shape on the basis of biological data are a reminder for the importance of understanding and modeling of the interaction between various psycho-social factors and not just the influence of life event alone on the risk of cancer incidence (Michael et al. 2009). Ollonen et al., in their prospective study, realized the association between unsatisfactory coping and defending mechanisms and increased risk of breast cancer. They showed that women with breast cancer compared to women with benign breast diseases and healthy women tend to use defense mechanisms such as denial, intellectualization, rationalization and reaction formation (Ollonen et al., 2005). The results of a case-control study that has shown superiority of experience of stressful events of 2 years previous in women with breast cancer compared to healthy women, while pointing out the finding that women with breast cancer scored highly in the components related to repressive coping style such as anger, resignation and neuroticism (Cardenal et al., 2008). In the theoretical modeling that was discussed earlier, interaction between stress and psycho-social supports and the influence of this interaction on the individual's ability to cope with the stressor, has been identified as a factor for increased risk of cancer, and not just the life event per se (Michael et al. 2009). The prospective Price study, although did not achieve any results with regards to relationship between stressful events and incidence of breast cancer, it showed women that had experienced more severe stressful events 2 years previously, while not enjoying social and intimate support were more exposed to the risk of breast cancer (Price et al., 2001). Animal studies that investigated the interaction of social factors and genetic risk of breast cancer found the relationship between psycho-social support and altered mammary gland gene expression, increased tumor growth, and increased probability of cancer (Hermes et al., 2009; Williams et al., 2009). Generally, it appears that social support acts as a buffer between stress and the disease. That is, this factor may modulate the stress-related appraisal, thereby, eliminating or reducing the physiological reaction to stress (Turner-Cobb et al., 2000). So, when this buffer loses its meaning, individual's psychological vulnerability against invasion by events clearly shows itself and this is the time when the disease is expected. From this perspective, a

relationship between severe interpersonal problems with spouse and incidence of breast cancer in this study can be explained. Spouse is one of the most important sources of psycho-social support for women particularly in the Iranian culture. Hence, having severe communication problems with spouse can compromise this supportive factor and erode the perception of women from spousal support.

Another hypothesis of this study was that, women with breast cancer who had not reported any major event in their life spans prior to diagnosis had better disease-free survival and overall 5 years and 10 years survival compared to those in the same group who did have one or more experiences of major events. But, not only this hypothesis was not confirmed but results were quite the opposite. This difference remained even when confounding variables were controlled. Though, they were no longer significant. Accordingly, in a 23 year prospective study by Saito-Nakaya, the hypothesis that stress reduces survival of cancer was not confirmed (Saito-Nakaya et al., 2012). Maunsell's study did not achieve evidence confirming stressful events of 5 years prior to diagnosis have a negative effect on the survival of women with breast cancer, too (Maunsell et al., 2001). Another prospective study, in which biological factors including axillaries lymph nodes and grading were controlled had similar results. However, this study was somewhat different from the present study and studies mentioned. The difference was that in addition to the experienced events in the years prior to diagnosis, it had also included experience of events after the diagnosis in the investigation of relationship between events and survival of breast cancer patients. However, not only this study did not achieve any evidence confirming increased risk of recurrence in women with breast cancer who had experienced a major stressful event a year before diagnosis or during the 5 years after diagnosis, but it showed that women who had experienced one or more severe stressful events after their diagnosis compared to women with no such experiences were at lower risk of recurrence (Graham et al., 2002). Of course, alongside these findings there have also been studies that confirmed the relationship between experience of stressful event and survival.

Similar to what was mentioned about relationship between events and cancer incidence; some researchers have emphasized the mediating role of coping styles and social support on the relationship between stressful life events and breast cancer survival (Chida et al., 2008; Moreno-Smith et al., 2010). They believe that when the individual uses a fighting coping style instead of a resignation coping style, survival rate is higher (Cardenal et al., 2008). Regarding the role of psycho-social factors, results of a 10-year prospective study on 2835 women with breast cancer who were at clinical stages I to IV showed that women who were socially isolated before diagnosis compared to women who were socially integrated before their diagnosis, were at twofold increased risk of breast cancer mortality (Kroenke et al., 2006). Also, it has been recognized that better social support of women with breast cancer metastasis is accompanied by reduced cortisol levels (which has a role in the development of faster tumor

growth). As the last explanation, some of the resources could be mentioned that have supported the protective effects of certain levels of experience of stressful events against developing breast cancer (Michael et al., 2009). In our opinion, this theory is also applicable in respect of survival. Present findings confirm this opinion. We have reached the conclusion that experiencing certain levels of stressful events may protect patients with breast cancer against low survival rate. Of course, more research is required to confirm this claim.

This study also had some limitations. The first limitation was the recall bias, which is a common limitation in the case-control studies. Another limitation was selection of samples from hospital. Thus, it cannot be claimed that the studied groups fully represent women with breast cancer or women with benign breast diseases.

In this study, only "major interpersonal problems with spouse" showed a significant association with incidence of breast cancer. This finding could be helpful in the development of preventative policies. Additionally, survival rate of breast cancer patients did not reduce with experience of stressful events. Of course, the interaction between various psycho-social factors and stressful life events and breast cancer incidence or survival cannot be ignored.

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