



Depression and Anxiety Symptoms Before and After Breast-Cancer Diagnosis Among Young Women in the Northern Finland Birth Cohort 1966

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ABSTRACT

Objective: The aim of the study was to explore depressive, anxiety, and mental-health related somatic symptoms among young breast-cancer survivors by considering symptoms before and after cancer onset.

Materials and Methods: The study sample included females from the prospective Northern Finland Birth Cohort 1966. Symptoms were assessed with the Hopkins Symptom Checklist-25 at the age of 31 and 46 years. We studied both subscales of depressive, anxiety, and somatic symptoms and single symptoms in secondary analyses.

Results: Thirty-one cases and 3,077 controls were included. Females diagnosed with breast cancer 3–8 years before the 46-year follow-up had increased depressive ($p = 0.005$) and somatic symptoms ($p = 0.028$) at the 46-year follow-up compared with the 31-year follow-up. This was not observed among those diagnosed <3 or >8 years before or among controls. Females diagnosed with breast cancer reported more lack of strength or energy compared with controls at the 46-year follow-up ($p = 0.047$). Among females who did not report feeling that the future is hopeless at the 31-year follow-up, significantly more females diagnosed with breast cancer reported this feeling at the 46-year follow-up compared with controls ($p = 0.006$).

Conclusion: Depressive and somatic symptoms increased significantly among young females at 3–8 years after breast-cancer diagnosis compared with the time before the cancer diagnosis. Psychosocial measures of support for breast-cancer survivors should be provided over the long-term.

Keywords: Breast cancer; depression; anxiety; young women

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Key Points

- Depression and anxiety symptoms occurring before and after breast cancer diagnosis among young breast-cancer survivors are not well studied.
- At the post-diagnostic follow-up, depressive and mental-health related somatic symptoms increased significantly among those young breast-cancer survivors diagnosed 3–8 years before, while no differences were found among those diagnosed <3 or >8 years before or among controls.
- The occurrence of somatic symptoms during long-term follow-up of breast-cancer patients can be related to depression, which should be considered in clinical practice.
- More research is needed to assess how previous psychiatric symptoms of young breast-cancer survivors could help to identify and provide targeted psychosocial intervention for those who need it the most.

Introduction

Breast cancer in a women aged <50 years has a major impact at the individual and societal levels; many of these women tend to have a highly responsible role in the household as a provider and caretaker of young children, along with spouses. Furthermore, breast cancer may compromise their ability to work for an extended period and may even cause permanent household economic instability (1, 2). When compared with age-matched, cancer-free controls, the prevalence of both anxiety and depression symptoms is higher among breast-cancer survivors (3-5). Age at diagnosis seems to have a significant effect; younger breast-cancer survivors tend to more commonly report severe depressive or anxiety symptoms compared with older survivors (5-9). There is no universal definition of a young breast-cancer patient and the age limit generally varies between 40 to 50 years depending on the study (1, 2, 5, 6, 10). Previous psychiatric history can predict a more than 10-fold risk of post-diagnostic major depressive disorder among women who had surgery for breast cancer (11). In a prospective follow-up of 355 women (most aged between 51 to 64 years), major depression before breast-cancer diagnosis was associated with recurrence of depression during the first year after breast-cancer diagnosis. Similarly, generalized anxiety disorder (GAD) before breast cancer was associated with a recurrence of GAD (12). In the studies described above, data on mental health before breast-cancer diagnosis were assessed retrospectively (11, 12). To the best of our knowledge, only two studies prospectively collected data on mental health before breast-cancer diagnosis (8, 13), and only Kroenke et al. (8) explored a subgroup of young breast-cancer survivors. Thus, there is a knowledge gap on how previous psychiatric symptoms relate to mental health after breast-cancer diagnosis among young survivors.

We sought to evaluate how individual depression and anxiety symptoms occurring before breast cancer are related to corresponding symptoms after breast-cancer diagnosis. Using a large longitudinal cohort setting with a 15-year follow-up, we focused on breast cancer in young women, which is relatively rare. To our knowledge, this is the first prospective study where possible changes in individual psychiatric symptoms before and after breast-cancer diagnosis are explored among young breast-cancer survivors. We also analyzed change in somatic symptoms before and after breast-cancer diagnosis aggregated from the 25-item Hopkins Symptom Checklist (14).

Materials and Methods

Northern Finland Birth Cohort 1966

The Northern Finland Birth Cohort 1966 (NFBC1966) is a population-based epidemiologic study consisting of people who were expected to be delivered in the northernmost provinces of Finland in the year 1966 (15, 16). At baseline, 12,058 live-born children (5,890 girls and 6,168 boys) and their parents participated in the study, which represented 96.3% of births in the northernmost provinces (16). The data were collected prospectively using questionnaires and/or clinical examinations at the following timepoints: at birth and at 1, 14, 31, and 46 years of age. Our study used data collected on females at age 31 and 46 years. A detailed description of data collection is presented in Figure 1.

The NFBC 1966 31-year follow-up study was approved by the Ethical Committee of Oulu University Faculty of Medicine on 17 June 1996 and the 46-year study on 17 September 2012 (EETTMK 94/2011)

by the Northern Ostrobothnia Hospital District Ethical Committee. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and all individuals have provided a written consent for participation in this study.

The Hopkins Symptom Checklist

The Hopkins Symptom Checklist (HSCL)-25 is a 25-item self-report screening instrument developed for detecting psychiatric symptoms among various patient groups in primary care (14). Based on a two-phased epidemiologic study, the HSCL-25 is suitable for screening psychiatric disorders, such as anxiety and mood disorders, with a sensitivity and specificity of 48% and 87%, respectively (17). In this questionnaire, individuals are asked to describe their symptoms from the preceding seven days on a scale from 1 to 4, where 1 refers to "Not at all", 2 "A little", 3 "Quite a bit", and 4 "Extremely". HSCL-25 can be divided into the following two separate subscales: 15 items regarding depression and 10 items regarding anxiety. The levels of depression or anxiety symptoms are determined by calculating the mean scores of items of each subscale. For this study, we also aggregated an additional subscale consisting of eight items describing mental health related-somatic symptoms. All these symptoms are associated with depression, anxiety, or both and almost all are included as diagnostic criteria (difficulties in falling asleep, poor appetite, lack of energy or strength, and low libido for depression and palpitation and trembling for anxiety disorders, respectively) (18). Although headache is not an official criteria for depression or anxiety, according to the International Classification of Diseases (ICD)-10 headache is associated with depression, anxiety, or both in multiple studies (19, 20). All items of the HSCL-25 are presented in Table 1. In addition, we formed dichotomous variables from each item, where 1 represented asymptomatic (0) and 2-4 represented symptomatic (1).

National Registries

Invasive breast cancer cases (C50.0-C50.9) were collected from the Care Register for Health Care (CRHC) administered by the National Institute for Health and Welfare (21) and registers of the Social Insurance Institution of Finland and the Finnish Center for Pensions

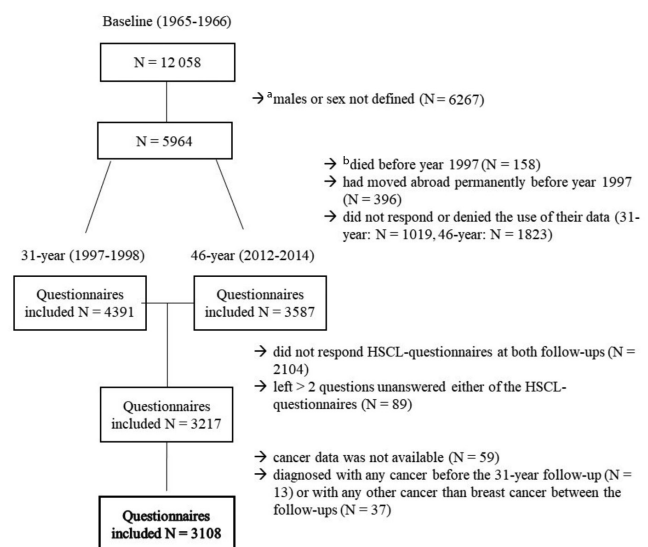


Figure 1. The selection of the study sample

HSCL: Hopkins symptom checklist

a: Live-births, 12,231 births overall

b: Stillborns also excluded, total = 173

based on the ICD-10 code. CRHC was preferred over the Finnish Cancer Registry due to the more recent update of cancer data (until the end of 2018). Data from national registers were linked to NFBC1966 using specific personal identification numbers.

Statistical Analysis

The exclusion process presented in Figure 1 was conducted prior to analysis. We chose to focus on female participants due to rarity of male breast cancer. Furthermore, we aimed to focus on breast cancer specifically so we excluded females diagnosed with other malignancies. We excluded females who left over 10% (>2 items) of HSCL unanswered. The analysis was conducted by comparing two groups, specifically individuals who were diagnosed with breast cancer between the follow-ups (BC group) and individuals who were not diagnosed with breast cancer between the follow-ups or who were not diagnosed with any cancer before the 31-year follow-up (controls). For primary analysis, Wilcoxon test was used to compare the subscale means (depression, anxiety, and somatic) between the 31-year and the 46-year follow-ups by forming the following subgroups of patients diagnosed with breast cancer: Patients diagnosed >8 years (the earliest BC group), 3–8 years (the middle BC group), and <3 years (the latest BC group) before the 46-year follow-up. For secondary analysis, we used cross-tabulation to review all 25 formed dichotomous variables separately at the 31-year and the 46-year follow-ups with Pearson’s χ^2 test and Fisher’s exact test, when appropriate. The obtained *p*-values were adjusted with Benjamini-Hochberg correction for multiple testing. Since one of our aims was to examine how a symptom occurred in the 46-year follow-up among individuals who did not have the symptom at the 31-year follow-up, we excluded individuals who had a reported symptom at the 31-year follow-up. Cells with a minimum frequency <5 were censored due to the Finnish legislation concerning patient data protection. The time period was determined by calculating the time from cancer diagnosis to date of completing the questionnaire form of the 46-year follow-up. Level of statistical significance was set to *p*<0.05 and all tests were two-tailed. Statistical analyses were performed using IBM SPSS Statistics, version 29.0 (IBM Corporation, Armonk, NY, USA).

Results

Overall, 3108 females were included for analysis and 31 (1.0%) were diagnosed with breast cancer between the 31-year and 46-year follow-ups according to national register data from 1997–2012. Mean \pm SD age at breast-cancer diagnosis was 40.7 \pm 3.45 years. Nine of the patients were diagnosed during 1997–2004 (approximately between the ages of 31 and 38 years), 10 during 2005–2008 (between 39 and 42 years), and 12 during 2009–2012 (between 43 and 46) years. Thirteen individuals were diagnosed with any cancer before the 31-year follow-up and 37 individuals were first diagnosed with other malignancies (ductal carcinoma *in situ* not included) than breast cancer between the follow-ups and were excluded from the analysis (Figure 1). Less than five individuals were diagnosed with other malignancies (ductal carcinoma *in situ* not included) after breast cancer between the follow-ups; these individuals were excluded for other reasons based on the exclusion process. Among females who participated in the 31-year follow-up, 41 died before the 46-year follow-up; breast cancer was a cause of death for less than five females.

In the primary analysis, we examined how the mean scores of subscales differed between the follow-ups among groups (the earliest BC group, the middle BC group, the latest BC group, and controls). At the 46-year follow-up, the middle BC group had a significantly higher mean score for depression (*p* = 0.0049) and for somatic subscale (*p* = 0.028) compared with the 31-year follow-up. Other groups did not have significant differences between the follow-ups at any subscales. The results of Wilcoxon tests are presented in Table 2.

When depression and anxiety symptoms at both follow-ups were explored separately, the BC group more frequently reported lack of strength or energy at the 46-year follow-up compared with controls (71.0% and 53.1%, respectively; *p* = 0.047). The proportions were similar at the 31-year follow-up (61.3% and 58.8%, respectively; *p* = 0.78). Although the feeling that their whole life has been continuous exertion was more common among the BC group (51.6%) than among controls (36.9%) at the 46-year follow-up, the difference was not statistically significant (*p* = 0.09). All results of cross-tabulations

Table 1. Anxiety and depression subscales of Hopkins Symptom Checklist and somatic subscale created for this study

Anxiety	Depression	Somatic
1. Headache	2. Difficulties of falling asleep	1. Headache
4. Being strained or stressed	3. Feeling that the future is continuous	2. Difficulties of falling asleep
7. Episodes of panic or anxiety	5. Feeling lonely	11. Dizziness or a feeling of fainting
8. Such a strong feeling of restlessness that it has been difficult to sit still	6. Feeling that the whole life has been continuous exertion	13. Sexual interest missing or unable to enjoy sex
10. Being nervous and a feeling of restlessness	9. Feeling of worthlessness	14. Lack of strength or energy
11. Dizziness or a feeling of fainting	12. Worries	16. Trembling
16. Trembling	13. Sexual interest missing or unable to enjoy sex	17. Poor appetite
20. A sudden feeling of restlessness without a good reason	14. Lack of strength or energy	25. Palpitation
24. Anxiety	15. Suicidal thoughts	
25. Palpitation	17. Poor appetite	
	18. Crying easily	
	19. Feelings of being locked up or trapped	
	21. Self-reproach	
	22. Low spirits	
	23. Lack of interest	

Table 2. Results of Wilcoxon Single-Rank test for breast cancer groups

Subscale	The earliest BC group (n = 9) >8 years		The middle BC group (n = 10) 3-8 years		The latest BC group (n = 12) <3 years		Control group (n = 3077)	
	Mean	p	Mean	p	Mean	p	Mean	p
Anxiety 31-year	1.37	0.59	1.31	0.31	1.29	0.076	1.32	0.13
Anxiety 46-year	1.29		1.43		1.18		1.32	
Depression 31-year	1.39	0.95	1.36	0.0049*	1.27	0.86	1.38	0.68
Depression 46-year	1.38		1.63		1.29		1.39	
Somatic 31-year	1.50	0.91	1.34	0.028*	1.39	0.053	1.37	0.056
Somatic 46-year	1.51		1.53		1.27		1.39	

*: Statistical significance ($p < 0.05$); BC: Breast cancer

of individual items of HSCL at both follow-ups are presented in Supplemental Table 1. In the secondary analysis, where all 25 items of HSCL were explored separately, among females who were asymptomatic at the 31-year follow-up, the feeling that the future is hopeless occurred more frequently among the BC group than controls at the 46-year follow-up (42.3% and 20.4%, respectively; $p = 0.006$). Although no statistically significant differences were found among individuals who were already symptomatic at the 31-year follow-up, most results were censored due to the low number of events. All results of cross-tabulations of individual items of HSCL are presented in Supplemental Table 2.

Discussion and Conclusion

To the best of our knowledge, this is the first study where prospectively assessed psychiatric symptoms before and after breast-cancer diagnosis were explored both individually and grouped into subscales. Our main finding was that individuals diagnosed with breast cancer 3–8 years before the 46-year follow-up reported significantly more symptoms of depression and mental-health related somatic symptoms than before the cancer diagnosis. Individuals diagnosed >8 years or <3 years before the 46-year follow-up had no significant changes in psychiatric symptoms. A large proportion of somatic subscale symptoms assessed in this study, such as headache, difficulties falling asleep, loss of sexual interest or inability to enjoy sex, lack of strength or energy, and poor appetite are related to depression (19, 20, 22) and these symptoms were also included in the depression subscale. This may explain why the means of both subscales were significantly higher among the middle BC group. The increase in symptoms among individuals diagnosed 3–8 years before assessing post-cancer symptoms may be explained by ongoing adjuvant treatment or long-term side effects of treatments, which may lead to experiencing more depressive and somatic symptoms. Our finding is consistent with findings from a prospective follow-up study of 164 women with breast cancer by Breidenbach et al. (23), where depression levels increased at 5 to 6 years post-diagnosis follow-up when compared with levels at 40 weeks post-diagnosis follow-up. Younger age (<50 years) was one of the predictors for depression at 5 to 6 years after diagnosis (23). An explanation for the finding that there was no increase in symptoms in the earliest BC group (where cancer was diagnosed >8 years previously) may be that they have lived the longest period after cancer diagnosis when participating in the 46-year follow-up. The tumor biology of

earlier-onset breast cancer tends to be more aggressive, which increases the risk of recurrence and leads to poorer disease-free survival (24). This may explain why >8 years cancer-free time feels more secure and breast cancer would accordingly have less impact on mental health. However, the possibility of small-sample bias has to be considered due to relatively small subgroup sizes.

The latest BC group reported no significant changes in any psychiatric symptom subscales even though this group was diagnosed with breast cancer a relatively short time ago (within 3 years before the 46-year follow-up). In the short-term, there is a possibility of a well-being paradox, when becoming severely ill reshapes an individual's perception of health and priorities in life, such as the value of relationships and the ability to work (25). In addition, coping strategies, such as focusing on positivity amidst negativity, may be present (25, 26). Cancer treatments often require frequent hospital visits and check-ups, which may bring a sense of security during the treatment period. Therefore, transitioning from the treatment to follow-up period may give space for negative emotions regarding the cancer diagnosis. At least two earlier studies that used the Hospital Anxiety and Depression scale at pre-treatment and post-treatment follow-ups have shown that depressive and anxiety symptoms are highest at the diagnostic phase but are already decreasing by the treatment period (27, 28). Avis et al. (9) also reported that among women aged 24 to 54 years diagnosed with breast cancer, depressive symptom levels were highest at baseline but decreased during the follow-up of 24 months. However, the depressive symptom levels were higher compared to women aged ≥ 55 years (9). In the 20-year follow-up of the Women Health Initiative (WHI) observation study by Jones et al. (13), depressive symptoms increased, peaking at 1-year post-diagnosis compared with pre-diagnostic levels, and continued to be higher until after 10 years post-diagnosis, when the levels returned to pre-diagnosis levels.

When exploring all 25 items of HSCL individually, individuals diagnosed with breast cancer more often reported a lack of strength or energy compared with controls at the 46-year follow-up, which is consistent with previous studies of fatigue among breast-cancer patients (4, 29). This finding highlights that somatic symptoms, such as fatigue, should be considered as an important factor when evaluating the mental health of females diagnosed with breast cancer. Seventy-one percent who reported lack of strength or energy is a relatively high proportion, which further highlights the clinical importance of this symptom. However, this excess may also be explained by the

dichotomous variable setting, where a mild (“a little”) experience of symptom is considered as a positive symptom. Nevertheless, these single question in this part of the HSCL cannot be considered as a straightforward comparison of cancer-related fatigue, which can be assessed using specific instruments (29, 30). Consistent with the life-threatening nature of breast cancer, when compared with individuals who did not have the feeling that the future is hopeless at the 31-year follow-up, significantly more individuals diagnosed with breast cancer reported this feeling at the 46-year follow-up compared with controls. As discussed above, breast cancers in younger women are usually more aggressive subtypes (24), and young breast-cancer survivors often experience the uncertainty of the future while having a crucial role not only as a caretaker but also being in a critical phase of career progression (31).

To the best of our knowledge, only two previous studies prospectively examined the mental health of women diagnosed with breast cancer (including the pre-diagnostic phase when there is no suspicion of cancer) (8, 13). Kroenke et al. (8) compared pre- and post-diagnostic levels of general mental health and revealed that general mental health declined more among survivors aged <40 years compared to older survivors. However, the status of mental health was not thoroughly explored (8). Jones et al. (13) examined levels of depressive symptoms at pre-diagnosis phase in the WHI observation study from 1993 to 2013. According to a systematic review, anxiety peaked after completing treatment among young breast-cancer survivors and in those who had previous mental health problems, but this also included the mental health status at baseline and was not limited to the pre-diagnosis period (32). Like our study, some of the previous studies did not specify the treatment types the patients received (13, 27) or the treatment types were not adjusted with the results (23, 28). The mean age of breast-cancer patients in the studies described above was 47.2 to 56.9 years (4, 27, 28, 33). However, the study of WHI was limited to postmenopausal women (mean age 62.7 years) (13). Similar to our study, none of the studies focused on prospectively assessed depression and anxiety symptoms before and after breast-cancer diagnosis specifically in younger breast-cancer patients.

Some limitations of the study should be acknowledged. Due to the small number of individuals diagnosed with breast cancer between the follow-ups, we were not able to interpret all results due to the requirement to ensure anonymity. The small sample size of breast-cancer survivors may lead to higher variability of reported results and further to bias. While most previous studies focused on disease-free survivors, the recurrence or treatment status of individuals with breast cancer at the 46-year follow-up was not known in this study. Survival bias may also be present as we excluded those who died between the follow-ups. Fewer than five individuals who died between the follow-ups had breast cancer as a cause of death. However, due to Finnish legislation, we were not able to classify which time period the deaths occurred in and if the individuals had breast-cancer diagnosis at the 31-year follow-up. We were also not able to adjust for possible confounders, such as characteristics of breast-cancer biological subtype, staging, administered treatments, or characteristics of an individual (age at diagnosis, marital status, family income, body mass index). When exploring somatic symptoms, we could not exclude those who had other somatic diseases besides breast cancer. However, this effect is likely very small, as Bekhuis et al. (22) did not find any chronic somatic diseases as a confounder while showing significant independent associations of multiple somatic symptom clusters among individuals with depression, anxiety disorders, or both.

The HSCL questionnaire asks individuals to report symptoms during the past week, which may lead to recall bias. The somatic subscale of HSCL was aggregated empirically for this study to explore changes in reported somatic symptoms between the follow-ups and therefore have not been validated in a clinical arrangement. It is also important to acknowledge that many other factors such as childhood traumas and other adverse life-events, current financial, psychological and social burdens and different levels of mental resources may play a role in mental health of a female with breast-cancer diagnosis at the follow-ups. Although it was not possible to conduct due to small sample size in this study, these should be considered as potential confounders in future studies.

The study also has multiple strengths. This study used prospective and structured information on psychiatric symptoms collected in the pre-diagnosis period, particularly before suspicion of breast cancer, and compared these data to post-diagnosis data. HSCL is a reliable tool for comprehensive symptom assessment and screening of depression and anxiety disorders (17). The combination of a socioeconomically and demographically diverse population of NFBC1966 and universal healthcare allowed for conditions similar to real life, at least in high-income regions. Moreover, the amount of reported cancer cases is highly reliable due to the accurate registry data (34).

This study prospectively examined collected pre- and post-diagnosis psychiatric symptoms of young females diagnosed with breast cancer. To the best of our knowledge, such a study has not been conducted before. Individuals diagnosed >8 years or <3 years before the 46-year follow-up had no differences in anxiety, depression, or somatic symptom subscales of HSCL between the follow-ups, while individuals diagnosed 3–8 years before reported significantly more depression and somatic symptoms. The occurrence of somatic symptoms, such as headache, lack of strength or energy, lack of sexual interest, and poor appetite during long-term follow-up of breast-cancer patients may be related to depression, which should be considered as potential indicators of mental health problems and may be a way to identify and provide targeted psychosocial intervention for those who need it the most. Although we explored a broad selection of psychiatric symptoms prospectively before and after breast-cancer diagnosis, apart from the feeling that the future is hopeless, individual symptoms of HSCL reported before breast-cancer diagnosis did not significantly predict the psychiatric symptomatology at the post-diagnosis follow-up. However, most of the symptoms were censored due to the low event count. Therefore, more research with larger study populations is needed to assess how previous psychiatric symptoms of young breast-cancer survivors may play a role in their mental health after breast cancer.

Ethics Committee Approval: Study was approved by the Ethical Committee of Oulu University Faculty of Medicine on 17 June 1996 and the 46-year study on 17 September 2012 (EETTMK 94/2011) by the Northern Ostrobothnia Hospital District Ethical Committee.

Informed Consent: All individuals have provided a written consent for participation in this study.

Authorship Contributions

Concept: A.T., A.J., P.K., J.M., S.R.; Design: A.J., P.K., J.M., S.R.; Data Collection and/or Processing: A.T., A-E.A., T.N.; Analysis and/or Interpretation: A.T.; Literature Search: A.T.; Writing: A.T., A.J., A-E.A., T.N., P.K., J.M., S.R.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Supplemental Table 1. Symptoms of Hopkins Symptom Checklist (HSCL) at the 31-year and the 46-year follow-ups

HSCL symptoms	Follow-up	Asymptomatic (1 = not at all)		Symptomatic (2 = a little bit, 3 = quite a bit, 4 = extremely)		Comparison between symptomatic and asymptomatic stratified by BC status
		Controls, n (%)	Individuals with BC, n (%)	Controls, n (%)	Individuals with BC, n (%)	
1. Headache (A, S)	31-y	1181 (38.5)	9 (29.0)	1887 (61.5)	22 (71.0)	0.28
	46-y	1307 (42.6)	10 (32.3)	1760 (57.4)	21 (67.7)	0.25
2. Difficulties in falling asleep (D, S)	31-y	2073 (67.4)	22 (71.0)	1002 (32.6)	9 (29.0)	0.67
	46-y	1890 (61.6)	18 (58.1)	1178 (38.4)	13 (41.9)	0.69
3. Feeling that the future is hopeless (D)	31-y	2229 (72.6)	26 (83.9)	841 (27.4)	5 (16.1)	0.16
	46-y	2222 (72.5)	19 (61.3)	844 (27.5)	12 (38.7)	0.17
4. Being strained or stressed (A)	31-y	1015 (33.1)	6 (19.4)	2056 (66.9)	25 (80.6)	0.11
	46-y	1048 (34.2)	10 (32.3)	2020 (65.8)	21 (67.7)	0.82
5. Feeling lonely (D)	31-y	2192 (71.2)	≥27 (≥87.1)	885 (28.8)	<5 (<12.9)	**
	46-y	2205 (71.9)	24 (77.4)	860 (28.1)	7 (22.6)	0.50
6. Feeling that the whole life has been continuous exertion (D)	31-y	2113 (68.8)	21 (70.0)	960 (31.2)	9 (30.0)	0.88
	46-y	1941 (63.1)	15 (48.4)	1133 (36.9)	16 (51.6)	0.090
7. Episodes of panic or anxiety (A)	31-y	2603 (84.7)	≥27 (≥87.1)	469 (15.3)	<5 (<12.9)	**
	46-y	2629 (85.8)	25 (80.6)	434 (14.2)	6 (19.4)	0.43 ^a
8. Such a strong feeling of restlessness that it has been difficult to sit still (A)	31-y	2713 (88.3)	≥27 (≥87.1)	361 (11.7)	<5 (<12.9)	**
	46-y	2766 (90.0)	≥27 (≥87.1)	309 (10.0)	<5 (<12.9)	**
9. Feeling of worthlessness (D)	31-y	2288 (74.5)	24 (77.4)	782 (25.5)	7 (22.6)	0.71
	46-y	2270 (73.9)	24 (77.4)	803 (26.1)	7 (22.6)	0.65
10. Being nervous and a feeling of restlessness (A)	31-y	1680 (54.8)	13 (41.9)	1384 (45.2)	18 (58.1)	0.15
	46-y	1940 (63.2)	21 (67.7)	1129 (36.8)	10 (32.3)	0.60
11. Dizziness or a feeling of fainting (A, S)	31-y	2433 (79.1)	23 (74.2)	643 (20.9)	8 (25.8)	0.51
	46-y	2454 (79.9)	≥27 (≥87.1)	618 (20.1)	<5 (<12.9)	**
12. Worries (D)	31-y	877 (28.6)	8 (25.8)	2191 (71.4)	23 (74.2)	0.73
	46-y	1011 (32.9)	8 (25.8)	2064 (67.1)	23 (74.2)	0.40
13. Sexual interest missing or unable to enjoy sex (D, S)	31-y	1768 (57.5)	19 (61.3)	1306 (42.5)	12 (38.7)	0.67
	46-y	1835 (59.8)	16 (51.6)	1233 (40.2)	15 (48.4)	0.35
14. Lack of strength or energy (D, S)	31-y	1268 (41.2)	12 (38.7)	1807 (58.8)	19 (61.3)	0.78
	46-y	1440 (46.9)	9 (29.0)	1630 (53.1)	22 (71.0)	0.047*
15. Suicidal thoughts (D)	31-y	2984 (97.0)	≥27 (≥87.1)	93 (3.0)	<5 (<12.9)	**
	46-y	2955 (96.1)	≥27 (≥87.1)	119 (3.9)	<5 (<12.9)	**
16. Trembling (A, S)	31-y	2933 (95.3)	31 (100)	144 (4.7)	0 (0)	0.40 ^{ab}
	46-y	2912 (94.8)	≥27 (≥87.1)	161 (5.2)	<5 (<12.9)	**
17. Poor appetite (D, S)	31-y	2795 (90.9)	25 (80.6)	281 (9.1)	6 (19.4)	0.060 ^a
	46-y	2821 (91.9)	≥27 (87.1)	249 (8.1)	<5 (<12.9)	**
18. Crying easily (D)	31-y	2137 (69.5)	22 (71.0)	937 (30.5)	9 (29.0)	0.86
	46-y	2287 (74.6)	22 (71.0)	780 (25.4)	9 (29.0)	0.65

Supplemental Table 1. Continued

HSCL symptoms	Follow-up	Asymptomatic (1 = not at all)		Symptomatic (2 = a little bit, 3 = quite a bit, 4 = extremely)		Comparison between symptomatic and asymptomatic stratified by BC status
		Controls, n (%)	Individuals with BC, n (%)	Controls, n (%)	Individuals with BC, n (%)	
19. Feelings of being locked up or trapped (D)	31-y	2863 (93.1)	≥27 (≥87.1)	212 (6.9)	<5 (<12.9)	**
	46-y	2924 (95.2)	31 (100)	147 (4.8)	0 (0)	0.40 ^{ab}
20. A sudden feeling of restlessness without a good reason (A)	31-y	2701 (87.8)	≥27 (≥87.1)	375 (12.2)	<5 (<12.9)	**
	46-y	2748 (89.4)	≥27 (≥87.1)	325 (10.6)	<5 (<12.9)	**
21. Self-reproach (D)	31-y	2318 (75.4)	25 (80.6)	757 (24.6)	6 (19.4)	0.50
	46-y	2368 (77.0)	23 (74.2)	706 (23.0)	8 (25.8)	0.71
22. Low spirits (D)	31-y	1783 (58.0)	18 (58.1)	1290 (42.0)	13 (41.9)	1.00
	46-y	1847 (60.1)	20 (64.5)	1227 (39.9)	11 (35.5)	0.62
23. Lack of interest (D)	31-y	1954 (63.5)	19 (61.3)	1121 (36.5)	12 (38.7)	0.80
	46-y	1971 (64.2)	19 (61.3)	1100 (35.8)	12 (38.7)	0.74
24. Anxiety (A)	31-y	2609 (84.8)	31 (100)	466 (15.2)	0 (0)	0.010 ^{*ab}
	46-y	2612 (85.4)	25 (80.6)	448 (14.6)	6 (19.4)	0.44 ^a
25. Palpitation (A, S)	31-y	2565 (83.4)	26 (83.9)	511 (16.6)	5 (16.1)	0.94
	46-y	2330 (76.3)	≥27 (≥87.1)	725 (23.7)	<5 (<12.9)	**

^a: More than 20% of cells in this subtable have expected cell counts less than 5 and Fisher’s test is conducted.

^b: The minimum expected cell count in this subtable is less than one.

^{*}: Statistical significancy ($p < 0.05$, Benjamini-Hochberg)

^{**}: p -value is censored due to cell count being less than five, non-cancer controls total = 3071 and individuals with breast cancer (BC) total = 31. A = A symptom of anxiety subscale, D = a symptom of depression subscale and S = a symptom of somatic subscale

Supplemental Table 2. Symptoms of Hopkins Symptom Checklist (HSCL) occurring at the 46-year follow-up among individuals diagnosed for breast cancer (BC group) and non-cancer controls

HSCL symptoms	Group	Did not have the symptom at the 31-year follow-up			Had the symptom at the 31-year follow-up		
		Total, n	Occurs at the 46-year follow-up, n (%)	p	Total, n	Occured at the 46-year follow-up, n (%)	p
1. Headache (A, S)	Controls	1180	493 (41.7)	**	1878	1264 (67.0)	0.93
	BC group	9	≥5 (≥55.6)				
2. Difficulties in falling asleep (D, S)	Controls	2067	654 (31.5)	0.99	999	522 (52.1)	**
	BC group	22	7 (31.8)				
3. Feeling that the future is hopeless (D)	Controls	2222	454 (20.4)	0.0062*	2048	1493 (72.6)	0.73
	BC group	26	11 (42.3)				
4. Being strained or stressed (A)	Controls	2184	456 (20.8)	0.94	959	542 (56.5)	**
	BC group	28	6 (21.4)				
6. Feeling that the whole life has been continuous exertion (D)	Controls	2111	590 (27.9)	0.30	9	≥5 (≥55.6)	0.61
	BC group	21	8 (38.1)				
7. Episodes of panic or anxiety (A)	Controls	2593	293 (11.3)	0.13 ^a	1382	699 (50.5)	0.61
	BC group	29	6 (20.7)				
8. Such a strong feeling of restlessness that it has been difficult to sit still (A)	Controls	2711	202 (7.4)	**	18	8 (44.4)	0.61
	BC group	29	<5 (<13.8)				
9. Feeling of worthlessness (D)	Controls	2285	444 (19.4)	**	2189	1634 (74.6)	0.94
	BC group	24	<5 (<20.8)				
10. Being nervous and a feeling of restlessness (A)	Controls	1674	425 (25.3)	**	1304	673 (51.5)	**
	BC group	13	<5 (<30.8)				
11. Dizziness or a feeling of fainting (A, S)	Controls	2430	390 (16.0)	**	1806	1145 (63.4)	0.35
	BC group	23	<5 (<17.4)				
12. Worries (D)	Controls	877	424 (48.3)	**	19	14 (73.7)	0.35
	BC group	8	≥5 (≥62.5)				
13. Sexual interest missing or unable to enjoy sex (D, S)	Controls	1761	559 (31.6)	0.64	281	55 (19.6)	0.60 ^{ab}
	BC group	19	7 (36.8)				
14. Lack of strength or energy (D, S)	Controls	1262	484 (38.2)	**	934	362 (38.6)	**
	BC group	12	≥8 (≥66.7)				
15. Suicidal thoughts (D)	Controls	2981	95 (3.2)	1.00 ^{ab}	9	<5 (<44.4)	**
	BC group	30	0 (0)				
16. Trembling (A, S)	Controls	2929	125 (4.3)	**	2858	113 (3.9)	0.63 ^a
	BC group	31	<5 (<12.9)				
17. Poor appetite (D, S)	Controls	2788	194 (6.9)	**	6	0 (0)	0.60 ^{ab}
	BC group	25	<5 (<16.0)				
18. Crying easily (D)	Controls	2130	417 (19.5)	0.17 ^a	9	<5 (<44.4)	**
	BC group	22	7 (31.8)				
19. Feelings of being locked up or trapped (D)	Controls	2858	113 (3.9)	0.63 ^a	30	0 (0)	0.63 ^a
	BC group	30	0 (0)				

Supplemental Table 2. Continued

HSCL symptoms	Group	Did not have the symptom at the 31-year follow-up			Had the symptom at the 31-year follow-up		
		Total, n	Occurs at the 46-year follow-up, n (%)	p	Total, n	Occured at the 46-year follow-up, n (%)	p
20. A sudden feeling of restlessness without a good reason (A)	Controls	2697	212 (7.8)	**			
	BC group	27	<5 (<14.8)				
21. Self-reproach (D)	Controls	2315	395 (17.0)	**			
	BC group	25	<5 (<16.0)				
22. Low spirits (D)	Controls	1781	494 (27.7)	1.00 ^a	1289	732 (56.7)	0.44
	BC group	18	5 (27.8)		13	6 (46.2)	
23. Lack of interest (D)	Controls	1950	513 (26.3)	0.30	1119	585 (52.2)	0.46
	BC group	19	7 (36.8)		12	5 (41.7)	
24. Anxiety (A)	Controls	2593	287 (11.0)	0.15 ^a			
	BC group	31	6 (19.4)				
25. Palpitation (A, S)	Controls	2547	519 (20.2)	**			
	BC group	26	<5 (<15.4)				

^a: More than 20% of cells in this subtable have expected cell counts less than 5 and Fisher's test is conducted.

^b: The minimum expected cell count in this subtable is less than one.

*: Statistical significancy ($p < 0.05$, Benjamini-Hochberg)

** : p -value is censored due to cell count being less than five, non-cancer controls total = 3071 and individuals with breast cancer (BC) total = 31.

A = A symptom of anxiety subscale, D = a symptom of depression subscale and S = a symptom of somatic subscale