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Impact of major life events on breast-cancer-specific mortality: A case fatality study on 8000 breast cancer patients

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ABSTRACT

Background: It has been suggested that long-term activation of the body's stress–response system and subsequent overexposure to stress hormones may be associated with increased morbidity. However, evidence on the impact of major life events on mortality from breast cancer (BC) remains inconclusive. The main aim of this study is to investigate whether major negatively or positively experienced life events before or after diagnosis have an effect on BC-specific mortality in women who have survived with BC for at least 2 years.
Methods: We conducted a case fatality study with data on life events from a self-administered survey and data on BC from the Finnish Cancer Registry. Cox models were fitted to estimate BC mortality hazard ratios (MRs) between those who have undergone major life events and those who haven't.
Results: None of the pre-diagnostic negative life events had any effect on BC-specific mortality. Regarding post-diagnostic events, the effect was greatest in women with moderate scores of events. As for event-specific scores, increased BC mortality was observed with spouse unemployment, relationship problems, and death of a close friend. By contrast, falling in love and positive developments in hobbies were shown to be associated with lower BC mortality (MRs 0.67, 95%CI: 0.49–0.92 and 0.74, 95%CI: 0.57–0.96, respectively). In an analysis restricted to recently diagnosed cases (2007), also death of a child and of a mother was associated with increased BC mortality.
Conclusions: Some major life events regarding close personal relationships may play a role in BC-specific mortality, with certain negative life events increasing BC mortality and positive events decreasing it. The observed favorable associations between positive developments in romantic relationships and hobbies and BC mortality are likely to reflect the importance of social interaction and support.

1. Introduction

Breast cancer (BC) is the second most common cause of cancer death in developed countries and the most common among women in Finland [1,2]. BC survival has improved over the years, but a high incidence rate still leads to high absolute mortality [3]. It has been suggested that long-term activation of the body's stress–response system and the subsequent overexposure to stress hormones is associated with increased morbidity. There is a relatively large literature on the effect of stressful life events on BC incidence, but the association between major life events and death from BC has drawn less attention. Most specifically, the effects of major positive life events in BC mortality are seldom studied.

Concerning studies on BC mortality and stressful life events, Falagas and colleagues have presented studies with mixed results in their systematic review of 31 studies on psychosocial factors and BC survival [4]. Satin et al. reported increased mortality for BC patients suffering from depression [5], but opposite results have also been presented [6]. The meta-analysis by Chida et al. concluded that psychosocial factors such as stressful life experiences are associated with poorer all-cancer survival and higher mortality. In cancer site-specific analyses, some psychosocial

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factors such as depression were associated with poorer survival in BC patients [7]. Maunsell and colleagues reported no association between stressful life events and BC-specific or all-cause mortality [8]. On the other hand, some studies have shown that positive aspects of life, such as hobbies, are associated with decreased BC mortality [9,10].

The underlying mechanism of the potential association between perceived stress and cancer incidence/cancer mortality is not clear. Hormones such as cortisol, adrenaline, catecholamine and epinephrine impair the immune system e.g. by reducing the number of T lymphocytes and lowering the cytotoxicity of natural killer (NK) cells, assumed to be essential in the immune defense against tumors [11,12]. NK cells have been shown to have a major impact on many diseases and by various mechanisms. Their role in the initiation of cancer and in accelerated tumor growth is under extensive research [13]. Mamessier, Ames and Reiche have all reported that high concentrations of catecholamines, opiates and corticosteroids are immunosuppressive, leading to impaired activity of NK cells and other lymphocytes [14–16]. Accordingly, it has been postulated that happiness may lead into changes in serum cortisol concentrations or immune function that could thus affect mortality [17]. There are also studies suggesting that certain levels of stress may suppress tumor progression [18,19] and that the effect between stress and cancer progression is greatly dependent on personal stress coping mechanisms [20]. The objective of the present study is to assess whether major negatively or positively experienced life events have an impact on BC-specific mortality in women surviving with BC for at least 2 years after adjusting for confounders, taking into account socioeconomic position and the timing of the life event (either before or after the BC diagnosis).

2. Material and methods

2.1. Data sources

The study material consisted of a survey on potential BC risk factors and cancer information from the national cancer registry. The Women's Health and Use of Hormones (WHH) survey was conducted as a self-administered questionnaire in 2009. The WHH survey was initially developed to collect information on exogenous hormone use, but it has also covered a wide variety of other lifestyle factors [21]. BC cases were identified from the Finnish Cancer Registry; women aged 18–60 years with BC diagnosed between 1st January 2000 and 31st December 2007 were considered eligible. Out of the 12,251 women to whom the survey was sent and to whom we were able to link the required data, 8364 (68%) responded. Details of the survey and data collection have been described previously [21,22].

The outcome measure was defined as death where BC was marked as the underlying cause of death according to the death certificate retrieved from Statistics Finland. Information on the deaths are updated annually to the cancer registry and linked via the unique personal ID number. Information on socioeconomic class was likewise obtained from Statistics Finland and linked through the ID number. The socioeconomic categorization in Statistics Finland is based on occupation, and in this study the information on occupation concerned the year of the diagnosis or a maximum of 2 years before this. The initial categories included self-employed persons; upper-level employees with administrative, managerial, professional and related occupations; lower-level employees with administrative and clerical occupations; manual workers; students; pensioners; others. These categories were further pooled in the analyses into three categories: high class including all upper-level officials, middle class including lower-level employees and manual workers, self-employed and entrepreneurs, and low class including students, unemployed people and retirees.

The primary exposure of interest was the occurrence of major life events and the resulting impact experienced. The survey provided information on a range of variables not available from standard registry-based sources, such as experiences of violence, financial difficulties, serious accidents etc. It also mapped out major positive changes in life. The respondent was asked if she had encountered a notable positive experience or event e.g. regarding family relationships, at work, financially, or in spiritual life. The respondents were also asked to indicate when the event – negative or positive – had occurred (within last 2 years, within last 5 years, earlier or never). The negative events were rated according to the impact experienced as not very hard, hard, or extremely hard. Positive experiences or events were not rated for their impact.

2.2. Data editing

Stress scores of the negative life events were calculated to facilitate estimation of the cumulative impact of the events (total stress score), experienced stress, and the possible dose–response relationship. For the individuals who reported the experienced impact of the event, the score was coded from 1 to 3 based on the impact; the category "not very hard" was given a score 1, "hard" was given a score 2 and "extremely hard" score 3. The score was given the value 0 for individuals who reported not having experienced the life event. The total stress score of reported negative life events was formed by adding all event-specific scores together, producing potential values from 0 to 66. The impact of experiencing a negative event always had the same value across different events: e.g., the death of a spouse that was experienced as extremely hard had the same value in the analysis as retirement that was also perceived as an extremely hard event. Differences between the levels of impact experienced were assumed to be linear in the analysis: i.e., the difference between "not very hard" and "hard" was equal to that between "hard" and "extremely hard". The average total stress score for negative life events was 14, the maximum was 51, and the quartiles were 9, 13 and 18. For positive life events no impact weights were available, and these were considered individually as either having or not having experienced an event, and cumulative scores were not calculated.

In order to compare the effects of the timing of the life events in relation to the BC diagnosis, the events were also classified as either pre- or post-diagnostic, according to their reported timing. Events occurring in the same year as diagnosis were excluded to ensure reliable timing, as only information on the year of the event was available. Therefore a separate model for each life event was fitted, where the effect of the life event varied by the timing of the event (pre- or post-diagnosis). For negative life events, continuous stress scores (ranging from 0 to 3) were used, and for positive life events yes/no dummies were used. Additionally, two separate total stress scores for pre- and post-diagnostic events were categorized according to quartiles of the total stress score regardless of timing (0–8, 9–12, 13–17, 18–66). Hence persons were not evenly distributed by categorized total stress score by event timing, but regardless of timing.

2.3. Statistical methods

Several Cox models were used to estimate BC-specific mortality hazard ratios (MRs) and their 95% confidence intervals for the different types of exposures. As our analyses included only women who returned the questionnaire (N = 8364), their observed survival times were conditional on surviving up to the questionnaire, which took place 2–9 years after the diagnosis. This delayed entry was