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Risk factors for depression in breast cancer survivors: An update

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ABSTRACT. Depression is the most common affective disorder in cancer patients. Understanding risk factors for depression or elevated depressive symptoms is key to early intervention and tailoring of treatment. In 2006, we published a study of risk factors for elevated depressive symptoms in breast cancer survivors. Our sample was sufficiently large to allow us determine the relative importance of 26 different candidate risk factors in a single hierarchical bivariate logistic regression analysis (N = 2,595). We reported that cancer-related variables were not meaningful risk factors for elevated depressive symptoms in this sample. Rather, this was better explained by distressing life events, less optimism, ambivalence over negative emotional expression, insomnia, and poorer social functioning. While our study was well-powered and examined a large array of candidate risk factors, we still only explained 32.4% of the variance in levels of depressive symptoms; thus, there is ample opportunity for the identification of other risk factors. In this paper, we examine subsequent studies to see what other potential risk factors have been identified in the literature and how they confirm, disconfirm or add to our 2006 findings.

KEYWORDS. Depression. Breast cancer. Risk factors. Theoretical study.

RESUMEN. La depresión es el trastorno más común en los pacientes con cáncer. Es fundamental entender los factores de riesgo para la depresión o síntomas depresivos elevados para las intervenciones tempranas y diseños de tratamientos. En 2006 publicamos un estudio sobre los factores de riesgo para síntomas depresivos elevados en

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supervivientes de cáncer de mama. La muestra era suficientemente grande como para permitir determinar la importancia relativa de 26 diferentes posibles factores de riesgo en un único análisis de la regresión logística jerárquico bivariado ($N = 2595$). Se encontró que las variables relacionadas con cáncer no eran factores de riesgo significativos para síntomas depresivos elevados en dicha muestra. Más bien se explicaba mejor por eventos vitales estresantes, menor optimismo, ambivalencia sobre expresiones emocionales negativas, insomnio y pobre funcionamiento social. Aunque nuestro estudio era potente y examinaba un gran conjunto de posibles factores de riesgo, sólo se alcanzó explicar un 32,4% de la varianza en los niveles de síntomas depresivos. Por ello, hay una amplia posibilidad de identificar otros factores de riesgo. En este trabajo, se examinan estudios posteriores para ver qué otros posibles factores de riesgo se han identificado en la literatura y cómo confirman, refutan o añaden información a nuestros hallazgos del año 2006.

PALABRAS CLAVE. Depresión. Cáncer de mama. Factores de riesgo. Estudio teórico.

Breast cancer survivors (BCS) may experience elevated prevalence of depression for a number of reasons. These include the distressing effects of a cancer diagnosis, metabolic/endocrine and emotional sequelae of treatment, fears of recurrence or living with a challenged sense of 'invulnerability', and job/financial repercussions. Most evidence suggests that the majority of these individuals do not develop Major Depressive Disorder. However, a significant subset (15-30%) complain of depressive symptoms of clinical importance. Depression is the most common mood disorder in cancer and can have a significant impact on the patient's quality of life (Bardwell *et al.,* 2006). Of late, the potential impact of subsyndromal levels of depressive symptoms has become a growing area of research interest (Bardwell, Moore, Ancoli-Israel, and Dimsdale, 2003). When left untreated, depression can result in diminished adherence to medical treatment (Colleoni *et al.,* 2000) extended inpatient admissions, and greater morbidity and even mortality in patients treated for breast cancer (BC) (Hjerl *et al.,* 2003).

A wide range of risk factors for depression or elevated depressive symptoms in BC have been reported. These include cancer severity (Aapro and Cull, 1999), type of treatment (Duffy, Greenberg, Younger, and Ferraro, 1999; Monti, Mago, and Kunkel, 2005), pain (Aapro and Cull, 1999; Wong-Kim and Bloom, 2005), time since diagnosis, age (Golden-Kreutz and Andersen, 2004; Wong-Kim and Bloom, 2005; Yeter *et al.,* 2006), physical activity (Yeter *et al.,* 2006), diet, menopausal symptoms/status (Monti *et al.,* 2005), physical functioning/symptoms (Aapro and Cull, 1999; Monti *et al.,* 2005), social functioning (Aapro and Cull, 1999; Wong-Kim and Bloom, 2005), pessimism (Epping-Jordan *et al.,* 1999; Schou, Ekeberg, Ruland, Sandvik, and Karesen, 2004), self-esteem (Wong-Kim and Bloom, 2005), ambivalence over expressing negative emotions, psychiatric history (Aapro and Cull, 1999) and insomnia. The challenge is to make sense of these varying and, sometimes, contradicting findings.

Prior study

We previously reported results of a study of psychosocial functioning in women who had completed initial treatment within four years for early-stage (Stage I (>1cm), II, IIIA) BC. These women were studied prior to participation in the longitudinal Women's Healthy Eating and Living (WHEL) Study, which examined the effects of a strict diet on breast cancer recurrence/survival. We assessed the importance of 26 potential risk factors for elevated depressive symptoms. While there was evidence in the literature for a relationship between each risk factor and depression in BC, we had sufficient power (N = 2,595) to determine their relative importance in a single multivariate analysis (Bardwell *et al.,* 2006). With few exceptions, prior studies were restricted in the number of risk factors that could be simultaneously examined. Thus, for example, studies that found evidence for relationships between cancer variables and depression were not able to examine these relationships in the presence of a wider range of variables.

We found no meaningful relationships between cancer-related variables (stage, time since diagnosis, initial treatment, tamoxifen use) and overall mental health (Bardwell *et al.,* 2004). We had expected significant relationships between cancer-related variables and mental health, though less strong than those for non-cancer-related variables.

We similarly hypothesized that depression would be better explained by non-cancer-related variables (Bardwell *et al.*, 2006). Participants were 2,595 women who completed initial treatment for early-stage BC within 4 years of enrollment. Participants reported information on: cancer-related variables (stage, time since diagnosis, initial treatment, tomixifen use); personal characteristics (age, education, race/ethnicity, marital status, body mass index (BMI); health behaviors (physical activity, alcohol intake, smoking status, dietary intake); physical functioning and symptoms (pain, vasomotor, genitourinary, gastrointestinal); and psychosocial factors (social support/strain, optimism, emotional expressiveness, hostility, life events, sleep). The dependent variable was the 8-item Center for Epidemiologic Studies—Depression screen. Scores $\geq$ 0.06 indicate clinically-elevated depressive symptoms (Burnam, Wells, Leake, and Landsverk, 1988). Using this cut-point, we dichotomized participants into 'high/low' depressive group. Significance was set at $p \leq .001$. Results of univariate analyse are:

- Cancer-related variables. None of the cancer-related variables differed significantly by depression group, although a protective effect for current tamoxifen use fell just short of significance with $p = .006$.
- Personal characteristics. The depression groups did not differ significantly for race/ethnicity nor education. However, women < 50 years of age had more depressive symptoms and women $\geq$ 60 years of age had fewer. Women who were obese or not currently married also reported more depressive symptoms.
- Health behaviors. Alcohol intake did not differ by depression group and quality of diet fell just short of significance, with a trend for those who ate more healthily being less depressed.
- Physical functioning/symptoms. As expected, better physical functioning was associated with being less depressed, and greater levels on all four physical symptoms (pain, vasomotor, genitourinary, gastrointestinal) were linked with being more depressed.

– Psychosocial functioning. Twelve of the 13 candidate risk factors showed meaningful differences: less depression was linked with better social functioning, more optimism, less hostility, fewer stressful life events, and better sleep. Less ambivalence over expressing negative emotions was linked with fewer depressive symptoms; however, actual expression of negative emotions did not differ by depressive symptom group.

Multivariate analysis. We used hierarchical binary logistic regression analysis, with forced entry of variables. With the two high/low depressive symptoms groups as the outcome variable, we entered the 26 candidate risk factors in the following order: cancer-related, personal characteristics, health behaviors, physical functioning/symptoms, and psychosocial. We presented results before and after the entry of psychosocial variables.

Prior to entering the psychosocial variables, we found that cancer-related variables were non-significant. Together, the cancer-related variables explained only 1.5% of variance in depression group (Nagelkerke's R^2 = .015; non-significant). Individually, none of the four cancer-related variables were significanct. Taken together, personal characteristics explained an additional 3.8% of depression variance (total Nagelkerke's R^2- = .053 at this point, $p \leq .001$). Being younger than 50 was a significant individual risk factor and being ≥ age 60 was protective. Being currently married was also protective; however, BMI, race/ethnicity and education were not individually significant. Health behaviors, taken together, significantly explained another 1.6% of variance (total Nagelkerke's R^2 = .069, $p \leq .001$); however, no individual health behavior was significant. Physical functioning/symptoms together contributed an additional 9.2% of variance. Better physical functioning was minorly protective (OR = 0.979); vasomotor (OR = 1.232) and gastrointestinal symptoms (OR = 1.488) were significant individual risk factors; pain and genitourinary symptoms were not individually significant. Thus, at this point, cancer-related variables, personal characteristics, health behaviors and physical functioning/symptoms accounted for a total of 16.1% ($p \leq .001$) of variance in high/low depression group status.

Next, psychosocial variables were entered. As expected, they together accounted for a significant portion of variance: 16.3%, bringing total variance explained to 32.4%. Individually, less depression was associated with greater social support (OR = 0.969), less social strain (OR = 1.087), greater optimism (OR = 0.881), less ambivalence over expressing negative emotions (OR = 1.392), fewer life events (OR = 1.343) and better sleep (OR = 1.053). Hostility and negative emotional expressiveness were not significant individual predictors.

We attempted a replication using RAND-36 Emotional Well-Being as a continuous outcome variable in hierarchical multivariate linear regression. Results were similar to those of the binary logistic regression. In addition, younger age and worse physical health were significant individual predictors (Bardwell *et al.,* 2006).

An editorial which corroborated our findings via analyses of the authors' own datasets accompanied our paper (Scheier and Helgeson, 2006). In 284 women diagnosed with Stage I, II or IV BC, depression was not linked with stage (r = -.04). Thus, they concluded that restriction of range of cancer stage did not explain our findings. In 312

recently-diagnosed women with early-stage BC (mostly Stage I-II), depressive symptoms were not related to stage, surgery or estrogen receptor status. They cited another article of theirs that did not find links between stage and mental functioning trajectories of 4 years (Helgeson, Snyder, and Seltman, 2004) Thus, they concluded that our range of time since diagnosis did not explain our findings either. Results of our analyses and those in the editorial suggest that cancer-related factors may not be meaningful risk factors for depression in women treated for BC.

As noted in the editorial, there may be more complex relationships between psychosocial variables and other risk factors. As the editorial authors speculated, optimism or stressful life events may have stronger relationships with depressive symptoms in patients with more severe BC. They also noted that our approach to the specification of initial treatment may have insufficiently sophisticated to detect links with depressive symptoms (Scheier and Helgeson, 2006) We agree with Drs. Scheier and Helgeson that these are reasonable possibilities. In addition, our participants were predominantly educated, non-Hispanic White women who were motivated to participate in a dietary intervention study. Also, much of our data was self-reported. Therefore, generalizability is limited by these factors (Bardwell e*t al.,* 2006).

Objectives of the current study

Here, we review related reports published since our 2006 paper. In our study, we explained approximately one-third of the variance in depressive symptom group (Bardwell *et al.,* 2006). Of course, this leaves plenty of room for further studies to explain the remaining variance. We wondered what new studies have been published that would corroborate or fail to corroborate our findings, or add to this literature by identifying other potential risk factors for depressive symptoms in survivors of BC.

Method

Our approach was two-fold: To identify new studies that referenced our 2006 study; and, to conduct a PubMed search using the following terms: breast cancer, survivor or survivorship, depression, depressed or depressive, and date of 2006 or later.

Entering these key words in the Pub Med search yielded 31 articles. Of these 17 were excluded from our review because: 12 were focused on a topic other than risk factors for depression; 4 involved non-survivors; and, 1 was a review study. This left 14 studies whose results we have summarized in Table 1 and discussed below.

Results

The 14 studies varied considerably, in terms of focus of the research, study design, sample size, number and type of candidate risk factors, measurement of depressive symptoms/depression, and analytic approach. Results are diverse; however, there are key themes to be reported. Findings from these studies are shown in Table 1.

TABLE 1. Selected studies of depressive symptoms in breast cancer survivors.

Authors and publication year	*Sample Size*	*Population*	*Dependent Variables*	*Sig.*		*N.S.*
				Bivariate	*Multivariate*	
Bower *et al.* (2011)	103	American BCS within 3 months of end of cancer treatment	BDI-II	+Fatigue (r = .54, p < .001) +Sleep disturbance (r = .55, p < .001)		Inflammatory markers
Chen *et al.* (2009)	1400	Chinese BCS		-Radiotherapy (p = .004) -Married (p = .006) -Income (p < .001) -Education (p = .28) +Menopausal symptoms (p < .001) -QOL (tot, phys, ment, phys fxn, soc fxn, ment hlt, gen hlt, role-phy, pain, vital, role-emot) (p < .001) +Comorbidity (p = .002)	-Radiotherapy (OR = 0.35, 95% CI = 0.35-0.8) +Age ≥ 60 years (OR = 3.91, 95% CI = 0.86-17.8) -Married (single OR = 2.84, 95% CI = 1.20-6.74) -Income (<1000 yuan OR=3.13, CI = 1.51-6.48)	Stage ER+ Surgery type Tamoxifen Chemotherapy Immunotherapy Menopausal status

Chen *et al.* (2010) (only wrote what was not reported in Chen *et at.*, 2009)	1,399 (same sample as Chen *et al.*, 2009)	Chinese BCS	CESD-20	+Age (p = .38) -Exercise (p = .009) -Tea Consumption inversely related (p = .01)	-Tea Consumption inversely related (OR = 0.64, 95% CI = 0.41-0.99) -Exercise (OR = 0.79, 95% CI = 0.6-1.03)	BMI Weight change Cigarette smoking Alcohol
Christie, Meyerowitz, and Maly (2010)	677	American Low income BCS 425 Hispanic 252 non-Hispanic	CESD-10	-Being partnered (p = .001) +Comorbidities (stats not reported)		
Deshields, Tibbs, Fan, and Taylor (2006)	84	American BCS who had radiotherapy	CESD-20	+Children living in home (p < .01) +Anxiety (r = .75, p < .01) -QOL (r = -0.81, p < .001)		

Gorman, Marlcarne, Roesch, Madlensky, and Pierce (2010)	131	American BCS (≤ 40 years old)	CESD-8	+No children (p = .01) +Reproductive concerns (p = .037) -Physical Health (p<.0001) -Reproductive concerns X Physical Health (stats not provided) Social support (p<.0001)	Live births after BC Wanted more children before BC Wanted more children after BC Fertility factor in tx decision making Tx related amenorrhea	
Karakoyun-Celik *et al.* (2010)	120	Turkish BCS	BDI	+Unaccompanied by spouse (p < .0001) +Request to see a psychologist (p < .02) +Using alternative treatment (p = .04) -Positive Ideas about general health (p = .002) +Difficulty sleeping (p < .05)	Age Education Marital status Income Sexual function/satisfaction	

+Emotional status ($p < .0001$)	
+Fatigue ($p < .0001$)	
+Pain ($p < .0001$)	
-Body image ($p < .0001$)	
-Physical function ($p = .002$)	
	Treatment methods (type/direction unclear) ($p = .001$)
	-Role performance ($p = .005$)
	+Cognitive condition ($p < .0001$)
	-Social status ($p < .0001$)
	+Future anxiety ($p < .0001$)
	+Anxiety ($p = .003$)

Kim *et al.* (2008)	1,933	Korean BCS	BDI	+Mastectomy and radiation ($p = .040$)	-Income OR = 2.62, 95% CI = 1.95-3.52	Stage	Time since surgery	
				+Lower education ($p < .001$)	+Musculoskeletal disease OR = 1.75, 95% CI = 1.18-2.58	Adjuvant tx	Marital status	
				-Income ($p < .001$)	+Dyspnea OR = 1.63, 95% CI = 1.01-2.64	Age	Employment status	
				+Being menopausal ($p = .004$)	+Insomnia OR = 2.94, 95% CI = 2.04-4.24	Cerebrovascular disease	Cardiac disease	
				+Diabetes mellitus ($p = .009$)	+Appetite loss OR = 3.68, 95% CI = 1.89-7.16	Liver disease	Lung disease	
				+Fatigue ($r = .455$, $p < .001$)	+Constipation OR = 2.37, CI = 1.58-3.57	Hypertension ($p = .002$)	Infectious disease	
				+Gastrointestinal disease ($p < .001$)	+Arm Symptoms OR = 2.06, 95% CI = 1.33-3.18	Kidney disease	Pain (in MV)	
				+Muskuloskeletal disease ($p < .001$)		Gastrointestinal disease (in MV)		

+Pain
($p < .001$)

+Dyspnea
($p < .001$)

-Insomnia
($p < .001$)

+Appetite loss
($p < .001$)

-Constipation
($p < .001$)

-Arm symptoms
($p < .001$)

-Diarrhea
($p = .004$)

+Breast symptoms
($p < .001$)

Naus, Price, and Peter (2005)	109	American BCS	BDI-II	+Anxiety (r = .51, p < .01)	+Anxiety (stats not provided) +External LOC regarding BC (p < .001) Types of LOC X anxiety (p < .001)	LOC (bivar)
Popoola and Adewuya (2011)	124	Nigerian BCS	MINI	+Advanced cancer stage (p = .013) +Years since diagnosis (p = .037) +Amount spent on treatment (p = .007) -Marital status (p = .005) -Perceived poor social support (p = .001) +Relative died of BC (p = .05)	+Advanced cancer stage (OR = 3.22, 95% CI 1.32-8.26) (p = .013) -Marital status (OR = 3.09, 95% CI 1.30-7.42) -Perceived poor social support (OR = 5.38, 95% CI 1.88-16.63) (p = .001)	Surgery Age Education Employment Income Alcohol Smoke

Qiu *et al*. (2011)	505	Chinese BCS	BDI MINI HAMD	+Recurrent BC ($p < .005$) -Marital status ($p = .03$) -Income ($p = .06$) +Psychiatric history ($p < .005$)	-Marital status (OR = 2.84, 95% CI = 1.13-7.13) -Time since surgery (> 1 year OR = 0.45, 95% CI = 0.23-0.87) +Psychiatric history (OR = 10.83, 95% CI = 4.93-23.78)	Type of surgery Stage ER status Radiation Chemotherapy Immunotherapy Income (in MV) Family psych hx
Rogers, Markwell, Courneya, McAuley, and Verhulst (2011)	483	American rural BCS	CESD-10	-Education ($r = -14, p < .01$) +Comorbidities ($r = .30, p < .01$) -Domestic gardening ($p = .003$)		Adjuvant tx Time since dx Age Race

Schlegel, Talley, Molix, and Bettencourt (2009)	232	American rural BCS	CESD-20	At 6 months f/u -Time since dx (p-value not reported) -Income (r = -0.28, p < .01) -Marital status (r = -24, p < .01) +Physical symptoms (r = .36, p < .01) -Positive reinterpretation (r = - .21, p < .01) -Religiousness (r = -.17, p < .01) +Focus/Venting emotions (r = .24, p = < .01) +Denial (r = .32, p < .01) +Behavioral disengagement (r = .34, p < .01)	Stage Age Education Being Active Planning Seeking instrumental support Seeking emotional support Acceptance Alcohol

Vahdaninia, Omidvari, and Montazeri (2010)	99	Iranian BCS	HADS	+Fatigue (r = .53, p < .001) +Pain (r = .50, p < .001) +Anxiety (r = .71, p < .001)	At 18month f/u -Marital status (OR = 0.02, 95% CI = 0.00-0.78) +Fatigue (OR = 1.06, 95% CI = 1.02-1.09) +Pain (OR = 1.05, 95% CI = 1.01-1.08)	Stage Age Education

Note. Only looked at latest follow up (longer survivorship) for studies that included assessments of multiple time points including during treatment. + indicates positive relationship with depression; - indicates inverse relationship with depression; BDI: Beck Depression Inventory; CESD: Center for Epidemiologic Studies Depression; HAMD: Hamilton Depression Scale; HADS: Hospital Anxiety and Depression Scale; MINI: Mini International Neuropsychiatric Interview (MINI); Yuan: Chinese currency.

Cancer-related variables

In bivariate analyses, several cancer-related variables were found to be significantly related to depression. Having had radiotherapy predicted fewer depressive symptoms in one study of 1,400 Chinese women survivors of Stage 0-IV BC (Chen *et al.,* 2009). In another, having had a mastectomy plus radiotherapy was linked with more depressive symptoms in Korean women survivors of Stage 0-III BC (Kim *et al.,* 2008). Two studies observed that later stage predicted worse depressive symptoms: one was a subset of the US WHEL Study population who were ≤ 40 years old (Gorman *et al.,* 2010); the other was a study of 124 Nigerian BCS (Popoola and Adewuya, 2011). Another report observed links between depressive symptoms and initial treatment in 120 Turkish BCS; they did not provide further detail on this finding (Karakoyun-Celik *et al.,* 2010). The Nigerian study reported that more years since diagnosis predicted more depressive symptoms (Popoola and Adewuya, 2011) while a study of 232 US rural survivors of stage 0-IV BC found the opposite relationship (Schlegel *et al.,* 2009). Estrogen receptor-positive status (Gorman *et al.,* 2010), recurrent BC (Qiu *et al.,* 2011), and having a relative who died from BC (Popoola and Adewuya, 2011) also predicted more depressive symptoms.

In multivariate analyses, Chinese women who had radiotherapy reported fewer depressive symptoms (Chen *et al.,* 2009); in another Chinese study, more years since diagnosis predicted fewer depressive symptoms (Chen *et al.,* 2010). The Nigerian study reported that later stage was linked to more depressive symptoms (Popoola and Adewuya, 2011).

Personal characteristics

Significant bivariate relationships between marital/partnership status and depressive symptoms were observed in 6 studies; those who were married/partnered reported fewer depressive symptoms (Chen *et al.,* 2009; Christie, *et at.,* 2010; Gorman *et al.,* 2010; Popoola and Adewuya, 2011; Qiu *et al.,* 2011; Schlegel *et al.,* 2009). Proxies for socioeconomic status showed positive relationships with depressive symptoms in 7 studies (Chen *et al.,* 2009; Karakoyun-Celik *et al.,* 2010; Kim *et al.,* 2008; Popoola and Adewuya, 2011; Qiu *et al.,* 2011; Rogers *et al.,* 2011; Schlegel *et al.,* 2009). Older age was linked with more depressive symptoms in a Chinese population (Chen *et al.,* 2010) while higher BMI (Gorman *et al.,* 2010) and having children at home (Deshields *et al.,* 2006) predicted more depressive symptoms in two US studies.

In multivariate analysis, being married/partnered remained significantly and inversely linked to depressive symptoms in four studies (Chen *et al.,* 2009; Popoola and Adewuya, 2011; Qiu e*t al.,* 2011; Vahdaninia *et al.,* 2010). Income was negatively linked to depressive symptoms in two studies (Chen *et al.,* 2009; Kim *et al.,* 2008).

Health behaviors

In bivariate analyses, more physical activity was associated with fewer depressive symptoms in one of the Chinese studies (Chen *et al.,* 2010, the study of US rural women (Rogers *et al.,* 2011) and the Gorman report of WHEL data (Gorman *et al.,* 2010). Greater green tea consumption predicted fewer depressive symptoms in another study (Chen

et al., 2010) while adherence to healthy dietary recommendations was linked to less depressive symptoms in the WHEL sample (Gorman *et al.,* 2010). The Turkish study observed that use of an alternative supplement was associated with more depressive symptoms (Karakoyun-Celik e*t al.,* 2010).

In multivariate analyses, only one study observed significant relationships between health behaviors and depressive symptoms. Physical activity and tea consumption were both inversely associated with depressive symptoms in a Chinese sample (Chen *et al.,* 2010).

Physical functioning/symptoms

In bivariate analyses, greater fatigue predicted more depression in another US study of early-stage BCS (Bower *et al.,* 2011) a Chinese study (Chen *et al.,* 2009), the Turkish study (Karakoyun-Celik *et al.,* 2010), the Korean study (Kim *et al.,* 2008) and an Iranian study (Vahdaninia *et al.,* 2010). Worse menopausal symptoms predicted worse depression in Chinese (Chen *et al.,* 2009), Korean (Kim *et al.,* 2008) and US women (Gorman *et al.,* 2010). Comorbidities predicted worse depressive symptoms in five studies (Chen *et al.,* 2009; Christie *et al.,* 2010; Karakoyun-Celik *et al.,* 2010; Kim *et al.,* 2008; Rogers *et al.,* 2011). More pain was linked to more depressive symptoms in four studies (Chen *et al.,* 2009; Karakoyun-Celik *et al.,* 2010; Kim *et al.,* 2008; Vahdaninia *et al.,* 2010). Other physical symptoms predicting more depressive symptoms included dyspnea (Kim *et al.,* 2008), breast symptoms (Kim *et al.,* 2008) and general physical symptoms (Schlegel *et al.,* 2009). The study by Kim *et al.* identified significant bivariate relationships between depressive symptoms and diarrhea, constipation and arm symptoms; however, data were unclear as to direction of the relationships (Kim *et al.,* 2008). They also reported that appetite loss predicted more depressive symptoms (Kim *et al.,* 2008). Physical functioning and role performance also showed the expected inverse relationships with depressive symptoms (Chen *et al.,* 2009; Karakoyun-Celik *et al.,* 2010).

In multivariate analyses, fatigue (Vahdaninia *et al.,* 2010), physical health (Gorman *et al.,* 2010), pain (Vahdaninia *et al.,* 2010), comorbid musculoskeletal disease (Kim *et al.,* 2008), other physical symptoms (Kim *et al.,* 2008) and appetite loss (Kim *et al.,* 2008) were linked to more depressive symptoms.

Psychosocial functioning

Anxiety showed significant bivariate relationships with depressive symptoms in five studies (Deshields *et al.,* 2006; Karakoyun-Celik *et al.,* 2010; Naus *et al.,* 2005; Vahdaninia *et al.,* 2010). Poor sleep was also linked with depressive symptoms in the expected positive direction (Bower *et al.,* 2011; Karakoyun-Celik *et al.,* 2010; Kim *et al.,* 2008). More reproductive issues were positively linked with depressive symptoms (Gorman *et al.,* 2010). Better overall quality of life was associated with fewer depressive symptoms in two studies (Chen *et al.,* 2009; Deshields *et al.,* 2006). Better social support/functioning (Gorman *et al.,* 2010; Karakoyun-Celik *et al.,* 2010; Popoola and Adewuya, 2011) and religiosity (Schlegel *et al.,* 2009) predicted fewer depressive symptoms. Emotional distress (Karakoyun-Celik *et al.,* 2010; Schlegel *et al.,* 2009), maladaptive coping (Schlegel *et al.,*

2009) and psychiatric history (Qiu *et al.,* 2011) predicted more depressive symptoms, while adaptive coping (Schlegel *et al.,* 2009) predicted fewer. Also, poor body image (Karakoyun-Celik *et al.,* 2010) and more life events (Gorman *et al.,* 2010) predicted worse depression.

In multivariate analyses, poorer social support/functioning (Gorman *et al.,* 2010; Popoola and Adewuya, 2011), insomnia (Kim *et al.,* 2008), anxiety (Naus *et al.,* 2005), psychiatric history (Qiu *et al.,* 2011), external LOC (Naus *et al.,* 2005), reproductive concerns (Gorman *et al.,* 2010) and not having children (Gorman *et al.,* 2010) were linked to more depressive symptoms.

Discussion

Depressive symptoms are common complaints in BCS. Understanding relevant risk factors is important for early identification and to tailor depression treatment. While there have been numerous studies of depression in BC reported over the years, we still only partially understand the full picture.

The importance of multivariate studies using an array of variables is supported by the results of this review. In terms of cancer-related variables, 10 significant risk factors were identified in bivariate analyses, while only 3 remained significant in multivariate analyses. For personal characteristics, the results were 18 (bivariate) and 6 (multivariate); health behaviors, 6 (bivariate) and 2 (multivariate); physical functioning/symptoms, 30 (bivariate) and 8 (multivariate); and psychosocial variables, 29 (bivariate) and 9 (multivariate). Thus, bivariate analyses identified 93 risk factors for depression yet only 29 remained significant in multivariate analyses. We suspect that the number of significant risk factors in multivariate analyses would be reduced if all studies included a broad range of candidate variables.

Focusing on non-cancer-related risk factors, following is a summary of those that were significantly linked with depressive symptoms in multivariate analyses. Among personal characteristics, being married/partnered was mood-protective in 4 studies and greater income in 2. These findings are well-supported by the literature. However, marital status (Kim *et al.*, 2008) and income (Popoola and Adewuya, 2011; Qiu *et al.,* 2011) were not significant risk factors in two other multivariate studies. In terms of health behaviors, greater physical activity and tea consumption were protective factors. For physical functioning/symptoms, more fatigue, worse physical health, more pain, arm symptoms, constipation, dyspnea and musculoskeltal disease predicted worse depressive symptoms. While specifics might vary, the literature supports links between physical functioning/symptoms and depressive symptoms in the expected direction. For psychosocial symptoms, less social support, a psychiatric history, poorer sleep and anxiety, external LOC, and reproductive issues are linked with more depressive symptoms; all of which are plausible relationships.

As a reminder, the take-home message of our 2006 paper was that non-cancer-related factors explain depressive symptoms better than cancer-related variables. So, it is not surprising that the above relationships occur. The question is why cancer-related variables remained significant in some multivariate studies but not in others.

Cancer-related risk factors that remained significant in multivariate analyses included cancer stage (higher stage, greater depressive symptoms), having radiotherapy (fewer depressive symptoms compared with women did not have radiotherapy), and more time since diagnosis (associated with lower depressive symptoms). The study of 1,400 Chinese BCS found that radiotherapy was protective against depressive symptoms (Chen *et al.,* 2009). The study of 124 Nigerian BCS found that cancer stage was positively related to depressive symptoms. Finally, the study of 505 Chinese survivors showed a negative link between time since diagnosis and depressive symptoms. These variables were characterized in a manner similar to those in our 2006 study, yet we did not find any cancer-related variables to be significant. Possible explanations for differencse in findings may be because those studies included 12-14 variables in the multivariate analyses while our included 26. Also, there may be cultural explanations reflected in the differences in the samples (US, Chinese, Nigerian).

As mentioned by Scheier and Helgeson in their editorial, more sophisticated characterization of cancer-related variables may help identify relationships with depression that are obscured by simpler measures of these variables. In addition, relationships amongst risk factors (*e.g.,* mediational, moderational, interactional, and non-linear models) may reveal other significant findings (Scheier and Helgeson, 2006). We recognize these as limitations to our 2006 study; in addition, our range of candidate risk factors could have been even broader. However, we can indeed conclude that larger scale studies should continue in order to determine the relative importance of the risk factors identified in the literature. Also, standardization of culturally-sensitive measurement approaches (*i.e.,* PROMIS) hold promise for a better understanding of these phenomena.

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