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Associations of Depression Status and Hopelessness with Breast Cancer: A 24 year Follow-up Study

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Abstract

The current study extended the literature by examining whether three profiles of depression predicted breast cancer status. In 1,076 women of the Baltimore Epidemiologic Catchment Area Study, depression status and hopelessness were measured at baseline and breast cancer status was ascertained 24 years later. Double depression, but not major depression or dysthmia, was associated with breast cancer. Hopelessness predicted *fewer* new cases of breast cancer. When double depression and hopelessness were simultaneously entered as predictors, the regression weights of both predictors *increased*. The role of severe *and* extended duration depression as well as possible explanations for unexpected findings are discussed.

Keywords

major depression; dysthymia; chronic depression; hopelessness; breast cancer; longitudinal design

Introduction

Breast cancer has been identified as one of the most prevalent and deadly forms of cancer. According to the American Cancer Society (2014) statistics regarding cancer, breast cancer is projected to rank first in the development of new cases and second in death in 2014. Given the large-scale impact of breast cancer, psychological phenomena related to the illness development and trajectory have been explored. One particular psychological contribution that has been studied in the literature is depressive symptoms (for a meta-analysis see Pössel et al., 2012).

The relationship between depressive symptoms and breast cancer was described as noteworthy as early as 1893 (Snow, 1893) and several biobehavioral theories have posited explanations for this association. First, the relationship between depressive symptoms and breast cancer may be due to compromised immune functioning. More specifically, depressive symptoms negatively affect immune functioning and in turn, impaired immune functioning increases susceptibility to breast cancer (Ader et al., 1995). Associations between depression and the production of pro-inflammatory cytokines support such theory. For example, studies have revealed elevated levels of IL-6 in individuals who are depressed, as compared to individuals who are not depressed (Kop and Gottdiener, 2005; Pizzi et al., 2008). Second, the relationship between depressive symptoms and breast cancer may result from a dysregulation in the release of cortisol by the hypothalamic-pituitary-adrenal-axis (HPA-axis). Because cortisol plays an influential role in cell growth and activity, disruption (i.e., flattening of the diurnal cortisol rhythm) of the release of cortisol throughout the day will likely increase the risk of cancer. This hypothesis is supported by studies showing that flattened diurnal cortisol patterns throughout the day are associated with an increase in the risk of breast cancer (Pulaski et al.,

2005; Su et al., 2005; Ticher et al., 1996). Further, research has shown that greater levels of depressive symptoms are associated with elevated IL-6 and flatter diurnal cortisol rhythms (Sjögren et al., 2006a; Sjögren et al., 2006b). While multiple theories and studies reveal insight into why the relationship between depressive symptoms and breast cancer may exist, limited research has explored how the conceptualization of depression may influence or contribute to this association.

A recent meta-analysis (Pössel et al., 2012) revealed that 12 of 15 prospective studies reported a positive association between depressive symptoms at baseline and a later diagnosis of breast cancer. While the estimated overall correlation r = +0.025 +/- 0.027 (95% confidence interval) was not significant, the meta-analysis demonstrates that the time frame is of crucial importance. To be more precise, while only 70% of the studies using inappropriate short time frames between the assessment of depressive symptoms and the development of breast cancer (< 18 years) found a positive association between both variables, 100% of the studies with appropriate long time frame found such association (Pössel et al., 2012). Research conducted by Gross, Gallo, and Eaton (2010) revealed that a longer duration, but less severe episode, of depressive symptoms is associated with an increased risk of breast cancer. Specifically, this particular study revealed that while major depression (minimum duration 2 weeks, greater severity) did not significantly predict breast cancer incidence and mortality, the relationship between dysthymia (minimum duration 2 years, less severity) and breast cancer was significant. Additional research found that individuals reporting depressive symptoms at three time points across six years were more likely to experience breast cancer than an individual who was experiencing depressive symptoms at two or fewer time points (Penninx et al., 1998). Thus, one could propose that the duration of depression is critical for the development and trajectory of

breast cancer. However, findings of a recent study revealed marginally significant associations between the number of depressive symptoms and breast cancer incidence and mortality (p = .06; Gross et al., 2010). Studies have also supported a relationship between greater symptoms of cancer, such as pain or fatigue, and greater severity of depressed mood (Bower et al., 2000; Spiegel et al., 1994). Further, a reduction in depressive symptoms has been associated with a longer survival rate in breast cancer patients (Giese-Davis et al., 2011). Thus, it seems that the severity of depressive symptoms may be a factor of consideration in the strength of the relationship between depressive symptoms and breast cancer. While no study to depression and breast cancer incidence and mortality considered a combined effect of both duration and severity of depression, a longitudinal study exploring the effect of depression on risk of breast cancer *hospitalization* did (Jacobs and Bovasso, 2000). The authors of this study found that both duration and severity of depression were important in contributing to a significant relationship between depression and increased risk of breast cancer *hospitalization*, as compared to only duration or severity. A combined effect of duration and severity of depression, defined as double depression for the purposes of this study, makes sense considering that both duration and severity (Sjögren et al., 2006a; Sjögren et al., 2006b) of depression are associated with significant changes in the immune system.

Finally, research suggests that there may be an association between hopelessness and breast cancer incidence (Eskelinen and Ollonen, 2011). Although hopelessness often occurs with severe episodes of depression (Brown and Harris, 1978), it is not recognized as a symptom of depression in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013) and two prominent models in the literature consider hopelessness a risk factor, rather than a symptom, of depression (Abramson et al., 1989; Beck, 1976).

Additionally, studies have noted the distinct and important role of hopelessness in the relationship between depressive symptoms and the above mentioned biological risk factors of breast cancer IL-6 and cortisol. For example, hopelessness is - mediated through depressive symptoms - associated with diurnal cortisol rhythm (Pössel et al., 2015) and hopelessness is associated with IL-6, even when controlling for depressive symptoms (Mitchell et al., 2013). Thus, it may be the case that hopelessness is the "active" ingredient in the relationship between depression and breast cancer.

One purpose of the study was to evaluate whether the number of depressive symptoms, the chronicity of the symptoms, or a combination of severity and duration of symptoms (i.e., double depression) predict breast cancer incidence and mortality. The *severity hypothesis* predicts that major depressive disorder and double depression, but not dysthymia, would be significantly associated with breast cancer status. The *duration hypothesis* predicts that dysthymia and double depression, but not major depressive disorder, would be significantly associated with breast cancer status. The *combined hypothesis* predicts that only double depression, but not dysthymia and major depressive disorder, would be significantly associated with breast cancer status. Based on the existing literature to depressive symptoms and breast cancer (Gross et al., 2010; Jacobs and Bovasso, 2000; Penninx et al., 1998) as well as to depression and immune system (Sjögren et al., 2006a; Sjögren et al., 2006b) it was predicted that the combined hypothesis would be confirmed.

The second purpose of the study was to examine whether hopelessness (not part of the DSM symptom criteria but nevertheless independently predictive of important outcomes such as suicide; Kuo et al., 2004) and depressive symptoms differentially relate to breast cancer incidence and mortality. The *hopelessness hypothesis* predicts hopelessness and depression

would be independently associated with breast cancer status. But the relationship of depressive disorder with breast cancer status would be significantly reduced when controlling for hopelessness, whereas the relationship between hopelessness and breast cancer status would not be influenced by depression. Again, based on the research described above (Eskelinen and Ollonen, 2011; Mitchell et al., 2013; Pössel et al., 2015) it was predicted that the hopelessness hypothesis would be confirmed.

Method

Participants

The Baltimore Epidemiologic Catchment Area (ECA) Study is a 24-year longitudinal study in which psychopathology and physical health in the general adult population are measured. The baseline assessment took place in 1981 and the most recent follow-up assessments occurred in 2004 and 2005. At baseline, adults aged 18 years and older were sampled probabilistically from the population residing in households in Eastern Baltimore. As breast cancer is about 100-times more common in women than in men (American Cancer Society, 2014), the analyses in this study focus exclusively on women. Protocols of the Baltimore ECA Program were reviewed and approved by the Committee on Human Research of the Johns Hopkins Bloomberg School of Public Health. Further, the procedures were in accordance with the Helsinki Declaration. Informed consent was obtained from each participant prior to their inclusion in the study.

Materials

Diagnostic Interview Schedule (DIS). *Depression status* at baseline was measured using the DIS (Robins et al., 1981). The DIS is a standardized interview which includes questions that provide information about the appropriateness of Diagnostic and Statistical Manual of Mental

Disorders (DSM)-III diagnoses of mental disorders based on symptoms and co-occurrence of symptoms in time. Information about major depressive disorder and dysphoria was available at the symptom level and a computerized algorithm was used to construct DSM-III diagnoses. The DIS has been found to be a conservative measure of depressive disorder when compared to a psychiatrist's examination (Eaton et al., 2000). For the present study, respondents were separated into four mutually exclusive groups: Participants with (a) double depression (both diagnoses of major depression and dysthymia), (b) major depressive disorder, (c) dysthymia, or (d) neither double depression, major depression, or dysthymia at baseline.

Hopelessness. As hopelessness is not part of depression based on the DSM (APA, 2013), no item in the depression section of the DIS measures for hopelessness. Instead, hopelessness at baseline was assessed using the question, "Has there ever been a period of time when you felt that life was hopeless?" from the somatization section of the DIS (Robins et al., 1981). Participants responded "yes" or "no" to the question.

Breast Cancer Incidence and Mortality. Breast cancer incidence and mortality were collapsed to define breast cancer status. Information was ascertained through participants' self-report during the 24-year follow-up interviews or the National Death Index (NDI) through 2007. Breast cancer was considered present if it was either the primary or a contributing cause of death on a death certificate. Year of breast cancer onset was determined during the 24-year follow-up interviews by asking about the year of the first breast cancer diagnosis for those who reported having breast cancer. Time of breast cancer diagnosis was not available for cancers ascertained through the NDI. First time diagnosis dates were used to exclude participants that reported having breast cancer before baseline.

Covariates. All variables considered as covariates were selected based on a priori theory (Gallo et al., 2000; Gross et al., 2010). Age, self-reported race/ethnicity, smoking status, and socioeconomic status (SES) were considered as possible covariates in the analyses. As in previous studies testing for associations between depression and cancer using The Baltimore Epidemiologic Catchment Area (ECA) Study sample (Gross et al., 2010), smoking status at 24-year follow-up was coded into one of four groups: never smoked (0), stopped smoking (1), currently smoking less than one pack of cigarettes per day (2), and currently smoking more than one pack per day (3). SES at baseline was represented by a composite score aggregating occupational status, annual household income level, and highest level of education completed (Gallo et al., 2000). To identity their race/ethnicity, participants could choose between American Indian (*n* = 23; 2.1%), Asian (*n* = 4; 0.4%), Pacific Islander (*n* = 2; 0.2%), Black (*n* = 402; 37.4%), Hispanic (*n* = 9; 0.8%), and White (*n* = 636; 59.1%; code = 1). Because of the low number of most minority groups, all racial/ethnic minority groups were collapsed into one category (*n* = 440; 40.9%; code = 2).

Data Analysis

To evaluate the duration, severity, and combined hypotheses, three Cox proportional hazards regression models were conducted with breast cancer status as the dependent variable and with depression status as independent variable: one model with dysthymia vs. no dysthymia as the predictor, one model with major depression vs. no major depression as the predictor, and one model with double depression vs. no double depression as the predictor. The severity hypothesis would be classified as correct when major depression and double depression, but not dysthymia, significantly predict breast cancer status. The duration hypothesis would be classified as correct when dysthymia and double depression, but not major depression,

significantly predict breast cancer status. The combined hypothesis would be classified as correct when double depression, but not dysthymia and major depression, significantly predict breast cancer status.

To evaluate the hopelessness hypothesis, one additional Cox proportional hazards regression model with hopelessness vs. no hopelessness as the predictor and a paired t-test were calculated. The t-test was conducted to evaluate the regression coefficients from the significant models with one predictor (depression status *or* hopelessness) to the model with both predictors (depression status *and* hopelessness). This hypothesis would be classified as correct when a) hopelessness and depression status both significantly predict breast cancer status when not controlling for each other; b) the regression coefficient of depression status, but not hopelessness, is significantly reduced in the model with both predictors (depression status *and* hopelessness) compared to the models with one predictor (depression status *or* hopelessness).

Results

The Baltimore ECA cohort sample at baseline consisted of 1,945 women and complete data for depression status and hopelessness at baseline as well as breast cancer status 24 years later exist for 1,076 of these women (55.32% of the baseline population). Participants that reported to have been diagnosed with breast cancer before the baseline interviews ($n = 6$) were excluded from the data analyses. Thus, 1,070 women, ranging from age 19 to 87 years (mean age = 43.91 years, $SD = 17.17$) at baseline, remained in the analysis sample. The participants that remained in the analysis sample, compared to participants excluded from further analyses, were not significantly different with regard to race/ethnicity ($\chi^2(1)=0.42$; $p = .516$), hopelessness ($\chi^2(1)=0.30$; $p = .585$), dysthymia ($\chi^2(1)=0.70$; $p = .404$), major depression ($\chi^2(1)=1.36$; $p = .243$), or double depression ($\chi^2(1)=1.71$; $p = .191$) at baseline. However, participants that

dropped out were significantly older than the ones that remained in the analysis sample ($t(2068.10) = 12.66$, $p < .001$).

Within the analysis sample, at baseline 22 women fulfilled the criteria of dysthymia, 42 women fulfilled the criteria of major depression, and 10 women fulfilled the criteria of double depression at baseline. Thus, 996 women did not fulfill the criteria of any depression diagnosis at baseline. Further, 208 women answered that they had felt hopeless and 862 answered they did not feel hopeless in the baseline interview. Finally, within the analysis sample, 43 women were diagnosed for the first time with breast cancer between 1981 and 2005 and/or died with breast cancer being either the primary or a contributing cause of death. Of the women with dysthymia, major depression, and double depression at baseline 4.8%, 4.8%, and 20%, respectively, were diagnosed for the first time with breast cancer between 1981 and 2005 and/or died with breast cancer being either the primary or a contributing cause of death. Of the women without any depression diagnosis at baseline 3.5% were diagnosed for the first time with breast cancer between 1981 and 2005 and/or died with breast cancer being either the primary or a contributing cause of death.

Age, self-reported race/ethnicity, smoking status, and SES were considered as possible covariates in the analyses. Because of concerns about over-fitting models due to low counts of breast cancer incidents, smoking status and SES were dropped as covariates as they did not significantly correlate with any of the depression variables, hopelessness, or breast cancer status (Table 1). Like expected, age and race/ethnicity were positively related with breast cancer status. Thus, higher age and racial/ethnical minority status were associated with a higher likelihood of breast cancer.

To test the duration, severity, and combined hypotheses three Cox proportional hazards regression models adjusting for age and race/ethnicity were conducted. Consistent with the combined hypothesis, only double depression (p = .018) but not dysthymia (p = .903) or major depression (p = .685) at baseline predicted breast cancer status at the 24 year follow up (Table 2). These analyses demonstrated that double depression at baseline was associated with more breast cancer incidents and mortality within the next 24 years.

To test the hopelessness hypothesis two additional regression analyses were calculated. Contrary to the hypothesis, the regression with only hopelessness revealed that hopelessness at baseline significantly predicted *fewer* new cases of breast cancer and mortality in the following 24 years (p = .043; Table 2). Moreover, the adjusted Cox model that included both double depression and hopelessness as predictors of breast cancer status revealed that double depression (p = .005) and the absence of hopelessness at baseline (p = .026) remained significantly associated with breast cancer status in the following 24 years (Table 2). Finally, paired t-tests comparing the regression weights in the Cox models with only one predictor (double depression *or* hopelessness) with the regression weights in the Cox models with both predictors (double depression *and* hopelessness) were calculated. The tests revealed that the regression weights of double depression ($t(1060) = 2.96$; p = .003) and hopelessness ($t(1060) = 22.02$; $p < .001$) were actually significantly *increased* when adjusting for each other (Table 2).[1]

Discussion

Breast cancer status significantly associated with both depressive symptoms and hopelessness. Follow-up analyses examining the associations separated for breast cancer

[1] This pattern of findings is identical when only breast cancer incidents were used as dependent variable. When only breast cancer mortality was used as dependent variable, neither depression nor hopelessness were significant predictors.

incidents and mortality demonstrated that breast cancer incidents, but not mortality, were significantly associated with both depressive symptoms and hopelessness. As expected and consistent with the combined hypothesis, but contrary to the expectations regarding the duration and severity hypotheses, only double depression at baseline predicted an increase of breast cancer incidents in the following 24 years. While this finding may seem inconsistent with previous studies to breast cancer which found effects of duration (Gross et al., 2010; Penninx et al., 1998) or severity (Gross et al., 2010) of depression on breast cancer incidents and mortality, neither of the previous analyses tested for a combined effect of duration and severity. However, a longitudinal study exploring the multiplicative effect of duration and severity of depression on risk of breast cancer *hospitalization* (Jacobs et al., 2000) found that both were important in contributing to a significant relationship between depression and increased risk of breast cancer *hospitalization*, as compared to only duration or severity. Thus, the findings of the present study extend support for the role of the combined effect of severity and duration of depressive symptoms on breast cancer incidents, consistent with prior research on other breast cancer outcomes.

Regarding the hopelessness hypothesis, the analyses revealed two surprising findings. First, hopelessness at baseline was expected to be associated with *more* breast cancer incidents and *higher* mortality rate in the next 24 years. Instead, hopelessness is associated with *fewer* breast cancer incidents and not with mortality at all. Second, when controlled for each other, the strengths of the associations of double depression and hopelessness with new cases of breast cancer increased instead of becoming weaker as predicted.

Based on the findings from the current study, it may be that hopelessness is associated with less participation in breast cancer screenings, thus resulting in less breast cancer incidents

reported. Research examining hopelessness and breast cancer screening beliefs in 382 women revealed that women who expressed hope for the future were more likely to endorse motivation to engage in breast cancer screenings. Further, women with greater hope for the future reported more benefits and less barriers to the screening process (Çam et al., 2009). Thus, it is likely that greater hopelessness may be associated with less motivation and greater barriers to the breast cancer screening process, resulting in less breast cancer incidents reported. While this interpretation may explain why hopelessness was associated with fewer new breast cancer incidents, it remains unclear why hopelessness was not associated with breast cancer mortality as one would expect less breast cancer screening is associated with later discovered cases of breast cancer and therefore a higher likelihood of breast cancer mortality (for a discussion of the benefits of breast cancer screening see Gøtzsche and Jørgensen, 2013). Women who do not participate in breast cancer screenings have been found to have a higher mortality rate than women who participate in screenings (Nyström et al., 1993). However, it may be that other factors associated with breast cancer screening participation, such as knowledge or beliefs about breast cancer screenings or treatment (Magai et al., 2007), play a more significant role in mortality as an outcome, as compared to hopelessness. Future research should examine the association between hopelessness and participation in breast cancer screenings, as well as other known predictors of breast cancer screening participation and mortality, to better understand how these constructs operate together.

The study findings highlight the importance of depression screening in clinical care, particularly considering both depression severity and duration, for the prevention of future breast cancer incidents and mortality. While the prevalence of double depression is low, cases of double depression are associated with poor social and physical functioning across an extended

period of time (Rhebergen et al., 2010) and poor quality of life (Rapaport et al., 2005). Thus, it is likely that treatment services of double depression will improve quality of life and reduce economic costs associated with such mental health concerns. In sum, for the purposes of the current study, screening and treatment of patients with double depression may be an effective method of reducing future breast cancer incidence and prevention.

The results of the study should be viewed with consideration of the limitations. Hopelessness was evaluated using only one item. However, the item is comprised of the larger and comprehensive Diagnostic Interview Schedule (DIS; Robins et al., 1981), which has shown acceptable reliability and validity scores (Robins et al., 1981). Additionally, as described in other articles, one limitation associated with the ECA sample is drop-out during follow-up (see Eaton et al., 2008; Gross et al., 2010). Further, results were not adjusted for other factors that have been associated with breast cancer incidence, such as stress (Chida et al., 2008) or physical activity (Monninkhof et al., 2007). Finally, it needs to be considered that only a relatively small number of women fulfilled the diagnostic criteria of dysthymia (n = 22), major depression (n = 42), and double depression (n = 10) at baseline. Thus, while the ECA has crucial strengths, including a large representative population-based sample, an extended follow-up, and the usage of a structured interview to assess depression and hopelessness future research should replicate the present study using a multi–item instrument to measure hopelessness, measuring and controlling for more potential confounding variables, and oversampling women with dysthymia, major depression, and double depression.

In summary, the current study revealed that double depression, but not dysthymia and major depression, was positively associated with breast cancer at the 24-year follow-up; whereas, hopelessness was negatively associated with breast cancer in the next 24 years. Thus, not

severity or duration of a depressive disorder but a combination of both is crucial for the association of depression with breast cancer in the following 24 years. Future research should measure the duration and severity of depression as continuous variables and include participation in breast cancer screening and expression of negative emotional experiences as additional variables to replicate and explore possible explanations for the findings of the present study.

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