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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.
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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

taken into account in the analyses by starting follow-up at the time of diagnosis but only analyzing survival from the questionnaire onwards. The follow-up ended at death or censoring or the end of the investigated period (the end of 2013).

The primary end point in all Cox models was death from BC. We inspected scaled Schoenfeld residuals of the Cox models to ensure that the proportional hazards assumption held in our models. Based on the inspection we formulated all models to include different baseline hazards by age group (0–54, 55–59, and 60+) and by a dummy for the missingness of the socioeconomic group. This also adjusted MRs in all models for these factors. We also fitted models separately by socioeconomic group.

To reduce confounding, we initially included socioeconomic group, parity, age at menarche, body mass index (BMI), smoking, family history of BC, use of hormonal contraceptives, physical activity, use of alcohol, cancer stage, cancer type (ductal, lobular, other), and cancer behavior in a model including all events as separate covariates. Based on personal judgement and assisted by inspection of the confidence intervals of the MR estimates, Akaike's information criterion (AIC) of potential submodels, and the effect of the covariates on other MR estimates, we retained only parity (yes or no), BMI (categorized to quartiles 0–23.1,23.2–25.5, 25.6–28.7, 28.7+ or retained in the "missing" group when it was not possible to compute BMI), cancer stage (localized or metastasized), cancer type (ductal, lobular or other), cancer behavior (in-situ or invasive), physical activity (low, moderate, high) and alcohol use (never, ever) as controlling variables in all models. In event-specific analysis, each life event was considered in a separate model, adjusting for the aforementioned background variables.

3. Results

3.1. Baseline description

The characteristics of the women with BC who responded and did not respond to the survey are presented in Table 1. There were slightly more invasive cancers among the responders than among the non-responders (92.0% versus 90.4% invasive). The proportion of women with high socioeconomic class was slightly higher among the responders than the non-responders (15% and 13%, respectively). MRs for adjusted background variables – such as alcohol use, parity and BMI, as well as total stress score for negative life events – are presented in Appendix A.

3.2. Statistical analysis on the effects of major life events

Regarding individual negative life events, none of the impact-weighted pre-diagnostic events had any effect on BC-specific mortality. As for post-diagnostic events, retirement (1.87, 95%CI: 1.59–2.19), illness causing work disablement (MR 1.29, 95%CI: 1.16–1.44), unemployment of spouse (MR 1.28, 95%CI: 1.02–1.61), relationship problems with spouse (MR 1.23, 95%CI: 1.08–1.41) and death of a close friend (MR 1.19, 95%CI: 1.04–1.36) were associated with increased BC-specific mortality (Table 2).

When estimating the effect of retirement by age group, BC MRs were significantly increased in the two youngest age groups, MRs being 1.95 (95%CI: 1.57–2.41) and 1.76 (95%CI: 1.31–2.35) in women aged 25–52 and 53–59 years at survey, respectively. In contrast, no association was observed for women having reached the common retirement age (MR 1.09, 95%CI: 0.79–1.51). Data not shown.

With respect to positive life events, falling in love before BC diagnosis and positive developments in hobbies after diagnosis were associated with decreased BC-specific mortality, the observed MRs being 0.67 (95%CI: 0.49–0.92) and 0.74 (95%CI: 0.57–0.96), respectively (Table 2). In these event-specific analyses, each life event was considered separately in the model, adjusted for the confounders mentioned.

No association was observed between higher total stress score from pre-diagnostic negative life events and death from BC. Table 3 shows the effects of the pre- and post-diagnostic total stress scores on BC mortality by different score levels. The greatest effect was observed for women with a moderate stress score (9–12) from post-diagnostic negative life events, resulting in an MR of 1.81 (95% CI: 1.23–2.67).

Associations between major life events and BC-specific mortality varied slightly in the models fitted by socioeconomic class. In the lowest socioeconomic class there was a statistically significant

Table 1
Characteristics of breast cancer cases who responded (responders) and did not respond (non-responders) to the survey.

	Responders (%)	Non-responders (%)
Total	8364 (100)	3887 (100)
Cancer stage		
Localized	4918 (58.8)	2293 (59.0)
Metastasized	3107 (37.1)	1431 (36.8)
Missing	339 (4.1)	163 (4.2)
		P-value = 0.894
Cancer behavior		
In-situ	672 (8.0)	373 (9.6)
Invasive	7692 (92.0)	3514 (90.4)
		P-value = 0.004
Socioeconomic status[a]		
High	1295 (15.5)	512 (13.2)
Middle	4558 (54.5)	2070 (53.3)
Low	1297 (15.5)	707 (18.2)
Missing	1214 (14.5)	598 (15.4)
		P-value <0.001
Age at diagnosis		
≤39	478 (5.7)	240 (6.2)
40–49	2487 (29.7)	1214 (31.2)
50–54	2462 (29.4)	1188 (30.6)
55–60	2937 (35.1)	1245 (32.0)
		P-value = 0.009
Year of diagnosis		
2000	875 (10.5)	414 (10.7)
2001	925 (11.1)	445 (11.4)
2002	948 (11.3)	487 (12.5)
2003	1034 (12.4)	476 (12.2)
2004	1089 (13.0)	518 (13.3)
2005	1128 (13.5)	545 (14.0)
2006	1220 (14.6)	514 (13.2)
2007	1145 (13.7)	488 (12.6)
		P-value = 0.162
Age at entry (at survey)		
≤39	171 (2.0)	NA
40–49	1171 (14.0)	NA
50–54	1770 (21.2)	NA
55–59	2474 (29.6)	NA
60–64	2256 (27.0)	NA
65+	522 (6.2)	NA
Time since diagnosis (years)		
2	1144 (13.7)	NA
3	1218 (14.6)	NA
4	1128 (13.5)	NA
5	1086 (13.0)	NA
6	1033 (12.4)	NA
7	948 (11.3)	NA
8	922 (11.0)	NA
9	874 (10.4)	NA
Observed survival		
At 5 years	98.5%	97.4%[b]

[a] Socioeconomic status based on the occupational information at the year of the diagnosis or maximum of 2 years before this. High class included all upper level officials; middle class included lower level officials, employees and entrepreneurs; low class included students, unemployed and retirees.

[b] The difference in 5-year observed survival between the responders and non-responders was statistically significant with $P < 0.001$.

Table 2
Effects of the pre- and post-diagnostic event-specific stress scores on breast cancer (BC) mortality.

Event	Pre-diagnostic		Post-diagnostic		Number of BC deaths observed
	N of exposed	MR[a] (95%CI)	N of exposed	MR[a] (95%CI)	
Negative events					
Death of spouse	162	0.77 (0.53–1.11)	174	1.08 (0.83–1.42)	21
Death of child	108	1.27 (0.99–1.63)	49	1.00 (0.62–1.62)	19
Death of father	2032	1.07 (0.93–1.22)	626	1.09 (0.90–1.31)	270
Death of mother	1237	1.11 (0.98–1.26)	879	1.07 (0.92–1.25)	200
Death of other close relative	1340	1.03 (0.88–1.21)	1787	0.94 (0.81–1.09)	265
Death of close friend	505	1.06 (0.86–1.30)	1116	**1.19 (1.04–1.36)**	**142**
Serious illness of family member	860	1.02 (0.88–1.18)	1396	1.05 (0.93–1.19)	214
Abortion	629	1.07 (0.89–1.29)	22	0.97 (0.41–2.30)	77
Miscarriage	665	1.10 (0.93–1.31)	26	0.86 (0.34–2.18)	86
Troubles with boss	403	0.99 (0.81–1.22)	561	0.93 (0.77–1.14)	91
Troubles with co-workers	331	1.07 (0.86–1.33)	535	0.80 (0.63–1.02)	71
Financial problems	653	0.96 (0.80–1.14)	797	1.11 (0.95–1.27)	135
Divorce or separation	922	1.13 (0.99–1.30)	301	1.12 (0.90–1.38)	132
Relationship problems with spouse	654	1.10 (0.93–1.29)	879	**1.23 (1.08–1.41)**	**152**
Break-up with close friend	417	0.95 (0.74–1.21)	595	1.03 (0.84–1.25)	89
Loss of job	510	1.00 (0.82–1.23)	428	1.13 (0.93–1.38)	97
Retirement	150	1.06 (0.66–1.69)	1339	**1.87 (1.59–2.19)**	**140**
Unemployment of spouse	450	1.00 (0.79–1.26)	400	**1.28 (1.02–1.61)**	**87**
Illness causing work disablement	291	1.13 (0.89–1.44)	2234	**1.29 (1.16–1.44)**	**262**
Serious accident	176	0.82 (0.55–1.22)	223	0.71 (0.45–1.12)	29
Physical or sexual violence	295	1.08 (0.89–1.32)	65	1.18 (0.80–1.72)	42
Emotional violence	527	1.08 (0.93–1.26)	517	1.12 (0.96–1.30)	103
Positive developments in					
Family	951	0.89 (0.60–1.33)	3303	0.85 (0.62–1.17)	296
Work	726	0.83 (0.55–1.26)	2275	0.96 (0.73–1.26)	213
Personal relationships	788	0.85 (0.57–1.28)	2514	1.09 (0.83–1.44)	239
Spiritual life	366	0.71 (0.40–1.25)	842	1.22 (0.89–1.67)	104
Financial situation	561	0.74 (0.47–1.16)	1773	0.94 (0.73–1.22)	153
Living conditions	1060	0.92 (0.65–1.30)	1636	0.88 (0.65–1.19)	223
Hobbies	507	0.90 (0.58–1.39)	2437	**0.74 (0.57–0.96)**	**179**
Falling in love	1681	**0.67 (0.49–0.92)**	647	1.01 (0.69–1.47)	223

[a] Breast cancer-specific mortality hazard ratio from a multivariate model, adjusted for parity, body mass index, physical activity, use of alcohol, cancer stage, cancer type, cancer behavior, age and socioeconomic group. N, number of cases in the specific category; MR, mortality hazard ratio, CI, confidence interval.

Table 3
The effect of the pre- and post-diagnostic total stress scores on breast cancer mortality.

Total stress score[x]	Pre-diagnostic		Post-diagnostic		Number of BC deaths[c]	Mean follow-up time (years)
	N[b]	MR (95%CI)	N[b]	MR (95%CI)		
0–8	4519	1.0 Ref	4834	1.0 Ref	47	4.86
9–12	464	0.99 (0.62–1.59)	410	**1.81 (1.23–2.67)**	47	4.87
13–17	275	1.04 (0.59–1.84)	156	1.70 (0.92–3.14)	70	4.82
18–66	200	0.92 (0.47–1.81)	58	1.37 (0.51–3.69)	80	4.83
Missing[a]	*2906*		*2906*			

[x] The total stress scores were categorized into quartiles regardless of timing. The pre- and post-diagnostic stress scores are not distributed uniformly across these categories.
[a] Timing-specific total stress scores were calculated by adding the score of the event only if the timing of the event occurrence was as defined. If timing for the event was missing or the score was missing for any of the events, timing-specific total stress score became missing.
[b] Number of cases in the respective total stress score category. MR, mortality hazard ratio; CI, confidence interval.
[c] Number of BC deaths in the respective total stress score group, pre-and post-diagnostic groups combined.

association with break-up with close friend and increased BC mortality (MR 1.82, 95%CI: 1.06–3.12). In the middle class, a positive association between retirement and death from BC (MR 1.67, 95%CI: 1.20–2.33) and an inverse association between having hobbies and BC-specific mortality (MR 0.64, 95%CI: 0.41–0.99) was observed. In the highest socioeconomic class, statistically significant associations were observed with respect to unemployment of spouse (MR 1.86, 95%CI: 1.12–3.11) and illness causing work disablement (MR 1.48, 95%CI: 1.05–2.08). No significant dose–response relationship with respect to different levels of impact scores was observed in any of the individual negative life events (data not shown).Time since the diagnosis likely affects the reporting of life events. When restricting the analysis to cases diagnosed more recently (2007) and thus with shorter time between diagnosis and the survey, significant associations were observed with respect to pre-diagnostic death of a child (MR 1.63, 95%CI: 1.17–2.27) and post-diagnostic death of a mother (MR 1.51, 95%CI: 1.05–2.17). Also post-diagnostic relationship problems with spouse and retirement remained significant (MR 1.42, 95%CI: 1.01–2.01 and 1.98, 95%CI: 1.06–3.71, respectively). With respect to positive events, post-diagnostic positive developments in family matters and living conditions decreased mortality in the recently diagnosed cases (MR 0.42, 95%CI: 0.19–0.97 and MR 0.32,

95%CI: 0.11–0.93, respectively). Falling in love or hobbies seemed no longer to have an effect on BC-specific mortality.

4. Discussion

It has been suggested that changes in the levels of stress-related hormones in the body may affect essential immune functions and could thus, by various mechanisms, affect mortality. Some of the results obtained in this study support this assumption, with certain negative life events increasing BC-specific mortality and certain positive life events decreasing it. As for event-specific impact-weighted stress scores, increased BC-specific mortality was observed for post-diagnostic retirement, illness causing work disablement, unemployment of spouse, relationship problems with spouse, and death of a close friend. The observed associations between retirement and illness causing work disablement and death from BC are likely a result of the onset of breast cancer. The cancer diagnosis may have resulted in a period of sick leave or early retirement. In contrast, falling in love and positive developments in hobbies were shown to reduce deaths from BC; falling in love before the BC diagnosis decreased BC-specific mortality by 33%, and positively experienced developments in hobbies after diagnosis lowered it by 26%. Furthermore, when limiting the analysis to women diagnosed in 2007, associations between death of a child or mother and increased BC mortality were observed. There were only minor differences in the observed estimates between the socioeconomic classes, and the results are thus not reported here separately.

The association between falling in love pre-diagnostically and lower BC-specific mortality is an intriguing finding. It may be a proxy for marriage or a relationship that in turn has been previously suggested to be associated with a healthier life style. This may have some effect on a better prognosis after cancer diagnosis and increased possibilities for cancer survival. Regarding post-diagnostic life events, it is apparent that the BC diagnosis itself is the cause for many of the events. This is more likely with respect to retirement, illness causing work disablement, and perhaps regarding spouse's retirement and relationship problems with spouse. The nature and severity of BC may naturally also affect coping with other life stresses; more aggressive cancer or poor response to cancer treatments may worsen the effects of such an additional burden. Negative life events occurring after a BC diagnosis may in some cases have drastically different effects on a person compared to a situation where the event had taken place before they fell ill, as the overall state of mind after a BC diagnosis may generally be more vulnerable. Information on the effects of post-diagnostic life events, however, is valuable as such as it highlights the importance of carefully planned, personalized mental support after BC diagnosis.

New hobbies seemed to have a favorable effect on survival from BC. We were unfortunately unable to determine the types of hobbies, and the respondents may have referred to hobbies based on physical activity or (for example) new artistic endeavors. We cannot thus know if all types of hobbies are beneficial in terms of survival from cancer, or whether it merely relates to increased physical activity. Our results support the findings of Tominaga et al., who observed that having a hobby and the number of hobbies are associated with better survival of BC patients [10].

As stated in the introduction, the impact of major life events on BC mortality has very rarely been studied. There is also rather little known about the effects of stressful life events in all-cause mortality. Regarding overall mortality, Li and others observed it to be increased in women whose child had died [23]. A study by Phillips et al. showed that health-related life events – such as depression or accident causing injury – were associated with greater all-cause mortality, but the effect was not seen with respect to other types of life events: for example, those related to relationships or work [24].

The observed beneficial effect of both falling in love and having hobbies may relate to greater release of the hormone oxytocin. Oxytocin has been suggested to affect various types of disease outcomes, such as pain response [25], and it has also been considered as a mediator of the effects of social support on buffering physiological and behavioral stress responses [26]. However, the actual mechanism of the suggested harmful effect of stress hormones in morbidity and disease survival, and accordingly the potential beneficial effects of certain other hormones, remains to be determined.

4.1. Concerning validity

Perceptions of life events as well as stress coping mechanisms vary from one person to another, and so does the impact of the occurred events. The description and meaning of the given answer categories for the experienced impact of the events in the survey has probably not been completely unambiguous, and the respondents are likely to have understood and interpreted them slightly differently.

The exposure information collected in the survey was considered appropriate to obtain information not available in the national registries. Studies based on self-administered, retrospective surveys are, however, susceptible to recall bias. This is particularly a problem within case–control designs, but may also be present in our study, where respondents are at different phases of their disease. Time since the diagnosis varies between around 2 and 9 years, and more recently diagnosed respondents may report life events more accurately than those with a longer time since the diagnosis, who may have a poorer recollection of the events. This could, to some extent, lead to overestimations of the MRs, but we consider that it does not play a significant role as many of the surveyed events are big, memorable happenings in a person's life.

There were some observed differences when restricting the analysis to recently diagnosed cases. Most notably, death of a child or of a mother was shown to be significantly associated with higher BC-specific mortality among the recently diagnosed cases. Instead of over-reporting, this is likely to result from more accurate and thorough reporting of major life events among women with recent BC diagnosis. Also, there are fewer missing values, as the higher the response rate the less time elapsed between the diagnosis and the survey. When looking into this effect in more detail, it was noted that even when considering all diagnostic years (2000–2007), a statistically significant association between death of a child and increased BC mortality was observed in the youngest responders (aged $<$55 years at survey) but not in the older age groups. This may relate to the fact that a younger BC case is likely to have younger children, compared to an older BC case. Responders aged $<$55 years at the time of the survey were 45–52 years old at diagnosis, and as the event had occurred before the diagnosis, it is presumable that the child who died was relatively young. Death of a young child may have a more severe impact on mental health than that of an older or adult child.

The beneficial effect of falling in love and hobbies in turn disappeared when only women diagnosed in 2007 were included in the analyses. As the point estimates remained more or less of similar magnitude, we are most probably lacking power to obtain statistically significant results with a smaller cohort of cases.

It is, however, evident that we missed out the most aggressive types of BC due to the time elapsed between diagnosis and survey. While 37% of the responded cases had a metastasized cancer, out of the BC cases who died before the survey sampling, 76% had a metastasized tumor. Observed 5-year survival differed by 1% between the responders and non-responders. Therefore the results

are only generalizable to women with presumably less aggressive types of BC and a broadly better prognosis, owing to the fact that they needed to survive for at least 2 years with BC.

In the framework of this study and with the present study design it was not possible to assess whether the experienced life events have the same impact in women without BC as with BC, or whether women with BC are particularly vulnerable to certain types of life events such as divorce or financial difficulties.

Validity of the WHH data has been evaluated previously [21]. In the validity assessment, the selection bias was largest among the youngest study participants, most specifically regarding variables such as parity and level of education, where the proportions of academically educated and parous women was higher than in the general Finnish population. By contrast, regarding WHH respondents aged 35 or over, the distribution of the marital status, educational level and parity status primarily corresponded that of the general population. To further reduce the possibility of reporting bias, in this study we used information of the socioeconomic status collected from Statistics Finland.

The strengths of this study lie in the population-based design and large sample size, in addition to the possibility of adjusting for several other factors – such as BMI, alcohol use, physical activity and tumor-specific factors – which could potentially contribute to BC-specific mortality.

5. Conclusions

Our data suggest that certain major life events after BC diagnosis have an effect on BC mortality in women. Even if causality cannot be determined with the present study design, the results imply that certain negative life events increase BC mortality and correspondingly certain positive life events decrease it. Besides physical well-being, the mental well-being of the patient after diagnosis also deserves attention, especially if the patient encounters further hardships soon after falling ill. In Finland, active follow-up of BC patients is usually continued for 4–5 years, after which the patient continues to go to normal, biennially organized BC mammography screenings or, if considered necessary, she may be directed to further regular clinical and laboratory examinations. The Finnish Physician's Handbook offers guidance to pay attention to the patient's mental well-being in the follow-up visits, but there are no pre-planned or established consultations with a psychologist or psychiatrist. In the light of the results obtained in this study, such a practice could be justified.

The observed favorable associations between positive developments in romantic relationships and hobbies and death from BC are intriguing, and are likely to reflect the importance of social interaction and support from friends and family, as well as the meaning of an active, forward-oriented life style in times of illness. The results also in part strengthen previous assumptions on higher mortality among women who have encountered major negative life events.

Author's contribution

Sanna Heikkinen: Study design, data editing, data analysis, interpretation of the data, writing the article and final approval of the version to be published.

Joonas Miettinen: Data analysis, interpretation of the data, writing the article, critical review of the article and final approval of the version to be published.

Eero Pukkala: Study design, data collection, interpretation of the data, writing the article, critical review of the article and final approval of the version to be published.

Markku Koskenvuo: Study design, data collection, critical review of the article and final approval of the version to be published.

Nea Malila: Interpretation of the data, writing the article, critical review of the article and final approval of the version to be published.

Janne Pitkäniemi: Study design, data editing, data analysis, interpretation of the data, writing the article and final approval of the version to be published.

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Conflicts of interest

None declared.

Appendix A.

See Tables A1 and A2

Table A1
Distribution of age at survey of the retired responders.

Age at survey	Not retired (%)	Retired (%)	Total
0–39	154 (93.3)	11 (6.7)	165
40–49	1047 (94.7)	59 (5.3)	1106
50–54	1387 (89.8)	157 (10.2)	1544
55–59	1557 (79.0)	415 (21.0)	1972
60–64	725 (38.4)	1164 (61.6)	1889
65+	39 (8.9)	401 (91.1)	440
Total	4909 (69.0)	2207 (31.0)	7116

Table A2
Mortality hazard ratios for adjusted background variables and total stress score for negative life events.

Covariate	Mortality hazard ratio (95% CI)
Alcohol use, ever vs.never[a]	0.70 (0.53.0.91)
Physical exercise, moderate[b]	0.71 (0.49–1.02)
Physical exercise, high	0.84 (0.59–1.19)
Parity, no vs. yes	1.46 (1.03–2.06)
BMI (0,23.1]	1.34 (0.87–2.07)
BMI (25.5,28.7]	1.82 (1.21–2.75)
BMI (28.7100]	2.19 (1.47–3.26)
Cancer stage, metastasized vs. localized	3.47 (2.58- 4.67)
Cancer type, lobular vs. ductal	1.69 (1.25–2.27)
Cancer type, other vs. ductal	0.65 (0.29–1.47)
Tumor behavior, in situ vs. invasive	0.11 (0.02–0.78)
Total stress score, as continuous variable	1.02 (1.01–1.04)

[a] Women reporting using "Never" or "Only in special occasions" categorized as never-users (referent), all others considered as ever-users.

[b] Women reporting exercise less than once/month categorized as low-level exercisers (referent). Moderate-level includes those reporting minimum of 2–3 times per month, or approximately once/week. High-level comprises those reporting exercising multiple times/week or daily.

See Fig. A1

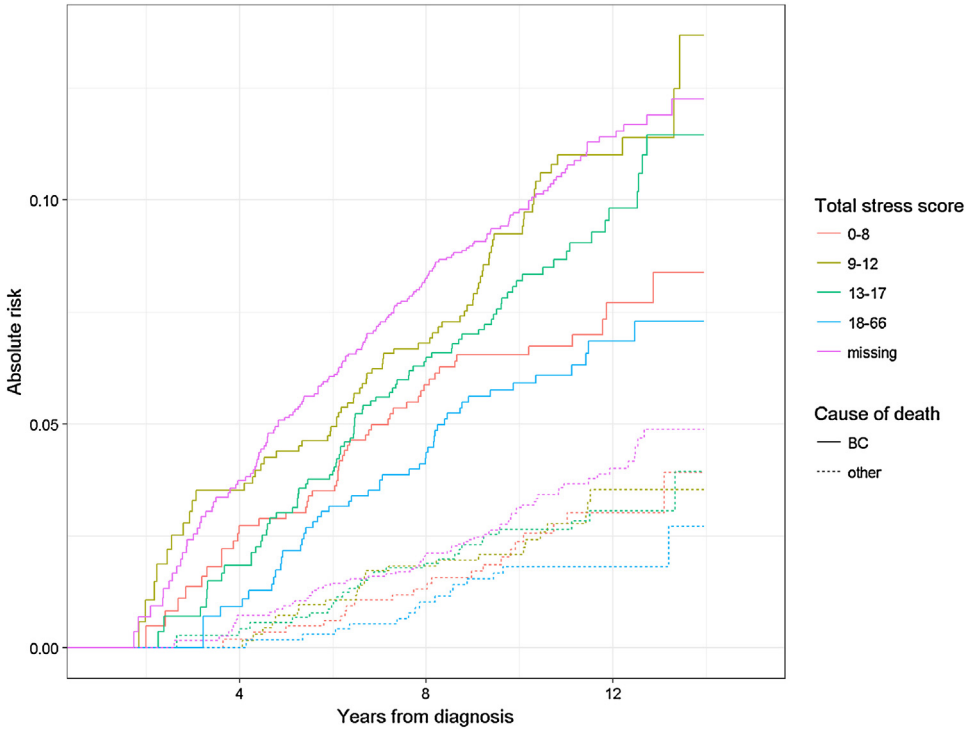

Fig. A1. Breast-cancer-specific and other-cause mortality by total stress score.

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