J Cancer Surviv (2015) 9:620–629
DOI 10.1007/s11764-015-0438-y

Depression and quality of life before and after breast cancer diagnosis in older women from the Women's Health Initiative

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Received: 20 October 2014 / Accepted: 6 February 2015 / Published online: 24 February 2015

Abstract
Purpose Distress and reduced quality of life (QOL) are common among people with cancer. No study has compared these variables after breast cancer diagnosis to pre-cancer diagnosis levels.
Methods Data on women with breast cancer 50 years of age or older (n=6949) were analyzed from the Women's Health Initiative (1993–2013). Health-related QOL (physical function, mental health) was measured using Rand-36. Depressive symptoms were measured with the six-item Center for Epidemiologic Studies Depression scale. Assessments occurred before and after the cancer diagnosis. Hierarchical linear modeling compared pre-cancer QOL and depressive symptoms to levels post-diagnosis and tested whether pre-cancer physical activity, stressful life events, sleep disturbance, and pain predicted post-diagnosis outcomes.
Results Compared with pre-cancer levels, depressive symptoms increased (20.0 % increase at 0–6 months, 12.9 % increase at 6–12 months), while physical function (−3.882 points at 0–6 months, −3.545 at 6–12 months) and mental health decreased (−2.899 points at 0–6 months, −1.672 at 6–12 months) in the first year after diagnosis (all p<.01). Depressive symptoms returned to pre-cancer levels after 10 years, but QOL remained significantly lower. At more than 10 years post-diagnosis, physical function was 2.379 points lower than pre-cancer levels (p<0.01) while mental health was 1.922 points lower (p<0.01). All pre-cancer predictors were associated with all outcomes. Pain predicted uniquely greater decreases in physical function post-diagnosis.
Conclusions Depressive symptoms increased and QOL decreased following breast cancer diagnosis compared with pre-cancer levels, particularly in the first year.
Implications for Cancer Survivors QOL may remain lower for years after breast cancer diagnosis, although decreases are small.

Electronic supplementary material The online version of this article (doi:10.1007/s11764-015-0438-y) contains supplementary material, which is available to authorized users.

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Keywords Breast cancer · Neoplasm · Depression · Distress · Health-related quality of life · Women's health

Introduction

Breast cancer is a stressful experience [1] and can lead to elevated levels of depressive symptoms and lower quality of life (QOL) [2]. Several meta-analyses [3, 4] have documented elevated levels of depressive symptoms and higher prevalence of major depressive disorder in people with cancer compared with rates reported in the general population. Subclinical depressive symptoms are more common after breast cancer than a diagnosis of major depression, although care must be taken in measuring these symptoms due to overlapping somatic symptoms of depression and cancer treatment [5, 6]. Depressive symptoms adversely affect physical functioning and adherence to medical care [7] and are related to increases in inflammation in cancer populations [8, 9]. Depressive symptoms in people with cancer also are related to increased mortality [10, 11], indicating that the comorbidity of depressive symptoms and cancer represents a substantial public health problem for people with cancer.

One notable absence in the literature is epidemiological studies comparing depressive symptoms and QOL before and after breast cancer diagnosis. Currently, nearly all studies compare women with breast cancer to either women without cancer [12] or women with benign findings on a second mammogram or biopsy [13]. One problem with this line of research is that there may be differences between women who do and do not develop breast cancer, which could affect level of depressive symptoms and QOL such as higher levels of symptoms before diagnosis. However, while research has supported depression as a risk factor for non-cancer diseases [14], research findings indicating depression and stress as risk factors for incident cancer have been mixed [15, 16], so it is unclear whether women who develop breast cancer differ from those who do not on depressive symptoms and QOL. Another alternative may be to ask women to report symptoms retrospectively before the cancer diagnosis, but this may be confounded by recall bias. A study that assesses pre-cancer diagnosis levels of distress would be ideal to determine whether depressive symptoms and QOL change after cancer diagnosis compared with pre-cancer levels. Only one study examined QOL in 26 women with breast cancer before and after the diagnosis and compared them to healthy controls [17]. This study found that women who developed incident breast cancer had lower QOL than controls after diagnosis and lower QOL compared with their pre-cancer levels. Comparing depressive symptoms and QOL after cancer diagnosis to pre-cancer levels would help inform whether the cancer diagnosis itself elevates depressive symptoms and lowers QOL and whether women with cancer can expect these sequelae to return to their pre-cancer levels. Whether they can expect these symptoms to return to the pre-cancer state may be a question that many women with breast cancer will have.

The Women's Health Initiative (WHI) Observational Study and Clinical Trials provide a unique opportunity to compare pre-cancer depressive symptoms and QOL to post-diagnosis levels in women with incident breast cancer. We chose these particular outcomes, depressive symptoms and QOL, as previous research has frequently compared women with breast cancer to non-cancer controls on these outcomes both in the WHI [18] and in other studies [19, 20]. Our aim was to extend this research by using pre-cancer levels as a comparison instead of healthy controls. In the prior WHI study, cross-sectional data from the baseline assessment of the WHI Observational Study compared women with a history of breast cancer to women without a history of cancer at study entry [18]. This study found that breast cancer survivors had lower QOL and more depressive symptoms than women without a history of cancer. The current study extends this work by examining changes in depressive symptoms and QOL in women who develop incident breast cancer during follow-up. As the baseline/screening visits occurred before women developed breast cancer, this dataset provides a unique opportunity to examine depressive symptoms and QOL before and after the breast cancer diagnosis in a large cohort of women. We hypothesized that depressive symptoms would increase and QOL would decrease compared with pre-cancer levels. We also examined associations of different pre-cancer predictors on depressive symptoms and QOL in women with breast cancer. These predictors included age, physical activity, stressful life events, pain, and sleep disturbance. We hypothesized that less physical activity, more stressful life events, more pain, and more sleep disturbance would be related to more depressive symptoms and worse QOL.

Methods

Participants

The WHI Program started in 1993 and originally consisted of two major components: the Clinical Trials and the Observational Study [21]. A diverse study population of postmenopausal women aged 50 to 79 years was recruited from 40 clinical centers across the USA to participate in the WHI (n=161,808). After 2005 when the first phase of the program ended, all women who remained alive and under active surveillance were reconsented for participation in two Extension Study (ES) phases from 2005 to 2010 (n=115,400 who consented to ES1) and then from 2010 to 2015 (n=93,500 who consented to ES2). Of the initial 161,808 women in the WHI, 10,348 were diagnosed with breast cancer during the study through September 2013. See Fig. 1 for a flow chart of

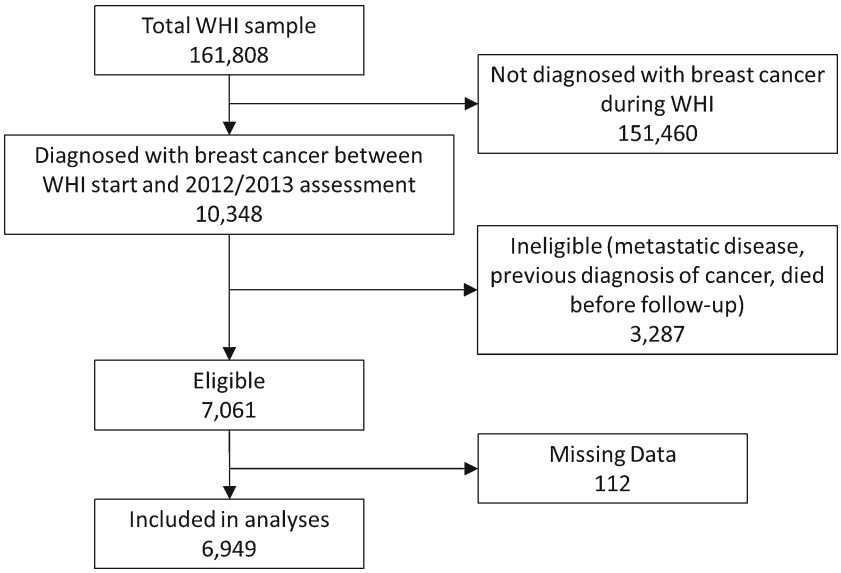


Fig. 1 Flow diagram of participants included in the analyses from the Women's Health Initiative

which participants were included in the current study. Breast cancer diagnosis was centrally adjudicated. We limited our sample further to those who were initially cancer-free upon study entry, developed non-metastatic breast cancer over the follow-up period as the cases of self-reported metastatic disease were limited (n=106), did not develop another type of cancer over follow-up (second primary), and survived until 2012, when the most recent data collection of depression and QOL began. This most recent data collection occurred 13–19 years after baseline. Women were retained if they reported other medical conditions at baseline. In total, 7061 women were eligible, and 6949 with complete data on covariates and at least one measurement of the outcomes (depression and QOL) were included in the study. Overall rates of missing data on covariates were low (range 0 to 6.2 %) except for HER2neu status (19.7 %) which was likely due to Herceptin being introduced in 1998, 5 years after the start of the study.

Procedures

Women completed questionnaires at study entry and at varying times after baseline, either through the mail or by telephone, as needed. In the Clinical Trials, women completed the depressive symptoms and QOL measures at baseline, and approximately 1, 3, 6, and 9 years later. In the Observational Study, women completed the depressive symptoms and QOL measures at baseline and 3 years later. Participants in both studies who participated in the extension studies completed the measures again 13 to 19 years later. These analyses are based on a total of 6949 WHI women with incident breast cancer (n=2948 from the Clinical Trial program and n=4001 from the Observational Study), of which 797 were assessed in the first year after diagnosis.

Outcome variables

Depressive symptoms We used the six-item short form of the Center for Epidemiological Studies Depression scale (CESD-SF; [22]). Participants rated each item on a 0 (rarely) to 3 (most or all the time) scale. One item, enjoying life, is reverse-scored before all six items are summed to create total scores ranging from 0 to 18. Higher scores indicate more depressive symptoms with a score of 5 indicating elevated distress. This short form was particularly well suited to examining depressive symptoms in women with cancer because it only contains one somatic item (sleep disturbance). Cronbach's alpha at baseline for this sample was 0.65. We used both a continuous score and a dichotomous variable (elevated distress yes/no) in the analyses. Because the continuous measure of depressive symptoms was positively skewed, we used a natural log transformation before analyzing the depressive symptom measure.

Quality of life QOL was measured with two of the eight subscales of the Rand-36 [23]. For physical QOL, we used the physical function subscale that asks participants to rate their level of limitation in performing 10 tasks (e.g., walking a block and climbing stairs). For mental health QOL, we used the mental health subscale that asks participants to rate how often they felt certain emotions (happy, blue) on a 1 (all the time) to 6 (none of the time) scale. Positive items for the mental health subscale are reverse-scored. Scores for both the physical function and mental health subscales are standardized so scores range from 0 to 100 with higher scores indicating better function.

Pre-cancer predictor variables

A series of four protective and risk factors were examined as predictors of depressive symptoms and QOL. These variables have been related to depressive symptoms and QOL in previous studies [24–27] and were measured throughout WHI using consistent measurement tools, allowing us to choose the measure closest to cancer diagnosis. To avoid analyzing measurements made while women were undergoing diagnostic procedures and experiencing symptoms shortly before diagnosis, the predictor measurements were taken more than 6 months before diagnosis, but otherwise the closest measures to breast cancer diagnosis were selected for analysis.

Physical activity Physical activity was assessed using a questionnaire that queried women about the duration and frequency of their physical activity at various intensities [28, 29]. Total Met-hours per week of physical activity were then calculated from mild, moderate, and strenuous exertion and from walking.

Stressful life events Stressful life events (SLEs) were measured by counting the number of stressful life events a participant reported in the year prior to baseline. Participants were asked to indicate if any of 11 events (e.g., ill spouse, relationship breakup, and financial problems) had occurred. A total score of number of life events was used.

Sleep disturbance Sleep disturbance was measured using the five-item WHI Insomnia Rating scale [30]. Item content included waking up during the night and trouble falling asleep. Participants indicated how often they experienced each symptom in the past 4 weeks on a scale of 0 (not experienced) to 4 (more than 5 times per week). Total scores ranged from 0 to 20, and higher scores indicated more sleep disturbance. Cronbach's alpha for this sample at baseline was 0.78.

Pain Pain was measured using the Rand-36 pain subscale [23]. This scale has two items, one about level of pain and the other about pain interfering with activities. Level of pain is rated on a 0 to 5 scale, and pain interference is rated on a 1 to 5 scale. The total score is standardized so scores ranged from 0 to 100 with higher scores indicating less pain and better functioning.

Covariates

Socioeconomic status was assessed by self-reported level of both education and income at baseline. We dichotomized education into women with a bachelor's degree or higher and women with some college or less. Income was categorized into those with a family income of $35,000/year or greater, those with less than $35,000/year, and unknown income. These groups were chosen based on the median income at the time the data collection started in 1993. Race/ethnicity was categorized as black/African-American, Asian-American, Hispanic-American. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$ as measured at baseline. A variable indicating participation in the Clinical Trials or Observational Study was also included as a covariate. Breast tumors were characterized according to stage (localized or regional with in situ as the reference), estrogen receptor (positive/not positive) and progesterone receptor (positive/not positive) status, and HER2neu receptor status (positive/not positive or not tested). Surveillance, Epidemiology, and End Results (SEER) second edition staging was used to code stage [31]. Breast cancer treatment data were not routinely collected for incident cancers in WHI.

Statistical analyses

Due to the nature of the data (assessments at varying years nested within participants) and missing data, we used hierarchical linear modeling (HLM) and generalized estimating equations (GEEs) to analyze the data. Years calculated from days since randomization (Clinical Trial participants) or enrollment (Observational Study participants) were nested within participants. Depressive symptoms (CESD-SF) and the QOL variables (physical function, mental health) were the dependent variables for the HLM, and whether participants were above the CESD cut-point was the dependent variable for the GEE. All models included cancer stage, ER/PR status, HER2neu status, study arm, education, income, age, BMI, and ethnicity as covariates. An autoregressive covariance structure was used, and random intercept and linear effects were included in all HLM models. The GEE used a binomial distribution with logit link function. The following categories were used to code time since cancer diagnosis at each assessment based on significant events along the course of cancer survivorship: (1) more than 6 months before cancer diagnosis (reference category, pre-cancer levels); (2) less than 6 months before cancer diagnosis—diagnostic period because of undergoing diagnostic tests, possibly having symptoms; (3) 0 to 6 months after cancer diagnosis—acute stress from diagnosis and undergoing treatment; (4) 6–12 months after cancer diagnosis—finishing treatment; (5) 1 to 2 years after diagnosis—finished treatment and possibly longer time between oncology follow-up appointments; (6) 2 to 5 years after diagnosis—longer time between oncology follow-up than during acute treatment but still have risk of recurrence; (7) 5 to 10 years after diagnosis—risk of recurrence decreases; and (8) more than 10 years after diagnosis—risk of recurrence decreases further. Similar categories have been used in studies of distress after cancer diagnosis [32]. Using the pre-cancer category (more than 6 months before cancer diagnosis) as the reference allowed us to compare depressive symptoms and QOL after the cancer diagnosis to

levels reported by women before the diagnosis and likely before any diagnostic procedures. Age was time varying and continuous so that age at each assessment reflected the participant's actual age and not age at study entry. For stressful life events (0.6 % missing), physical activity (4.3 % missing), and sleep problems (0.5 % missing), linear interpolation was used to impute missing data.

The first set of analyses examined time since diagnosis as the primary predictor of interest. For each of the outcomes (depressive symptoms from CESD-SF and CESD cut-point; physical function QOL; mental health QOL), models were constructed evaluating time since diagnosis in the categories described above and controlling for the covariates listed above. Plots of residuals were examined to assess normality for the HLM. As a natural log transform was used on depressive symptoms, the antilog of the coefficients was taken to determine the percentage change from pre-cancer levels.

Using parallel methods, the second set of analyses examined age and potential predictors for depressive symptoms (being above the CES-D cut-point) and QOL after cancer diagnosis. Models were constructed for each outcome adjusting for the covariates listed above. For the predictors (physical activity, stressful life events, sleep disturbance, and pain), both main effects and an interaction with first 12 months after diagnosis were entered into the model. We also tested main effects and an interaction for time-varying age. The interactions tested whether pre-cancer values on the predictors and age interacted with the acute stress of cancer diagnosis in predicting higher or lower depressive symptoms and QOL in the year after cancer diagnosis. The year after cancer diagnosis was chosen because this time period is when depressive symptoms tend to be highest following cancer diagnosis [33].

Results

Descriptive statistics are reported in Table 1. Consistent with women recruited for WHI, the average participant was 62.7 years of age at baseline. Most participants were married (65.9 %) and had yearly family incomes over $35,000 per year (61.0 %). At baseline, women reported few depressive symptoms (mean 2.20 out of a possible score of 18) and reported good QOL as measured by the physical function (mean 82.8) and mental health (mean 79.9) subscales of the Rand-36. These values were slightly higher than for the overall WHI sample (78.66 for physical function and 79.02 for mental health). Women were diagnosed with breast cancer an average of 6.8 years after baseline.

Time since diagnosis

Results for analyses examining time since diagnosis showed that women experienced an increase in depressive symptoms after breast cancer diagnosis (see Fig. 2). In the diagnostic period (0–6 months before diagnosis), women did not experience a significant change in depressive symptoms compared with pre-cancer levels (more than 6 months before diagnosis; $p>0.05$). However, during the first year after breast cancer diagnosis, depressive symptoms significantly increased compared with before the diagnosis (all $p<0.01$). (For regression coefficients and sample sizes at each time since diagnosis category, see Supplemental Materials.) All values reported in the text for depressive symptoms are the antilog and reflect the actual units of the scale. During the first 6 months after diagnosis, depressive symptoms increased by 20.0 % while symptoms increased by 12.9 % in the second 6 months after diagnosis compared with before the cancer diagnosis. Mental health decreased by 2.899 points in the first 6 months and by 1.672 points in the second 6 months post-diagnosis, compared with pre-cancer levels. Depressive symptoms did not significantly differ from pre-cancer levels during the first to second year after diagnosis ($p>0.06$). Depressive symptoms continued to remain significantly higher than pre-cancer levels until more than 10 years after diagnosis, at which point symptoms did not significantly differ from pre-cancer levels ($p=0.21$). Between 2 and 5 years post-diagnosis, depressive symptoms increased by 6.1 % compared with pre-cancer levels ($p<0.01$), and between 5 and 10 years post-diagnosis, symptoms increased by 5.3 % ($p<0.05$).

Although depressive symptoms continued to remain elevated, odds of reporting symptoms above the CESD cut-point remained elevated only in the first year after diagnosis. In the 6 months preceding diagnosis, there was not a significant increase in odds of being above the CESD cut-point compared with before the cancer ($p=0.089$). Women in the first 6 months after diagnosis had higher odds of being above the CESD cut-point (odds ratio (OR)=1.612, confidence interval (CI) 1.251, 2.077, $p<0.001$) as did women in the 6 to 12 months after diagnosis (OR=1.473, CI 1.159, 1.872, $p=.002$). Following the first year after diagnosis, odds of reporting symptoms above the cut-point were not significantly different compared with before the cancer (all $p>.07$).

Women experienced a decrease in QOL in the first year following cancer diagnosis that remained through the post-diagnosis period. In the first year after breast cancer diagnosis, physical function and mental health (QOL) significantly decreased compared with before the diagnosis (all $p<0.01$). Mental health QOL was not significantly different from pre-cancer levels during the first to second year after diagnosis ($p>0.06$). Mental health continued to remain worse than pre-cancer levels even more than 10 years after diagnosis where mental health was 1.922 points lower than pre-cancer levels (all $p<0.01$). However, the decreases for mental health were somewhat small, ranging from 1.268 to 2.899 points lower than pre-cancer levels on the 0–100 scale of the Rand-36. Physical function remained significantly lower than pre-

Table 1 Descriptive statistics of the WHI women with incident breast cancer (N=6949) for the total sample and by age at baseline

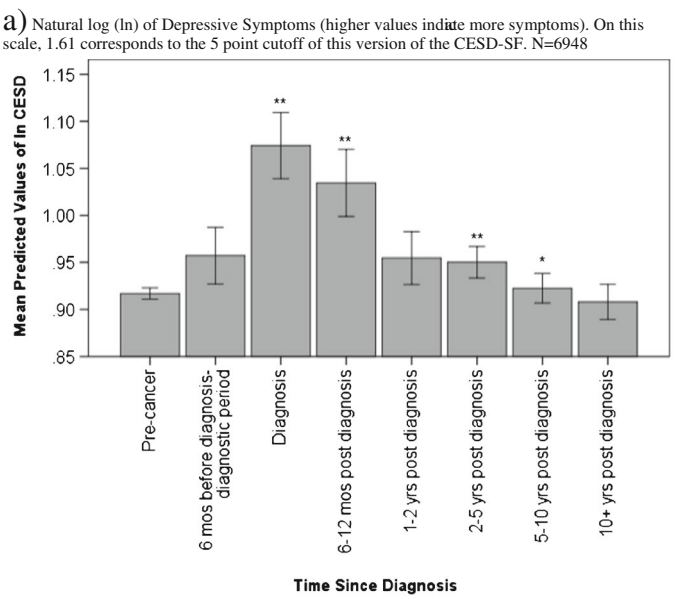
Variable	Total sample Mean (SD) or % (n)	Age group, 50–59, n=2403 Mean (SD) or % (n)	Age group, 60–69, n=3284 Mean (SD) or % (n)	Age group, 70–79, n=1262 Mean (SD) or % (n)
Age at baseline	62.68 (6.83)	55.21 (2.71)	64.30 (2.92)	72.76 (2.45)
Ethnicity				
Caucasian	87.0 % (6044)	83.5 % (2006)	87.7 % (2880)	91.8 % (1158)
African-American	7.0 % (483)	8.7 % (209)	6.8 % (224)	4.0 % (50)
Hispanic	2.4 % (167)	3.7 % (90)	2.0 % (66)	0.9 % (11)
Asian	2.3 % (161)	2.8 % (68)	2.2 % (71)	1.7 % (22)
Native American	0.3 % (20)	0.2 % (6)	0.3 % (10)	0.3 % (4)
Other	0.9 % (61)	0.3 % (20)	0.4 % (28)	0.2 % (13)
Missing	0.2 % (13)	0.1 % (4)	0.1 % (5)	0.1 % (4)
Married or long-term relationship	65.9 % (4581)	70.7 % (1698)	66.9 % (2196)	54.4 % (687)
Income				
Unknown	6.1 % (426)	5.4 % (130)	6.3 % (208)	7.0 % (88)
<$35,000/year	32.9 % (2285)	20.6 % (494)	36.8 % (1207)	46.3 % (584)
>$35,000/year	61.0 % (4238)	74.0 % (1779)	56.9 % (1869)	46.8 % (590)
Education				
Less than bachelor's	54.6 % (3793)	52.4 % (1260)	57.2 % (1878)	61.2 % (772)
Bachelor's or higher	45.4 % (3156)	47.6 % (1143)	42.8 % (1406)	38.8 % (490)
BMI	27.99 (5.71)	27.96 (5.94)	28.25 (5.78)	27.39 (5.01)
Clinical Trial participant	42.4 % (2948)	45.4 % (1092)	42.1 % (1384)	37.4 % (472)
Stage I	19.4 % (1355)	21.3 % (511)	19.5 % (639)	16.2 % (205)
Stage II	62.4 % (4353)	59.1 % (1419)	63.3 % (2078)	67.8 % (856)
Stage III	17.0 % (1185)	18.8 % (451)	16.6 % (544)	15.1 % (190)
Time from baseline to diagnosis, years	6.79 (4.09)	7.36 (4.23)	6.69 (4.06)	5.92 (3.77)
Positive ER/PR	73.0 % (5076)	71.4 % (1716)	73.3 % (2406)	75.6 % (954)
Positive HER2neu	9.8 % (678)	10.7 % (256)	9.3 % (306)	9.2 % (116)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Baseline values on outcomes				
Depressive symptoms, possible range 0–18	2.20 (2.39)	2.35 (2.54)	2.11 (2.29)	2.17 (2.32)
Depressive symptoms, median	1.20	2.00	1.00	2.00
Elevated depressive symptoms, % (n)	13.3 % (927)	15.5 % (368)	12.2 % (397)	13.1 % (162)
Quality of life				
Physical QOL, possible range 0–100	82.80 (18.42)	86.46 (16.95)	81.98 (18.47)	77.89 (19.58)
Mental QOL, possible range 0–100	79.87 (13.77)	78.64 (14.18)	80.37 (13.52)	80.91 (13.48)
Pre-cancer variables				
Physical activity	12.74 (13.50)	12.65 (13.27)	12.92 (13.72)	12.50 (12.61)
Stressful life events, possible range from 0 to 11	1.42 (1.28)	1.57 (1.36)	1.38 (1.25)	1.22 (1.11)
Sleep, possible range 0–20	6.54 (4.22)	6.26 (4.43)	6.63 (4.40)	6.85 (4.38)
Pain, possible range 0–100	73.54 (23.55)	74.61 (22.87)	72.95 (23.81)	72.96 (24.11)

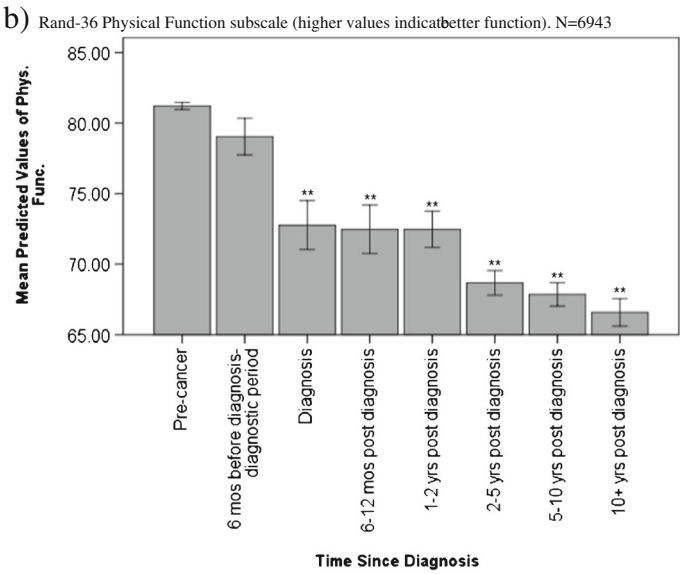
Physical activity was measured in metabolic expenditure

WHI Women's Health Initiative, *SD* standard deviation, *BMI* body mass index, *QOL* quality of Life, *ER/PR* estrogen receptor/progesterone receptor

cancer levels after the cancer diagnosis, including more than 10 years later when physical function was 2.379 points lower than pre-cancer levels (all $p<0.05$). Between diagnosis and 10 years after diagnosis, the decreases for physical function ranged from 2.077 to 3.882 points lower than pre-cancer levels on the 0–100 scale of the Rand-36.

Results are graphically displayed in Fig. 2 for continuous outcomes. The first graph shows that depressive symptoms are, on average, highest in the first few months after diagnosis, but these symptoms eventually return to pre-cancer levels. The second graph depicts a sharp decline in physical function after cancer diagnosis and physical function then levels off





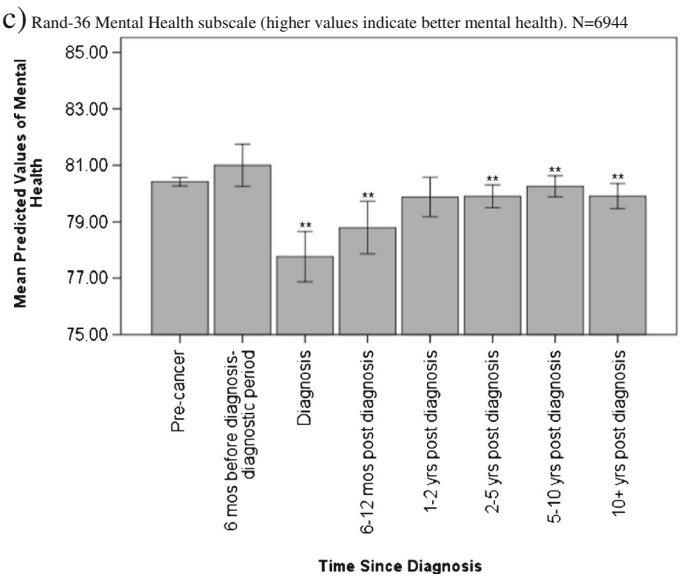


Fig. 2 Results for depressive symptoms (CESD-SF), physical function, and emotional function. Values are predicted levels from the hierarchical linear models, adjusted for age, ethnicity, education, income, cancer stage, ER/PR status, HER2neu status, study arm, and body mass index. *Error bars* indicate a 95 % confidence interval around the mean. When compared with pre-diagnosis levels, *$p<0.05$ and **$p<0.01$. **a** Natural log (ln) of depressive symptoms (higher values indicate more symptoms). On this scale, 1.61 corresponds to the 5-point cutoff of this version of the CESD-SF; $N=6948$. **b** Rand-36 Physical Function subscale (higher values indicate better function); $N=6943$. **c** Rand-36 Mental Health subscale (higher values indicate better mental health); $N=6944$

while still remaining lower than pre-cancer levels. The third graph depicts mental health, or emotional functioning, and similar to depressive symptoms, mental health worsens in the first few months after diagnosis and eventually returns to pre-cancer levels. However, unlike for depressive symptoms, the small differences in mental health 10+years after diagnosis are still significantly different from pre-cancer levels.

Pre-cancer predictors

Analyses examining the role of baseline protective and risk factors are reported in Table 2. Overall, several variables were associated with depressive symptoms, symptoms above CES-D cut-point, physical function, and mental health when entered simultaneously. However, only pain had unique effects during the first year following cancer diagnosis, indicating an interaction with the acute, post-diagnosis stress. Physical activity, stressful life events, pain, and sleep disturbance were all significantly associated with the four outcomes (all $p<0.01$) such that more physical activity, fewer life events, less pain, and less sleep disturbance were associated with fewer depressive symptoms, lower odds of being above the CES-D cut-point, better physical function, and better mental health. For example, a 1-point increase on the Rand-36 pain scale (indicating improvements in pain) predicted a 0.337 point increase on the physical function outcome (range 0–100), or a 10-point increase on the pain scale would correspond to a 3.37 increase in physical function. Age was not significantly related to depressive symptoms ($p=0.13$) but did have significant associations with physical function and mental health (both $p<0.01$) and the CES-D cut-point (OR=0.991, CI 0.983, 0.999, $p=.026$). Increasing age was related to worse physical function such that for each additional year of age, physical function declined 0.580 points, and for each additional 10 years, increase in age physical function declined 5.80 points (range 0–100). Conversely, increasing age was related to better mental health such that for each additional year of age, mental health improved 0.098 points, or for each additional 10-year increase in age, mental health improved 0.98 points (range 0–100). Having more pain before cancer predicted worse physical function in the 12 months after cancer diagnosis ($p<0.01$); no other interaction was significant.

Discussion

This study examined depressive symptoms and QOL in women from the WHI who developed incident breast cancer. Compared with pre-cancer levels, women reported more depressive symptoms and worse physical function and mental health and had higher odds of elevated depressive symptoms in the year following breast cancer diagnosis. While both depressive

Table 2 Hierarchical linear models examining protective and risk factors for depressive symptoms and quality of life in women with incident breast cancer

	Depressive symptoms $N=6935$		Physical function $N=6930$		Mental health $N=6931$	
Predictor variable	Regression coefficient (antilog of coefficient)	Standard error	Regression coefficient	Standard error	Regression coefficient	Standard error
Main effects						
Age	−0.001 (0.999)	0.001	−0.580**	0.025	0.098**	0.020
Physical activity	−0.001** (0.999)	0.0004	0.208**	0.012	0.045**	0.010
Stressful life events	0.086** (1.090)	0.005	−0.495**	0.131	−1.852**	0.106
Pain	−0.003** (0.997)	0.0003	0.337**	0.007	0.090**	0.006
Sleep disturbance	0.053** (1.054)	0.001	−0.228**	0.038	−0.660**	0.031
Interactions with 12 months after diagnosis						
Age	−0.002 (0.998)	0.003	0.018	0.071	0.048	0.053
Physical activity	−0.0002 (1.000)	0.002	0.030	0.040	−0.001	0.031
Stressful life events	−0.018 (0.982)	0.017	−0.683	0.412	−0.115	0.315
Pain	0.0003 (1.000)	0.001	−0.057*	0.024	−0.018	0.019
Sleep disturbance	−0.005 (0.995)	0.006	0.027	0.130	−0.180	0.101

Models adjusted for cancer stage, ER/PR status, HER2neu status, age, body mass index (BMI), income, education, and ethnicity. Predictors were measured more than 6 months before cancer diagnosis. Main effects indicate whether the predictor was related to the outcome overall. The interaction terms indicate whether the predictor had a unique effect during the first year after cancer diagnosis. The coefficients for depression are for the natural log-transformed values and the numbers in parentheses reflect the antilog of the coefficient reported (percent change, i.e., 0.999 reflects a 0.1 % decrease in depression for a 1-point increase in physical activity)

*$p<0.05$; **$p<0.01$

symptoms and mental health recovered between the first and second year after diagnosis, both continued to remain significantly lower after the second year following breast cancer diagnosis (although the decrease for mental health and increase for depressive symptoms were small). However, after more than 10 years after diagnosis, depressive symptoms eventually returned to pre-cancer levels. Physical function after diagnosis remained consistently lower than pre-cancer levels although these changes were small. All four pre-cancer factors examined (physical activity, stressful life events, sleep disturbance, and pain) were significantly related to depressive symptoms, physical function, and mental health over the course of the study. However, only pre-cancer pain predicted particularly low physical function in the first year following cancer diagnosis. Age was positively related to mental health, negatively related to physical function, and unrelated to depressive symptoms.

Results showing an increase in depressive symptoms and reduced QOL following breast cancer diagnosis are consistent with previous work. Studies that followed women with breast cancer from diagnosis through several years after diagnosis have found that distress tends to be highest right after diagnosis, during the first year, and then decreases [33, 34]. Previous studies on QOL have shown acceptable levels of QOL in long-term survivors of breast cancer although women may have specific areas of concern such as physical function and sexuality compared with healthy controls [35–37] and a significant minority still experience elevated distress [38]. This is consistent with our findings that depressive symptoms are elevated and QOL decreased in the first year, compared with before the cancer diagnosis. For physical function, although the predicted levels continued to be lower during all post-diagnosis periods, it is possible this was due to normal aging or other comorbid conditions and not necessarily from the cancer and cancer treatment.

While the four predictors examined were related to depressive symptoms and QOL overall, few protective and risk factors predicted even higher depressive symptoms and worse QOL in the year after breast cancer diagnosis compared with pre-cancer levels. For physical function, pain predicted worse function in the year after diagnosis. Pain likely reflects a higher burden of comorbidity or somatic symptomatology experienced by these women when diagnosed with cancer. As pain was measured before the cancer diagnosis and was probably not due to cancer, women who are diagnosed with breast cancer and have pre-cancer pain conditions may be at particular risk for decreased physical function. However, it is important to note that our physical function QOL and pain measures were both from the Rand-36 questionnaire.

The other variables may not have predicted additional distress during diagnosis and cancer treatment for several reasons. Protective and risk factors were assessed at specific time intervals across the WHI, and given that factors were often assessed years before the cancer diagnosis, these factors may have changed. Also, these factors may generally predict levels of depressive symptoms and QOL as shown in our analyses but do not confer any additional risk or protection during a high stress period, such as after a cancer diagnosis. Physical activity, stressful life events, sleep disturbance, and pain were still generally predictive of all three outcomes, suggesting that these factors still confer some protection or risk, although the risk is not modified by a cancer diagnosis.

Although this study provides a unique contribution, several limitations are noted. First, participants were assessed on different schedules, and not every woman was assessed during the year after cancer diagnosis. Due to the measure of depressive symptoms, results likely do not apply to actual psychiatric diagnoses and, as only depressive symptoms and QOL were examined, results may also not apply to other psychological constructs such as anxiety. Occurrence of psychiatric conditions and treatment were not collected in the WHI, and we were unable to account for psychiatric comorbidity or incident psychiatric diagnoses. The experience of cancer can vary widely by cancer site, and results might not generalize to other sites such as prostate and lung cancer. We were also unable to examine other important predictors of QOL and depressive symptoms such as social support. Due to the smaller number of women who had data in the year after diagnosis, we were also unable to examine interactions of predictors for depressive symptoms and QOL. As with the overall WHI, this sample was diverse, consistent with the US population in the 1990 Census. However, due to the sample size, we were unable to stratify analyses by ethnic group. The study had several strengths including a large number of breast cancer survivors from diverse race/ethnicity and age groups with assessments before their cancer diagnosis and multiple outcome variables.

Conclusions

This study provides strong evidence that women experience increased depressive symptoms and decreased QOL especially in the first year following breast cancer diagnosis compared with their reported levels before cancer. While depressive symptoms can eventually decrease to pre-cancer levels, aspects of QOL may not completely return to pre-cancer levels. Cancer survivorship support should continue to be offered during the acute diagnosis and treatment phase for women who need support. Future research should continue to identify which women are most in need of additional support after diagnosis and continued screening for distress in women with breast cancer would be warranted, particularly during the first year after diagnosis.

Acknowledgments The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of

Health and Human Services, through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C. Dr. Jones is funded by a fellowship from the National Institute on Aging (T32 AG027677).

Conflict of interest The authors do not have any conflicts of interest to report.

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