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EPIDEMIOLOGY

Depressive episodes, symptoms, and trajectories in women recently diagnosed with breast cancer

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Abstract Depression carries serious psychosocial, physical, and economic consequences for cancer survivors. Study goals were to characterize patterns and predictors of depressive symptoms and major depressive episodes in recently diagnosed breast cancer patients. Consecutively recruited women ($N = 460$) completed a validated interview (CIDI) and questionnaire measure (CES-D) of depression within 4 months after invasive breast cancer diagnosis and at six additional assessments across 12 months. Outcomes were major depressive episodes, continuous symptom scores, and latent symptom trajectory classes. Across 12 months, 16.6 % of women met criteria for a major depressive episode. Unemployment predicted depressive episodes after other correlates were controlled. Distinct trajectory classes were apparent: an estimated 38 % of women had chronically elevated symptoms (High trajectory), 20 % recovered from elevated symptoms (Recovery), and 43 % had lower symptoms (Low and Very Low trajectories). Although 96 % of episodes occurred in the High or Recovery classes, 66 % of women in the High trajectory did not have an episode. Women in the Low (vs High) trajectory were more likely to be older, retired, more affluent, and have fewer comorbid diseases and briefer oncologic treatment. Women in the Recovery trajectory (vs High) were more likely to be married and more affluent and have fewer comorbid diseases. Assuming available therapeutic resources, assessment of both depressive symptoms and episodes over several months after diagnosis is important. Identification of patients at risk for persistently high depressive symptoms (e.g., younger, longer treatment course) opens targeted opportunities to prevent and promote rapid recovery from depression.

Keywords Breast cancer · Depression · Survivorship · Trajectory

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Although transient depressed mood constitutes an expected result of the cancer experience, prolonged or severe depressive symptoms confer risk for profound psychosocial, physical, and economic impact. Depression in cancer survivors not only is painful in itself, but also delays return to work [1], predicts lower adherence to medical regimens and engagement in health-promoting behaviors [2–4], and prompts higher healthcare utilization and costs, as well as depression-associated hospitalizations [5, 6]. The risk of suicide is elevated in cancer survivors versus the general population [7, 8]. Depression also may confer risk for

mortality in cancer [9–11], a relationship for which plausible biological mediators exist [12]. In particular, unremitting (vs transient) depressive symptoms predict lower survival from chronic diseases, including cancer [13–15].

Potentially meaningful differences in the contributors to and consequences of depressive symptoms as a function of their intensity and duration render it essential to study depression over time in cancer patients and to identify predictive factors. Accordingly, a goal of this research was to characterize major depressive episodes and symptoms in a sample of women with breast cancer during the first 16 months after diagnosis. A second goal was to identify sociodemographic and medical markers of risk for the three primary endpoints: depressive episodes, depressive symptoms, and symptom trajectories.

Prospective studies demonstrate that depressive symptoms increase after a breast cancer diagnosis, with the highest burden during the first 6 months relative to prediagnosis levels [16]. A meta-analysis of interview-diagnosed major depression in cancer survivors in non-palliative care settings demonstrated a 16.3 % point prevalence of major depression (95 % CI 13.4–19.5; 14.1 % in breast cancer patients) [17]. Research documenting trajectories of depressive symptoms after diagnosis suggests that a minority has persistently high depressive symptoms, another group recovers from elevated symptoms over the first several months, and a sizeable proportion of cancer patients report low depressive symptoms from the point of cancer diagnosis onward [18–20]. Elevated distress during the re-entry phase after treatment completion can occur in a minority of cancer survivors [18, 21].

Relatively few studies involve assessment of depression at multiple points with both validated diagnostic interview and questionnaire methods, which is a primary goal of this study. Moreover, the concordance of major depressive episodes and symptom trajectories is unexplored and is important in its potential to reveal whether each characterization offers distinct information regarding survivors at risk. In addition to hypothesizing elevated symptoms and depressive episodes in women with recently diagnosed breast cancer relative to the comparable general population, we anticipated considerable overlap between the presence of depressive episodes and trajectory classes reflecting chronically high or recovering symptom trajectories. We explored whether the two approaches yielded unique information of potential clinical value.

Early identification of vulnerable cancer survivors is vitally important for preventive and intervention efforts. Accordingly, another goal was to examine the associated sociodemographic and medical factors that can be easily and routinely assessed in the oncologic setting. We hypothesized that younger age [18, 19, 22–26] and markers of socioeconomic disadvantage [18, 19, 23, 24, 26] would be associated with depression endpoints and explored other sociodemographic and medical factors [18–20, 23, 24, 27].

Patients and method

Patients

Participants were 460 women diagnosed with invasive breast cancer during the prior 4 months at three oncology clinics in the greater Los Angeles area and at the University of Arizona Cancer Center (Tucson). Of 823 women approached ($n = 406$ Arizona, $n = 417$ California), 61 were ineligible upon screening (8 %; $n = 46$ Arizona, $n = 17$ California). Of the 762 eligible women, 302 (40 %; $n = 198$ Arizona, $n = 104$ California) declined or were unreachable by telephone, and 460 (60 %; $n = 163$ Arizona, $n = 297$ California) consented and took part in the study entry assessment. Of the 460 participants, 428, 420, 411, and 411 completed assessments at Week 6, 12, 18, and 24, respectively. At 9 and 12 months, 390 and 372 completed assessments, respectively, yielding 81 % retention at 12 months.

Procedures

The University of California, Los Angeles, and University of Arizona institutional review boards approved research procedures. Research or clinic staff identified consecutive (within scheduling constraints), potentially eligible patients via medical records. Research staff introduced the study in person as designed to examine "women's emotional and physical experiences during and after treatment for breast cancer." Eligibility criteria were as follows: new diagnosis or first recurrence/second primary of invasive breast cancer (Stage 1–4), study entry session within 4 months following cancer diagnosis, and English literacy. Any standard medical treatment for cancer was allowed, as was additional medication. Exclusion criteria were as follows: younger than 21 years and current or past bipolar disorder, schizophrenia, and schizoaffective or neurocognitive disorder (e.g., dementia).

Study entry and 9-month in-person assessments

The first assessment, lasting approximately 3 h, was completed in a private room at the treating clinic or women's homes by post-baccalaureate research staff. After providing informed consent, participants completed self-report measures (and additional assessments not included here) via interview or computer-aided as facilitated by staff

(based on preference). The 1-h, 9-month assessment used the same procedure.

Telephone assessments

Frequent assessments were conducted to ensure documentation of major depressive episodes during the intensive medical treatment phase. Every 6 weeks for 6 months after study entry, as well as at 12 months, participants completed a 30-min phone assessment. Women received $60 compensation for in-person and $30 for phone assessments.

Measures

Sociodemographic and medical variables

Age, marital status, race/ethnicity, education, employment, yearly family income, subjective social status [28], number of comorbid physical diseases [29], and study recruitment site were self-reported at study entry.

Cancer stage, primary or recurrent diagnosis, and diagnosis date were obtained via medical record review, supplemented by self-report when the record was unavailable ($n = 39$). Other self-reported variables (confirmed through medical records) at each assessment were surgery, chemotherapy, radiotherapy, endocrine therapy, Herceptin, and oncologic treatment duration (the assessment point at which primary oncologic treatments were completed).

At each assessment, self-reported receipt of psychological or pharmacologic (confirmed through medical records) treatment of depression was assessed. Treatment was coded for minimal adequacy from evidence-based guidelines of receiving $\geq$2 months of an appropriate medication or $\geq$8 visits with a mental health professional averaging $\geq$30 min each [30].

Major depressive episodes and symptoms

At all assessments, trained and supervised research staff administered modules of the structured, computer-guided Composite International Diagnostic Interview (CIDI) [31, 32] to assess major depressive episodes, a primary endpoint. Two authors (ALS and KLW) reviewed CIDI data to ensure that any episode did not reflect solely the neurovegetative symptoms that can accompany cancer treatments [33].

At all assessments, participants completed the Center for Epidemiologic Studies-Depression scale (CES-D) [34]. The two major endpoints were continuously scored CES-D depressive symptoms and CES-D symptom trajectory classes. CES-D scores $\geq$16, the clinically suggestive threshold [35], also are reported.

Data analysis

Descriptive statistics were calculated on all variables. We examined variables related to missing data using a structural equation modeling framework in which the two outcomes were study dropout (months after diagnosis when dropout occurred), using a Cox proportional hazards model [36], and intermittent missingness, using an intercept-only logistic latent growth model.

Based on research on symptom trajectories in breast cancer patients [21, 37] and model complexity, we tested one- to five-class CES-D symptom trajectories using finite Gaussian mixture models [38] with latent growth curve modeling [39], using continuous months since cancer diagnosis and allowing for random linear and quadratic time trends. Each woman was assigned to one class based on highest individual probabilities.

Sociodemographic and medical variables were assessed as correlates of major depressive episodes (using logistic regression), continuous CES-D symptoms (using multilevel structural equation modeling), and CES-D depressive symptom trajectory classes (using multinomial logistic regression). Each correlate was entered individually and multivariately with all others.

Data were analyzed using R v. 3.1.3 [40] and Mplus v. 7.3 [41] via MplusAutomation v. 0.6-3 [42]. Full-information maximum likelihood was used to address missing data in all models [43]. The robust maximum likelihood estimator was used to provide model fit and standard errors robust to non-normality, and Chi-square difference tests (e.g., for evaluating the overall significance of a variable in the multinomial models for trajectory class) used the scaling correction factor [44].

Results

Sample characteristics

Table 1 contains sociodemographic and medical characteristics. Most women were college educated, married/living as married, and employed. Most had early-stage breast cancer and surgery, chemotherapy, and endocrine therapy during the study.

Missing data and study dropout

Of 460 participants, 63 (13.7 %) had intermittent missing data and 88 (19 %; $n = 9$ deaths) dropped out of the 12-month assessment. Missingness and dropout were not related significantly to major depressive episodes or CES-D symptoms. Higher rates of intermittent missing data were associated significantly with higher income and California

Table 1 Demographic and medical characteristics of recently diagnosed breast cancer patients ($N = 460$)

Characteristic	*n* (%)
Age, mean (SD; range) years	56.4 (12.6; 23–91)
Ethnicity	
Asian	24 (5.2)
Black/African American	10 (2.2)
Latina	89 (19.3)
Mixed race/ethnicity	8 (1.7)
Native American/Alaska Native	12 (2.6)
Native Hawaiian/Pacific Islander	3 (0.7)
Unreported	3 (0.7)
White/European American	311 (67.6)
Marital status	
Married/living as married	305 (67.0)
Single	42 (9.2)
Divorced/separated	72 (15.9)
Widowed	36 (7.9)
Income[a]	
<$50,000	124 (28.5)
$50,000–$74,999	97 (22.3)
$75,000–$100,000	57 (13.1)
>$100,000	157 (36.1)
Education[a]	
<High school	18 (4.0)
High school	96 (21.1)
Two-year college	91 (20.0)
College graduate	164 (36.1)
Master's degree	62 (13.7)
Ph.D., M.D., other professional terminal degree	23 (5.1)
Employment status	
Employed	236 (52.1)
Retired	134 (29.6)
Unemployed	83 (18.3)
Subjective SES, mean (SD)	6.98 (1.56)
Recruitment site	
Arizona	163 (35.4)
California	297 (64.6)
Number of comorbidities, mean (SD)	1.8 (1.9)
Cancer stage	
1	204 (44.4)
2	178 (38.8)
3	52 (11.3)
4	25 (5.4)
Cancer status	
Primary non-metastatic	387 (84.3)
Recurrence/2nd primary	47 (10.2)
Primary metastatic	14 (3.1)
Metastatic recurrence	11 (2.4)
Months since diagnosis at study entry, mean (SD)	2.1 (0.8)
Oncologic treatment duration, mean (SD)[b]	3.5 (2.0)

Table 1 continued

Characteristic	*n* (%)
Oncologic treatments received	
Chemotherapy	242 (53.0)
Radiation therapy	170 (37.2)
Surgery	414 (90.6)
Herceptin	128 (28.0)
Aromatase inhibitor/endocrine antagonist	293 (64.1)

SES Socioeconomic status

[a] For analysis, variables coded numerically starting from zero (total yearly income and years of education, respectively)

[b] Assessment interval (1–7) at which major oncologic treatments (surgery, chemotherapy, radiation) ended. Mean of 3.5 (2.0) = 6.38 ± 3.78 months after diagnosis

Table 2 Cross-classification of major depressive episode and CES-D symptom trajectory class with depression treatment and time since breast cancer diagnosis

	Major depressive episode		CES-D trajectory class			
			Very Low	Low	Recovery	High
		No	48 (100.0 %)	142 (97.9 %)	76 (84.4 %)	115 (66.1 %)
		Yes	0 (0.0 %)	3 (2.1 %)	14 (15.6 %)	59 (33.9 %)
Depression Treatment No. (%)	No	Yes				
Adequate	45 (11.8 %)	26 (34.2 %)	0 (0.0 %)	20 (13.8 %)	6 (6.7 %)	45 (25.9 %)
Inadequate/Indeterminate	47 (12.3 %)	16 (21.1 %)	3 (6.2 %)	8 (5.5 %)	18 (20.0 %)	34 (19.5 %)
None	290 (75.9 %)	34 (44.7 %)	45 (93.8 %)	117 (80.7 %)	66 (73.3 %)	95 (54.6 %)

Months since diagnosis	Major depressive episode	CES-D mean (SD)	CES-D ≥ 16[a]
0 to <3	20 (4.4 %)	12.55 (10.34)	134 (33.0 %)
≥3 to <6	21 (4.9 %)	11.99 (9.92)	169 (38.5 %)
≥6 to <9	20 (5.1 %)	10.23 (9.47)	122 (29.2 %)
≥9 to <12	10 (2.8 %)	8.15 (9.43)	56 (17.6 %)
≥12 to last assessment[b]	5 (1.6 %)	7.25 (8.43)	59 (15.6 %)
Total unique cases across time	76 (16.6 %)	–	260 (56.5 %)

Results are number (percentage) unless otherwise noted. For cross-classification, percentages are for columns. For depression over time, percentages are for number with a depressive episode or CES-D ≥ 16 versus not. *CES-D* Center for Epidemiologic Studies-Depression scale

[a] Scores ≥16 on the CES-D are suggestive of clinically relevant depressive symptoms (35)

[b] Last assessment ranged from 12 to 19 months since diagnosis, with a mean of 14.1 months

recruitment (vs Arizona) (see online supplement). More advanced cancer and California recruitment predicted earlier study dropout (see online supplement). Study dropout also was related significantly to cancer treatment variables, but interpretation is complicated by the fact that women who dropped out earlier necessarily had a shorter follow-up period and were thus less likely to be observed to have a specific treatment or long-duration treatment.

Characterization of depressive episodes, symptoms, and trajectories

Table 2 displays major depressive episodes and mean CES-D total scores in three-month intervals. Across the study period, 16.6 % of women met CIDI criteria for a major depressive episode, and 56.5 % met the CES-D cutoff of 16. Depressive symptom elevation and episodes were most likely to occur within 9 months of diagnosis. The estimated overall mean of CES-D scores indicates declining depressive symptoms over the 16 months (Fig. 1).

We selected the final four-class CES-D symptom trajectory model (Table 3) based on the best fit indices from the one- to four-class latent growth curve modeling solutions (five-class solution was unstable), yielding High, Recovery, Low, and Very Low depressive symptom trajectory classes. Entropy was acceptable (0.81), indicating that women could be classified into one specific class with

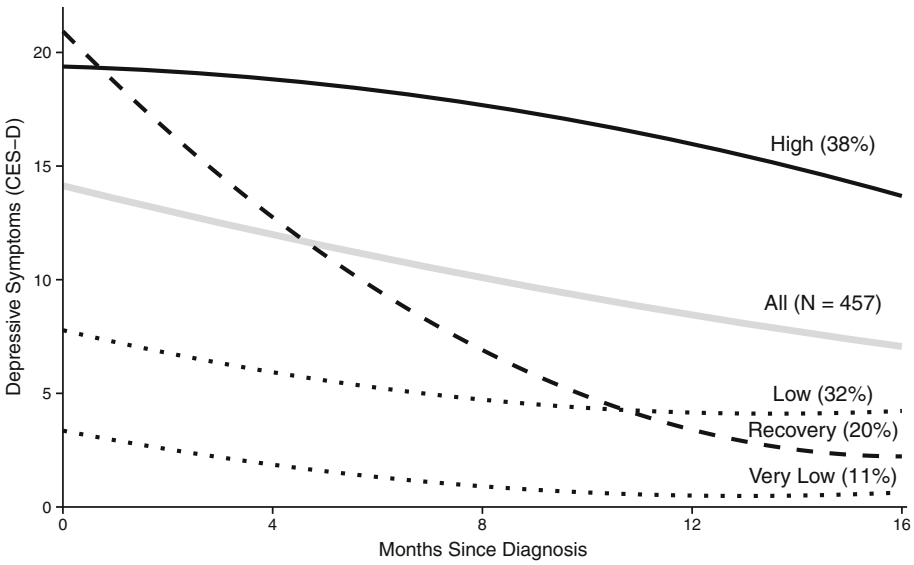

Fig. 1 Depressive symptom trajectories: overall mean CES-D trajectory and mean CES-D trajectories of the four classes identified through latent growth mixture modeling

Table 3 Fit indices from latent growth mixture models to identify depressive symptom (CES-D) trajectory classes

	1 Class	2 Class	3 Class	4 Class
Parameters	16	33	50	67
LL	−9641.23	−9144.75	−8989.19	−8915.16
AIC	19,314.46	18,355.49	18,078.39	17,964.32
BIC	19,380.46	18,491.61	18,284.62	18,240.68
aBIC	19,329.68	18,386.88	18,125.94	18,028.04
AICC	19,315.7	18,360.8	18,090.95	17,987.75
Entropy	1.00	0.86	0.87	0.81

$N = 457$ for all models. *CES-D* Center for Epidemiologic Studies-Depression Scale, *LL* log likelihood, *AIC* Akaike Information Criterion, *BIC* Bayesian information criterion, *aBIC* adjusted Bayesian information criterion, *AICC* Akaike Information Criterion with sample size correction

high probability. Mean trajectories and the proportion of women in each class are shown in Fig. 1.

Table 2 cross-classifies participants on major depressive episodes and CES-D trajectories. Depressive episodes occurred almost solely in the High or Recovery trajectory classes (96 % of 76 episodes), with rates of 34 %, 16 %, 2 %, and 0 depressive episodes in the High, Recovery, Low, and Very Low trajectory classes, respectively. However, 66 % of the estimated membership of the High trajectory class did not have a major depressive episode.

Sociodemographic and medical correlates of depression

Table 4 displays correlates of major depressive episodes and CES-D symptoms. Table 5 displays correlates of CES-D trajectory classes. As hypothesized, socioeconomic disadvantage and younger age were consistently associated with less favorable outcomes as indicated by higher likelihood of a major depressive episode (except younger age), higher depressive symptoms, and less favorable depressive symptom trajectories. Within socioeconomic indicators, retirement or higher perceived socioeconomic status was associated with more favorable status on the three endpoints, and unemployment (versus employment) was associated significantly with major depressive episodes and continuous CES-D. Being married or living as married also indicated advantage on the three outcomes, as did being recruited in Arizona. Being Latina (versus other ethnicity/race) evidenced largely non-significant relations with depression indicators.

Regarding medical factors, less favorable CES-D symptom trajectories occurred with more comorbid diseases. CES-D depressive symptoms and less favorable trajectory class increased with cancer stage. With regard to major depression (see online supplement), no woman with metastatic cancer ($n = 25$), either primary or recurrent, had an episode. Women with primary non-metastatic cancer had the highest likelihood of major depressive episodes (18.7 %; 72/385), followed by local recurrence/second primary (8.5 %; 4/47).

Longer oncologic treatment duration was related to higher depression on the three endpoints. Patterns for the specific cancer treatments were more complex. Having surgery or chemotherapy shortly after diagnosis was associated with lower CES-D scores, but a slower CES-D decline across time. Having radiation therapy early was associated with a faster decline in CES-D. Having endocrine therapy early was associated with lower CES-D.

Women who had a depressive episode were more likely to receive adequate (OR = 4.93, $P < 0.001$) or inadequate/

Table 4 Univariate associations of demographic and medical covariates with major depressive episodes (MDE) and continuous CES-D depressive symptoms

Covariate	Odds ratio for MDE	Univariate coefficients in mixed models of CES-D depressive symptoms		
		Intercept	Linear slope	Quadratic slope
Age (in years)	0.99 [0.97, 1.00]	−0.22*** [-0.32, −0.12]	0.01 [−0.01, 0.04]	0.00 [−0.00, 0.00]
Latina (ref = non-Latina)	1.18 [0.64, 2.16]	2.27 [−1.05, 5.59]	−0.33 [−1.15, 0.49]	0.02 [−0.03, 0.06]
Married (ref = non-married)	0.56* [0.33, 0.93]	**−3.75* [−6.68, −0.83]**	0.29 [−0.38, 0.96]	−0.02 [−0.05, 0.02]
Income	0.92 [0.75, 1.13]	0.34 [−0.71, 1.40]	**−0.18 [−0.42, 0.06]**	**0.01 [−0.00, 0.02]**
Education	0.99 [0.82, 1.20]	−0.34 [−1.39, 0.70]	0.10 [−0.14, 0.33]	−0.00 [−0.02, 0.01]
Employment (ref = employed)				
Retired	0.54 [0.28, 1.05]	**−6.44*** [−9.10, −3.78]**	0.61 [−0.02, 1.24]	−0.02 [−0.06, 0.01]
Unemployed	**1.93* [1.07, 3.48]**	**4.43* [0.68, 8.17]**	−0.02 [−0.86, 0.82]	−0.01 [−0.05, 0.04]
Subjective SES	0.80** [0.67, 0.95]	−1.32** [−2.26, -0.39]	0.01 [−0.20, 0.23]	0.00 [−0.01, 0.01]
Cancer stage	0.85 [0.64, 1.11]	1.64* [0.16, 3.11]	−0.20 [−0.54, 0.13]	**0.01 [−0.01, 0.03]**
Oncologic treatment duration[a]	1.19** [1.04, 1.35]	0.88** [0.26, 1.50]	0.02 [−0.12, 0.16]	−0.00 [−0.01, 0.00]
Surgery	1.57 [0.60, 4.14]	−2.78* [−4.93, −0.63]	**1.04** [0.34, 1.75]**	−0.06* [−0.10, −0.01]
Chemotherapy	1.27 [0.77, 2.09]	**−1.74 [−4.36, 0.88]**	**1.02* [0.14, 1.89]**	**−0.07* [−0.12, −0.01]**
Radiation therapy	0.92 [0.55, 1.53]	1.95 [−1.59, 5.49]	**−1.21* [−2.25, −0.16]**	**0.10** [0.03, 0.18]**
Herceptin	0.98 [0.56, 1.70]	0.10 [−2.61, 2.81]	0.39 [−0.32, 1.09]	−0.03 [−0.07, 0.01]
Comorbidities	1.04 [0.92, 1.18]	−0.35 [−1.08, 0.38]	0.07 [−0.09, 0.23]	−0.00 [−0.01, 0.01]
AI/EA therapy	0.64 [0.39, 1.05]	−1.69* [−3.31, −0.08]	0.11 [−0.22, 0.44]	−0.01 [−0.03, 0.01]
Recruitment site (CA vs. AZ)	1.97* [1.12, 3.48]	2.80* [0.23, 5.37]	−0.00 [−0.58, 0.57]	0.00 [−0.03, 0.03]

* Indicates statistical significance in the univariate tests, and bolded values indicate significance ($p < 0.05$) in the multivariate model (see online supplement for coefficients from the multivariate models). Cancer status (e.g., primary, recurrent) not included in analyses, owing to small subsample sizes. For major depressive episodes, surgery, chemotherapy, radiation therapy, Herceptin, and endocrine therapy are indicators of receipt during the study. In the mixed models, oncologic treatments are time-varying, within-subject factors. For all estimates, 95 % confidence intervals are shown in brackets

[a] Assessment interval (1–7) at which major oncologic treatments (surgery, chemotherapy, radiation) ended

CES-D Center for Epidemiologic Studies-Depression scale, *AI* aromatase inhibitors, *EA* endocrine antagonists, *CA* California (Los Angeles area), *AZ* Arizona (Tucson)

* $P < 0.05$

** $P < 0.01$

*** $P < 0.001$

indeterminate (OR = 2.90, $P = 0.002$) depression treatment (Table 2). Only 34.2 % with a depressive episode and 25.9 % in the High CES-D trajectory class had adequate treatment, however.

Discussion

This longitudinal study of 460 women with breast cancer diagnosed an average of 2 months previously yielded a 16.6 % rate of major depressive episodes over 12 months, as assessed via validated structured interview. This figure is nearly twice the 8.4 % 12-month prevalence in women in the general United States population [45]. Compared with a CES-D mean of 8.67 in community-residing women aged 50–96 years [35], depressive symptoms were elevated up to the ninth month after breast cancer diagnosis, but not thereafter. Similarly, the proportion of participants who met the clinically suggestive CES-D cutoff at some point in the 12 months (56.5 %) exceeded the 15 % 12-month rate in a community sample [35].

Depressive symptoms declined over time, but substantial heterogeneity was apparent, as indicated by four distinct symptom trajectory classes. The trajectory classes identified in the current study correspond to those of other studies. For example, although depressive symptoms were higher in the current sample, our High trajectory class (38 % of participants) roughly corresponds to the 45 % of 398 breast cancer patients with estimated CES-D scores of just above 16 through 6 months after surgery [18]. Considered jointly, our Low and Very Low classes (43 %) correspond to 39 % with consistently low depressive

Table 5 Odds ratios for univariate associations of demographic and medical covariates with latent CES-D depressive symptom trajectory class

Covariate	Low versus High	Very Low versus High	Recovery versus High	Low versus Recovery	Very Low versus Recovery	Low versus Very Low
Age (in years)	1.02* [1.01, 1.04]	**1.05*** [1.02, 1.08]**	**1.02 [1.00, 1.03]**	1.01 [0.99, 1.03]	1.03* [1.01, 1.06]	0.98 [0.95, 1.01]
Latina (ref = non-Latina)	0.52* [0.28, 0.95]	1.06 [0.49, 2.27]	1.02 [0.55, 1.87]	0.51 [0.25, 1.02]	1.04 [0.45, 2.40]	**0.49 [0.21, 1.13]**
Married (ref = non-married)	1.40 [0.87, 2.25]	1.76 [0.86, 3.63]	2.05* [1.15, 3.69]	0.68 [0.37, 1.26]	0.86 [0.38, 1.95]	0.79 [0.38, 1.67]
Income	1.13 [0.94, 1.36]	0.96 [0.73, 1.26]	1.18 [0.96, 1.44]	0.96 [0.78, 1.19]	0.82 [0.61, 1.09]	1.18 [0.89, 1.56]
Education	1.08 [0.90, 1.29]	1.09 [0.80, 1.47]	0.98 [0.80, 1.19]	1.11 [0.90, 1.35]	1.11 [0.81, 1.53]	0.99 [0.73, 1.35]
Employment (ref = employed)						
Retired	**2.06** [1.21, 3.50]**	3.68*** [1.81, 7.50]	1.63 [0.87, 3.06]	1.26 [0.69, 2.31]	2.26* [1.05, 4.85]	0.56 [0.28, 1.11]
Unemployed	0.57 [0.30, 1.07]	0.35 [0.10, 1.22]	0.97 [0.51, 1.86]	0.58 [0.28, 1.23]	0.36 [0.10, 1.32]	1.63 [0.44, 5.98]
Subjective SES	1.20* [1.03, 1.40]	**1.47** [1.11, 1.96]**	**1.30** [1.08, 1.55]**	0.92 [0.78, 1.10]	1.14 [0.86, 1.51]	**0.81 [0.62, 1.07]**
Cancer stage	1.01 [0.78, 1.30]	0.49** [0.29, 0.80]	0.79 [0.59, 1.06]	**1.28 [0.94, 1.73]**	0.62 [0.36, 1.04]	2.07** [1.25, 3.44]
Oncologic treatment duration[a]	0.88* [0.78, 0.98]	0.73*** [0.62, 0.88]	0.89 [0.79, 1.01]	0.98 [0.87, 1.11]	0.83* [0.69, 0.99]	1.19 [1.00, 1.42]
Surgery	0.77 [0.38, 1.55]	2.51 [0.56, 11.22]	1.85 [0.66, 5.20]	0.42 [0.15, 1.16]	1.35 [0.25, 7.21]	0.31 [0.07, 1.37]
Chemotherapy	0.67 [0.43, 1.04]	0.32*** [0.16, 0.64]	1.12 [0.67, 1.89]	**0.59 [0.35, 1.01]**	**0.29*** [0.14, 0.61]**	2.05* [1.03, 4.10]
Radiation therapy	1.42 [0.89, 2.27]	**2.08* [1.09, 4.00]**	1.66 [0.98, 2.81]	0.86 [0.50, 1.47]	1.26 [0.62, 2.54]	0.68 [0.35, 1.32]
Herceptin	0.68 [0.41, 1.11]	0.58 [0.27, 1.25]	1.10 [0.64, 1.90]	0.61 [0.34, 1.10]	0.53 [0.23, 1.20]	1.16 [0.53, 2.58]
AI/EA therapy	1.42 [0.89, 2.25]	1.83 [0.90, 3.71]	1.17 [0.69, 1.99]	1.21 [0.69, 2.10]	1.56 [0.72, 3.36]	0.77 [0.37, 1.60]
Comorbidities	**0.90 [0.79, 1.03]**	**0.94 [0.81, 1.08]**	**0.85* [0.73, 1.00]**	1.06 [0.89, 1.25]	1.10 [0.92, 1.32]	0.96 [0.82, 1.13]
Recruitment site (CA vs. AZ)	0.72 [0.45, 1.17]	**0.25*** [0.13, 0.49]**	**0.57* [0.33, 0.98]**	1.27 [0.74, 2.18]	0.44* [0.21, 0.89]	**2.90** [1.48, 5.68]**

* Indicates statistical significance in the univariate tests, and bolded values indicate significance ($p < 0.05$) in the multivariate model (see online supplement for coefficients in the multivariate model). Cancer status (e.g., primary, recurrent) not included in analysis, owing to small subsample sizes. Surgery, chemotherapy, radiation therapy, Herceptin, and endocrine therapy are coded as whether a woman ever had any. Estimates are odds ratios. 95 % confidence intervals are in brackets. *CES-D* Center for Epidemiologic Studies-Depression scale, *AI* aromatase inhibitors, *EA* endocrine antagonists, *CA* California (Los Angeles area), *AZ* Arizona (Tucson). In the univariate model, omnibus tests were significant for age, employment, subjective SES, cancer stage, oncologic treatment duration, chemotherapy, and recruitment site. In the multivariate model, omnibus tests were significant for employment, subjective SES, comorbidities, chemotherapy, and recruitment site

[a] Assessment interval (1–7) at which major oncologic treatments (surgery, chemotherapy, radiation) ended

* $P < 0.05$

** $P < 0.01$

*** $P < 0.001$

symptoms [18]. As did 20 % of the current sample, 15–25 % of cancer patients and other adults experiencing major life stressors demonstrate a recovery trajectory [21, 46]. No re-entry trajectory was apparent (including when analyses were conducted specifically to examine symptom patterns after treatment completion [data not shown]).

Regarding cross-classification of the depression indicators, the High and Recovery classes contained 96 % of the major depressive episodes. As previously demonstrated [47], many women with clinically significant levels of depressive symptoms (≥16 CES-D) did not meet criteria for a major depressive episode. The fact that an estimated 66 % of women in the High symptom class did not have a depressive episode reveals a need for clinical attention to women who report persistently elevated depressive symptoms, as well as indicating the unique value of repeated symptom assessments even in the absence of formal diagnostic evaluation.

The three depression indicators generally had similar correlates. Exceptions were that younger (vs older) age and advanced (vs early) cancer stage were significantly associated with chronically elevated depressive symptoms, but not with episodes (no woman with metastatic disease had an episode). In that they face attendant enduring and major life changes, perhaps younger women and women with metastatic disease are more likely to experience persistent (but subthreshold) depressive symptoms. No other predictor uniquely distinguished women who had a major depressive episode from those who reported relatively high and chronic symptoms. Both patterns are of clinical concern.

The trajectory class findings are useful in distinguishing women whose elevated depressive symptoms are likely to endure and warrant intervention versus those who recover in their natural environments. Compared to women who recovered from elevated symptoms, women with high and persistent depressive symptoms were significantly more likely to be younger, of lower perceived socioeconomic status, unmarried, diagnosed with comorbid diseases, and recruited from the Los Angeles area. Unemployment increased the likelihood of major depressive episodes, after accounting for other medical and sociodemographic factors. These significant correlates also are related to depression in the general population [48, 49], and it certainly is likely that some women in the High trajectory were depressed prior to cancer diagnosis. A recent prospective study demonstrated that an estimated 8 % of the sample reported high depressive symptoms prior to a cancer diagnosis, which endured after diagnosis [50].

Regarding limitations on generalizability of findings, the sample was younger (mean of 56 ± 13) than the median age of breast cancer diagnosis of 61 years [51]; a somewhat lower rate of depressive symptoms might be evident in older samples. African American women were underrepresented and Latinas over-represented relative to the US population with breast cancer (although representative of the local recruitment populations). Regarding recruitment site differences, competition for recruitment at Arizona's academic site versus California's primarily community sites likely accounts for Arizona's lower recruitment rate. California's higher attrition and depressive symptom rates are less explicable. Women with advanced cancer also were more likely to drop out of the study; however, total retention at 12 months exceeded 80 %, analyses addressed missing data, and attrition was not affected by depression status.

In light of the profound consequences of depression for the well-being and health of cancer survivors [5, 9], this novel simultaneous examination of major depressive episodes, depressive symptoms, and trajectory classes via multiple assessments across 12 months suggests the importance of assessing both major depressive episodes and unremitting depressive symptoms. It is heartening that several factors significantly associated with enduring (vs remitting or low) depressive symptoms can be assessed upon cancer diagnosis, and identification of additional factors that confer risk for major depression or prolonged symptoms warrants investigation. Psychosocial predictors of depressive symptoms also are documented in breast cancer survivors [e.g., 18, 22], and planned analyses will illuminate psychosocial processes indicating vulnerability or protection in the present sample of women. Whether interventions with distinct content or intensity are needed for disorder-level versus persistent subthreshold symptoms requires study.

The present and others' findings suggest that nearly 40 % of recently diagnosed breast cancer patients might need targeted intervention to prevent unremitting depressive symptoms, approximately 20 % could benefit from approaches to speed recovery, and 40 % are likely to garner sufficient resources in their natural environments. Nearly half of participants with major depressive disorder received no depression treatment, illustrating the importance of improving detection and treatment of depression. Psychological and pharmacologic approaches show promise in ameliorating major depression in cancer survivors [52, 53], and continued development of evidence-based interventions is needed to prevent and promote rapid recovery from depression.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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