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History of Major Depressive Disorder Prospectively Predicts Worse Quality of Life in Women with Breast Cancer

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Abstract

Background—Data are scarce about whether past history of major depressive disorder in the absence of current depression places breast cancer patients at risk for worse quality of life.

Purpose—The current study prospectively examined quality of life during chemotherapy in breast cancer patients with a history of resolved major depressive disorder ($n=29$) and no history of depression ($n=144$).

Methods—Women with Stages 0–II breast cancer were assessed prior to and at the completion of chemotherapy. Major depressive disorder was assessed via structured interview and quality of life with the SF-36.

Results—Patients with past major depressive disorder displayed greater declines in physical functioning relative to patients with no history of depression ($p = 0.01$).

Conclusions—Findings suggest that breast cancer patients with a history of resolved major depressive disorder are at increased risk for declines in physical functioning during chemotherapy relative to patients with no history of depression.

Introduction

There is growing recognition that depressive symptomatology and current major depressive disorder in cancer patients are associated with a variety of negative clinical outcomes. Major depressive disorder is a more severe form of depressive symptomatology in which patients

display multiple depressive symptoms for at least 2 weeks and exhibit significant distress or impaired functioning. Depressive symptomatology after cancer diagnosis is concurrently associated with worse satisfaction with medical care and more frequent hospitalizations [1, 2]. Cancer patients with current major depressive disorder report worse quality of life than patients without major depressive disorder [3, 4], while patients with recent major depressive disorder are less likely to receive treatment consistent with consensus standards [5]. A study by Colleoni and colleagues [6] found that breast cancer patients with current major depressive disorder were less likely to receive the prescribed dosage of adjuvant chemotherapy compared to patients without current major depressive disorder (51% vs. 92%). Depressive symptomatology and major depressive disorder near the time of diagnosis may also be associated with increased risk of breast cancer-related mortality [5] and all-cause mortality [5, 7], although evidence is conflicting [8, 9].

Due to concerns about the effects of depression and distress on clinical outcomes in cancer patients, the National Comprehensive Cancer Network recommends screening for distress in cancer patients and referral to appropriate psychosocial resources for patients exhibiting high distress and/or depressive symptomatology [10]. These guidelines are intended to identify patients with undiagnosed or under-treated current major depressive disorder or other significant distress and to provide appropriate supportive care. However, these guidelines do not currently recommend screening for past history of major depressive disorder. While Andersen [11] theorized in 1993 that a past history of major depressive disorder may place cancer patients at greater risk of poor clinical outcomes, few studies have examined this hypothesis empirically. Available retrospective data suggest that a past history of major depressive disorder is associated with greater depressive symptomatology after treatment [12] and increased rates of psychiatric disorders during breast cancer recurrence [13–15]. Additional research is needed to examine the effects of past history of major depressive disorder on patient quality of life. If past history of major depressive disorder is found to be a clinically important predictor of physical and mental health outcomes, existing guidelines may need to be changed to include screening for history of depression.

To investigate this issue, the present study prospectively examined quality of life outcomes in breast cancer patients with a past history of major depressive disorder but no current diagnosis of major depressive disorder and breast cancer patients with neither past nor current major depressive disorder. It was hypothesized that patients with a past history of major depressive disorder would report greater declines in quality of life from pre- to post-chemotherapy than patients without a history of major depressive disorder (i.e., a group by time interaction) or worse quality of life regardless of time (i.e., a main effect of group).

Methods

Participant Eligibility and Recruitment

As part of a larger, IRB-approved study examining quality of life during and after breast cancer treatment, women diagnosed with Stages 0–II breast cancer were recruited at the Moffitt Cancer Center and the University of Kentucky Markey Cancer Center. Eligibility has been documented previously [16]. Eligible women were recruited and informed consent was obtained during an outpatient clinic visit before the start of chemotherapy. Patients were recruited between November 1999 and June 2006. All patients completed a baseline assessment at this time (time 1). Patients were then reassessed at the conclusion of chemotherapy (time 2).

Measures

Demographic and Clinical Data—Age, race/ethnicity, marital status, education level, annual household income, and menopausal status were assessed in all participants via self-report. Disease stage and type of breast surgery were assessed in patients via chart review. A self-report version of the Charlson Comorbidity Index was used to assess medical comorbidities at time 1 [17].

Major Depressive Disorder—Current and past history of major depressive disorder were assessed prior to chemotherapy using the Structured Clinical Interview for the DSM-IV Axis I disorders (SCID) [18]. The SCID was administered in person or via telephone by trained, doctoral-level graduate students in clinical psychology. All interviews were tape-recorded. To determine inter-rater reliability, a second, independent rater listened to and scored a subset of 20 randomly selected interviews. The kappa coefficient for diagnosis of a DSM-IV axis I disorder for the two sets of ratings was 0.76.

Depressive Symptomatology—The Center for Epidemiological Studies–Depression Scale (CES-D) [19] was used to assess depressive symptomatology pre- and post-chemotherapy. The CES-D is a 20-item measure in which higher scores indicate greater depressive symptomatology. The validity of the CES-D has been demonstrated with a wide range of populations, including cancer patients [20, 21]. A score higher than 16 indicates clinically significant depression [19].

Quality of Life—The Medical Outcomes Study Short Form (SF-36) is a well-validated 36-item questionnaire [22]. It was used to assess self-reported health-related quality of life pre- and post-chemotherapy. The SF-36 is composed of a physical component score and mental component score as well as eight subscales: physical functioning (i.e., health limitations on physical activities), role physical (i.e., effect of physical functioning on work or daily activities), bodily pain (i.e., pain severity and limitations), general health (i.e., perceived overall health), vitality (i.e., lack of fatigue), social functioning (i.e., ability to carry out normal social activities), role emotional (i.e., effect of emotional functioning on work or daily activities), and mental health (i.e., frequency of positive affective states) [23]. Higher scores reflect better quality of life. The eight subscales were used in analyses rather than the component scores to provide a more nuanced examination of the relationship between past history of major depressive disorder and quality of life.

Statistical Analyses

Study participants were included in the present analyses if they did not meet criteria for current major depressive disorder at time 1. Patients with and without a past history of major depressive disorder were compared on demographic and clinical variables (i.e., age, race, menopausal status, marital status, education, household income, cancer stage, surgery type, chemotherapy regimen, comorbidities, days between study assessments). Group differences significant at $p < 0.10$ were controlled in later analyses. Repeated measures ANOVAs were used to examine the effects of past history of major depressive disorder on quality of life. To reduce the possibility of Type I error, the criterion for statistical significance for repeated measures ANOVAs was set at $p < 0.01$. For SF-36 subscales in which the group by time interaction was significant (i.e., $p < 0.01$), hierarchical linear regression analyses were performed in accordance with procedures set forth by Baron and Kenny [24] and MacKinnon [25] to examine whether change in depressive symptomatology over time mediated the effects of past history of major depressive disorder on change in quality of life. Sobel tests were used to test for the significance of indirect effects [26]. The criterion for statistical significance for Sobel tests was set at $p < 0.05$, as quality of life outcomes

selected for mediation analyses had already demonstrated a highly statistically significant relationship with past history of major depressive disorder.

Results

Preliminary Analyses

Two hundred forty-two patients undergoing chemotherapy agreed to participate. Following informed consent, 14 (6%) participants became ineligible due to change in treatment plans or the decision to pursue treatment elsewhere, 25 (10%) elected to discontinue participation before completing the post-chemotherapy assessment, 18 (7%) were dropped from analyses because they had a current diagnosis of major depressive disorder, and 12 (5%) were excluded because they did not provide data on key variables. Patients who completed the study were more likely to be married and have an annual household income greater than \$40,000 compared to patients who did not complete the study ($p < 0.05$). There were no other significant differences between patients who did complete the study versus those who did not.

Participants were 173 women with stages 0–II breast cancer; 29 participants (17%) met criteria for a diagnosis of past history of major depressive disorder at baseline and 144 (83%) did not. The mean number of days between assessments was 103 (range 50–217). Sample demographic and clinical characteristics are presented in Table 1; there were no differences in these variables between patients with and without a past history of major depressive disorder, with the exception of marital status and comorbidities. As such, marital status and comorbidities were entered as control variables in repeated measures ANOVAs and mediation analyses. Number of days between assessments was also entered as control variables to examine the effects of past history of major depressive disorder on quality of life independent of length of chemotherapy treatment and toxicity-related treatment delays.

Effects of Past History of Major Depressive Disorder and Time on SF-36 Subscale Scores

Adjusted means and analyses examining past history of major depressive disorder on SF-36 subscale scores are shown in Table 2. A significant past history of major depressive disorder by time interaction was found for the physical functioning subscale ($p < 0.01$), such that patients with a past history of major depressive disorder displayed greater declines in physical functioning than patients without a past history of major depressive disorder. Among the remaining subscales for which no interaction effects were observed, significant main effects for past history of major depressive disorder were evident for role physical and mental health ($p < 0.01$). Additional analyses indicated that at the pre-chemotherapy assessment, there were no differences in quality of life subscales between patients with and without a past history of major depressive disorder ($p > 0.01$). At the post-chemotherapy assessment, patients with a past history of major depressive disorder displayed worse quality of life on the physical functioning, role physical, bodily pain, general health, vitality, social functioning, and mental health subscales ($p < 0.01$).

Mediating Role of Changes in Depressive Symptomatology

Repeated measures ANOVAs were conducted to determine if there was an interaction between past history of major depressive disorder and time for CES-D scores. As seen in Table 2, a significant interaction effect was observed such that patients with past history of major depressive disorder showed greater increases in depressive symptomatology from pre- to post-chemotherapy ($p = 0.01$). Consequently, change in depressive symptoms from baseline to the end of chemotherapy was examined as a mediator of the relationship between past history of major depressive disorder and change in quality of life for SF-36 scales for which group by time interactions were statistically significant (i.e., physical functioning).

Change in depressive symptomatology mediated the relationship between past history of major depressive disorder and changes in physical functioning (Sobel=-2.32, $p=0.02$).

Discussion

The present study prospectively examined quality of life in 173 women with early-stage breast cancer who did not have a current diagnosis of major depressive disorder at the start of chemotherapy treatment. It was hypothesized that patients with a past history of major depressive disorder would report worse quality of life than patients without a history of major depressive disorder (i.e., a main effect of group), as well as greater declines in quality of life from pre- to post-chemotherapy (i.e., a group by time interaction). A group effect was found for the SF-36 role physical and mental health subscales. In addition, an interaction was found for the physical functioning subscale. In other words, not only did patients with a past history of major depressive disorder display worse role functioning due to physical limitations and worse mental health than patients without a history of major depressive disorder, they displayed greater declines in physical functioning from pre- to post-chemotherapy.

Existing National Comprehensive Cancer Network guidelines for distress management recommend that all cancer patients be screened for current distress prior to initial treatment and at regular intervals thereafter [10]. Screening in this manner might fail to identify patients with a past history of major depressive disorder but no current diagnosis of major depressive disorder. Findings from the current study demonstrate how it is important to screen breast cancer patients for a past history of major depressive disorder prior to treatment because these patients show increased depressive symptomatology and deterioration in quality of life during chemotherapy. Screening could be conducted using two items from the past major depressive disorder module of the SCID [18], “Have you ever had a period in your life when you felt depressed or down most of the day, nearly every day for two weeks or more” and “Has there ever been a time in your life when you lost interest or pleasure in the things you usually enjoyed, for two weeks or longer.” These items could be administered quickly as part of a routine medical intake evaluation for new patients. Patients responding yes to either of these questions could then be referred to psychosocial services for additional follow-up. Alternately, a more detailed screening measure for depression could be used [27]. It could be argued that greater depressive symptomatology and worse quality of life at the conclusion of chemotherapy could be captured by repeated screening for current distress as suggested by NCCN guidelines. Nevertheless, use of this approach would result in a missed opportunity for early intervention to prevent or reduce decrements in quality of life over the course of chemotherapy.

An important question when considering intervention is the mechanism(s) by which past history of major depressive disorder could contribute to worse quality of life. To this end, the current study examined change in depressive symptoms from pre- to post-chemotherapy as a mediator of the relationship between past history of major depressive disorder and changes in physical functioning. Findings indicate that increases in depressive symptoms mediated the relationship between past history of major depressive disorder and changes in SF-36 physical functioning. Relative to patients with no history of major depressive disorder, patients with a past history of major depressive disorder experienced larger decreases in physical functioning from pre- to post-chemotherapy that corresponded with larger increases in depressive symptoms during the same time period. These findings are consistent with research in non-cancer populations suggesting that a past history of major depressive disorder places individuals at risk for poor mental and physical health [28–30]. These findings are also consistent with the kindling hypothesis [31, 32], which suggests that an initial episode of depression may alter brain structure and function to become more

sensitized to subsequent life stress [31, 32], resulting in a greater likelihood of future depressive symptomatology. The kindling hypothesis argues for early intervention to prevent multiple recurrences of depression. A large body of existing research indicates that pharmacologic and behavioral interventions are effective in reducing depressive symptomatology in cancer patients [33–36]. Consequently, there are multiple effective supportive care options available for breast cancer patients with a past history of major depressive disorder.

Several study limitations should be noted. First, this study focused on quality of life in the period during chemotherapy treatment; as a result, it is not clear whether past history of major depressive disorder is also a predictor of longer term quality of life in breast cancer patients. Second, study participants were likely to be Caucasian, married, and have an annual household income greater than \$40,000. It is not known, therefore, whether findings are generalizable to a more diverse sample of breast cancer patients. Third, because the current study focuses on women receiving surgery and chemotherapy for breast cancer, it is unknown whether findings hold true for patients diagnosed with other types of cancer or undergoing other types of treatment. Women who undergo chemotherapy for breast cancer tend to be younger on average than women who undergo radiotherapy only; thus, our findings may not generalize to older breast cancer patients. Additional research will be needed to validate these findings in other cancer populations and extend them to the post-treatment period. In addition, we did not measure anxiety nor medical, financial, social, and other stressors that may have differentially impacted depressive symptoms and quality of life in women with and without a past history of major depressive disorder.

In summary, existing guidelines that recommend screening for current distress early in the treatment process may miss a subgroup of breast cancer patients who have a past history of major depressive disorder but do not meet criteria for current major depressive disorder. Findings from the current study suggests that these patients are at risk for worse quality of life at both the beginning and end of chemotherapy, as well as greater declines in certain aspects of quality of life over the course of treatment. Patients with a past history of major depressive disorder appear to be more likely to develop greater depressive symptoms during treatment, which, in turn, predict greater declines in physical functioning. Consequently, these patients may benefit from a proactive approach to management of depressive symptoms during the treatment process.

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Table 1

Sociodemographic and clinical comparisons between patients with and without previous major depressive disorder

	Full sample (n=173)	Past history of MDD (N=29)	No history of MDD (n=144)	Statistics
Site of recruitment				$\chi^2=0.11$
University of Kentucky	46 (27%)	7 (24%)	39 (27%)	
Moffitt Cancer Center	127 (73%)	22 (76%)	105 (73%)	
Age: M(SD)	50.95 (9.69)	50.45 (7.39)	51.06 (10.11)	$t=0.38$
Race: Caucasian	154 (89%)	27 (93%)	127 (88%)	$\chi^2=0.60$
Marital status: married	136 (79%)	16 (55%)	120 (83%)	$\chi^2=11.39^{**}$
Education: college graduate	77 (45%)	12 (41%)	65 (45%)	$\chi^2=0.16$
Annual household income: greater than \$40,000	122 (71%)	17 (59%)	105 (73%)	$\chi^2=1.64$
Menopausal status: postmenopausal	98 (57%)	15 (52%)	83 (58%)	$\chi^2=0.23$
Stage of disease				$\chi^2=0.75$
Stage 0	3 (2%)	0 (0%)	3 (2%)	
Stage I	47 (27%)	8 (28%)	39 (27%)	
Stage II	123 (71%)	21 (72%)	102 (71%)	
Surgery: mastectomy	47 (27%)	8 (28%)	39 (27%)	$\chi^2=0.06$
Chemotherapy regimen				$\chi^2=0.15$
Doxorubicin, cyclophosphamide	94 (54%)	15 (52%)	79 (55%)	
Doxorubicin, cyclophosphamide, taxotere	15 (9%)	3 (10%)	12 (8%)	
Doxorubicin, cyclophosphamide, paclitaxel	38 (22%)	9 (31%)	29 (20%)	
Cyclophosphamide, methotrexate, 5FU	13 (8%)	0 (0%)	13 (9%)	
Doxorubicin, taxotere	2 (1%)	0 (0%)	2 (1%)	
Cyclophosphamide, epirubicin, 5FU	5 (3%)	2 (7%)	3 (2%)	
Cyclophosphamide, epirubicin, 5FU, paclitaxel	2 (1%)	0 (0%)	2 (1%)	
Cyclophosphamide, epirubicin, 5FU, taxotere	2 (1%)	0 (0%)	2 (1%)	
Charlson Comorbidity Index score: M(SD) ^a	2.35 (.91)	2.11 (.32)	2.39 (.99)	$t=2.68^{**}$
Days between assessments ^b	103.59 (42.85)	112.66 (47.74)	101.76 (41.72)	$t=-1.25$

Statistics refers to comparisons between patients with and without a past history of Major Depressive Disorder. Statistics for chemotherapy regimen refers to doxorubicin and cyclophosphamide vs. other

MDD Major depressive disorder

^aFourteen patients had missing comorbidity data

^bOne patient had missing date of assessment data

* $p < 0.05$;

** $p < 0.01$

Table 2

Adjusted means and standard errors of measures of quality of life and depressive symptomatology and repeated measures ANCOVA in patients with and without a past history of major depressive disorders

	Baseline		End of chemotherapy		Group F		Time F		Group * Time F	
	No history of MDD	Past history of MDD	No history of MDD	Past history of MDD	No history of MDD	Past history of MDD	No history of MDD	Past history of MDD	No history of MDD	Past history of MDD
SF-36 Physical functioning subscale	74.15 (1.88)	70.55 (4.35)	65.80 (2.12)	49.67 (4.89)	4.71 *	3.11	6.97 **	0.05		
SF-36 Role physical subscale	56.08 (3.66)	34.78 (8.43)	38.93 (3.41)	15.24 (7.88)	9.22 **	13.71				
SF-36 Bodily pain subscale	72.74 (2.02)	65.86 (4.66)	73.33 (2.14)	59.52 (4.95)	5.39 *	2.53	1.41			
SF-36 General health subscale	72.39 (1.37)	67.48 (3.16)	70.32 (1.59)	58.97 (3.67)	5.60 *	4.53 *	3.98 *			
SF-36 Vitality subscale	58.14 (1.91)	52.94 (4.41)	44.20 (2.16)	28.12 (4.98)	5.71 *	4.34	4.02 *			
SF-36 Social functioning subscale	77.37 (2.20)	74.06 (5.08)	69.69 (2.22)	54.18 (5.13)	4.37 *	1.64	3.16			
SF-36 Role emotional subscale	79.12 (3.15)	61.34 (7.26)	71.59 (3.53)	61.14 (8.13)	4.58 *	0.59	0.45			
SF-36 Mental health subscale	77.57 (1.43)	70.27 (3.30)	79.84 (1.38)	64.63 (3.17)	13.66 **	2.19	4.33 *			
CES-D depressive symptoms	11.38 (.75)	13.55 (1.73)	11.38 (.76)	18.90 (1.75)	9.01 **	0.65	6.33 **			

Values adjusted for marital status, comorbidities, and days between assessments

SF-36 Medical Outcomes Study Short Form, CES-D Center for Epidemiological Studies-Depression, MDD major depressive disorder

* $p < 0.05$;

** $p < 0.01$