8-2012

Depression as a risk factor for breast cancer : investigating methodological limitations in the literature.

Patrick Pössel
University of Louisville

Erica Adams
University of Louisville

Jeffrey C. Valentine
University of Louisville

Original Publication Information

Pössel, Patrick, Erica Adams and Jeffrey C. Valentine. "Depression as a Risk Factor for Breast Cancer: Investigating Methodological Limitations in the Literature." 2012. *Cancer Causes & Control* 23(8): 1223–1229.

Running title: DEPRESSION AND BREAST CANCER

Depression as a Risk Factor for Breast Cancer:

Investigating Methodological Limitations in the Literature

Patrick Pössel, Dr. rer. soc., Erica Adams, PhD, and Jeffrey C. Valentine, PhD

Department of Educational and Counseling Psychology, University of Louisville

Corresponding author:

Patrick Pössel, Dr. rer. soc.

Department of Educational and Counseling Psychology

University of Louisville

2301 S. Third Street

Louisville, KY 40292

(502)852-0623 (office)

(502)852-0629 (fax)

e-mail: patrick.possel@louisville.edu

Condensed Abstract

Studies using a longer time frame found a stronger association than studies using a shorter time frame and somatic items in depression measures are positively correlated with associations of depression with breast cancer incidence. Thus, future studies should (a) ensure sufficient periods of time between the measurement of depression and the assessment of cancer, and (b) avoid measuring depression using somatic items.

Abstract

Purpose: A relationship between depression and the development of breast cancer has not been convincingly shown in the research conducted over the past three decades.

Methods: In an effort to better understand the conflicting results, a review was conducted focusing on the methodological problems associated with this literature, including time frame between the assessment of depression and the diagnosis of breast cancer and the use of somatic items in measuring depression. Fifteen breast cancer prospective studies were reviewed.

Results: While twelve of the studies found positive associations between depression and breast cancer development, three studies found negative associations. With regards to the predictive associations between depression and breast cancer incidence the findings revealed that (a) studies using a longer time frame found a stronger association than studies using a shorter time frame, and (b) studies utilizing depression measures that did not contain somatic items found a smaller association than studies utilizing depression measures that did contain these items.

Conclusions: Future studies should ensure that sufficient periods of time between the measurement of depression and the assessment of cancer and avoid measuring depression using somatic items.

Keywords: depression; time frame; somatic items; development; incidence; breast cancer

Breast cancer is consistently among the most prevalent and deadly forms of cancer. Although death rates from breast cancer have been steadily decreasing since 1990, it ranks second in cancer deaths among women (after lung cancer) and first in prevalence [1]. This might be one of the reasons for the longstanding interest in the effect of psychological factors on the development of breast cancer. Already Galen expressed the notion that psychological factors play a role in the development of cancer [2]. The author of the first statistical report relating cancer to psychological distress concluded that the cases in which breast cancer immediately follows depressive emotions were too great to be caused by chance [3]. Most modern theories proposing an influence of depression on the development of breast cancer hypothesize reduced immune function as the connecting factor between depression and breast cancer. In other words, depression impairs immune function, which in turn, predisposes an individual to the development of cancer [4]. These theories are supported by studies finding reduced numbers and functional measures of immunity in depressed individuals [5,6]. Another possible biological mechanism connecting depression with the development of breast cancer is that depression inhibits DNA repair mechanisms and, therefore, defense against cancer growth [7,8]. A final way in which depression might increase the risk of breast cancer is by causing an aberrant activity of the hypothalamic–pituitary–adrenal axis leading to a dysregulation of the stress hormone cortisol. Cortisol is involved in the control of cell growth and regulation of the cell cycle which explains why a flattening of cortisol levels throughout the course of a day has been shown to increase the risk for breast cancer [9-11].

Despite the high face-validity of the aforementioned theoretical explanations for the proposed association between depression and the development of breast cancer and more than 30 years of empirical research, including several published reviews, a clear connection, or the lack

thereof, between the presence of depression and the development of breast cancer has not been established [12-18]. Possible reasons for inconsistent results include insufficient consideration of growth rates of breast cancer and inadequate assessment of depression. The purpose of this review is to examine these possible methodological problems as they relate to the study of the development, or initiation, of breast cancer and to estimate the associations between depression and development of cancer after controlling for these confounding factors as far as possible.

Time Frame

Multiple reviews of empirical studies demonstrated that it takes more than 18 years for breast cancer with an average Tumor Volume Doubling Time (TVDT) of 280 days to grow from the first tumor cell to a tumor that is detectable [19-20]. This growth rate suggests that studies with time frames of less than 18 years are inadequate for examining the influence of major depression on the development of cancer; therefore, predictive associations are likely to be underestimated.

Thus, because this review seeks to illuminate the causative role in breast cancer, this review will focus only on studies utilizing a prospective design. Some interpret the pre-bioptic study design, which is used in some studies focusing on breast cancer, as a variation of the prospective design. These studies investigate people who come for diagnostic tests but do not yet know whether or not they have cancer [21-25]. Such patients often make guesses about their medical condition, and these expected diagnoses may influence their responses to measures of depression [14]. These studies are limited in their ability to evaluate causality and are not able to fully evaluate psychological variables in participants prior to the confirmation of benign, malignant or no breast disease under similar conditions; therefore, they will not be included in this review.

Assessment of depression

Deciding which symptoms are part of depression and which may be attributable to cancer is complex. There is evidence to suggest that the inclusion of somatic items may overestimate the association between depression and cancer. For example, one study explored the role of somatic items in the diagnosis of depression in cancer patients by dividing the Zung Self-Rating scale into a questionnaire with and without somatic items. The questionnaire with somatic items produced 5% more false-positive depressed cancer patients [26]. In addition, Wedding et al. [27] analyzed the extent to which the prevalence of major depression or depressive symptoms in cancer patients was related to somatic or affective items of the Beck Depression Inventory when compared to healthy controls. They found that major depression and depressive symptoms were mainly related to somatic, not affective, items and that differences compared to a healthy control group existed mainly in the somatic items. In light of this, Endicott [28] suggested substituting poor appetite disturbance, sleep disturbance, fatigue/loss of energy, and diminished ability to concentrate/indecisiveness. Other authors [29], however, conclude that, while somatic symptoms of depression are less useful than affective and cognitive symptoms, they could be used if they were severe and proportionate to the cancer stage. In addition, cultural differences in the expression of depression need to be considered. For example, somatic symptoms of depression are more clearly manifest in Asian cultures than affective and cognitive symptoms [30]. Thus, it would be important to identify the role somatic symptoms play in regards to the measured association between depression and breast cancer. To study this problem, the following symptoms, put forth as diagnostic criteria for a major depressive episode in the *Diagnostic and Statistical Manual of Mental Disorders (*4th ed.; DSM-IV) [31] were categorized as somatic: appetite disturbance, sleep disturbance, fatigue/loss of energy, and diminished ability to

concentrate/ indecisiveness [28,32]. Other depression symptoms encountered in this review were considered to be somatic if they were categorized as such by the measurement scale being used (e.g., Zung Rating Depression Scale) [33].

Method

This review explores the evidence regarding whether major depression plays a causal role in the development of breast cancer; therefore, we have focused only on studies utilizing a prospective design (i.e., assess depression at one point in time, and cancer at a second, later point in time). A literature search was conducted using Academic Search Premier, Medline, Psychology and Behavioral Sciences Collection, and PsycINFO. Key words were *depress** + *cancer, neoplasm, or tumor + longitudinal, or prospective + breast* in January 2012. Secondary searches were conducted through the references lists of relevant reviews and meta-analyses [12-18]. These searches identified 481 reports; however, after removing duplicates, screening the reports, assessing them for eligibility, and excluding all articles that did provide an indication of the direction of the effect, 15 reports remained (see Figure 1). Time frame, assessment of depression, analytical sample size, and incidence of breast cancer of these reports are described in Table 1. In those reports that presented separate data for males and females, analytical sample size and incidence of breast cancer are presented for females only.

Meta-analysis usually involves computing a weighted average effect size that represents the magnitude of the relations of interest. This procedure presumes that the standard errors for the effect sizes have the same conceptual meaning. Regression-based studies are challenging in this regard, because conceptually similar variables are rarely controlled across studies. This means that the population effects actually have different conceptual meanings across the studies, and unless the evidence base has a very large number of studies, meta-analysis would be difficult

due to the number of sparse or empty cells. Furthermore, prospective studies sometimes present data in ways that make combining effect sizes across studies more difficult. For example, some studies might carry out time-to-event analyses while others measure cross-sectional effects.

Given the conceptual differences in the meaning of effects across studies that examine the prospective relation between depression and breast cancer, we could not rely on traditional meta-analytic procedures. Instead, we conducted a weighted vote count of the directions of the effect [34]. Taking into account the sample sizes from the individual studies, this procedure exploits information about the proportion of positive to negative effects to bootstrap an estimate of an overall weighted average effects size and its confidence interval. It is a more conservative procedure in the sense that the resulting confidence intervals are wider than those that would arise from a more ideal analysis (e.g., a meta-analysis of regression coefficients based on models of exactly the same covariates across studies).

Results

Eighteen prospective studies, covering over 600,000 participants, were dedicated to investigating the risk of breast cancer incidence associated with depression. Of these 18 studies, three studies did not give an indication of the direction of the effect [35-37]. In other words, the authors simply stated that the results were not statistically significant and provided no clues regarding the sign of the effect. These three studies could not be used in the following analyses. Of the 15 studies providing information about the direction of the effect, twelve were positive (i.e., depression was associated with higher breast cancer incidence)[1], while three were negative. Assuming equal weights across studies (specifically, the harmonic mean sample size of 4,309), the estimated correlation is $r = +.04$. Taking sample size of the individual studies into account,

[1] It should be noted that Gross et al.'s [49] publication is an update of Gallo et al. [47] including an additional wave of data collection which extends the time frame from 13 to 24 years. In addition, both studies use only partially identical methodological control variables.

the estimated correlation is $r \approx +.025 \pm .027$ (95% Confidence Interval). Thus, the correlation is not significantly different from zero.

As discussed above, these estimates are associated with uncertainty due to the potential influence of different methodological problems (i.e., time frame between the assessment of depression and cancer, assessment of depression). Below we present data on how the different methodological issues were related to the effects observed in the studies. Ideally, we would have been able to conduct a moderator analysis to determine if these observed differences in rates were indicative of real differences in rates attributable to the study characteristics. In many cases, however, the presence of empty cells made these analyses impossible. Consequently, we show how different methodological choices are associated with estimated effects for some variables; for others, we were unable to carry out this analysis.

Time Frame

The time frame necessary to study the influence of depression on breast cancer is more than 18 years [19]. Although we recognize that the cost and time associated with conducting a study with 18+ years of follow-up would be substantial, this length of follow-up is considered ideal for empirical study. Of the 15 breast cancer studies in our analysis, only five had a time frame of more than 18 years (ranging from 24 to 33 years). Six studies had a time frame between 10 and 18 years, and four studies had a time frame of less than 10 years (Table 1). Separating the studies based on the time frame revealed that 100% (5 of 5 studies) of the studies with appropriate time frame (i.e., >18 years) found positive associations between depression and breast cancer. Of the studies with shorter time frames, 70% (7 of 10 studies) found positive associations between depression and breast cancer incidence rates.

Assessment of depression

The studies included in this review were appraised according to their use of somatic symptoms in assessing major depression. There was extreme variability in the methods used by the studies to assess for depression (See Table 1), and the instruments used varied significantly in the number and percentage of somatic items they contained (0% to 44%, Table 2). Only one of the 15 studies reviewed utilized assessment methods that did not include any somatic items [48]. Eleven studies, on the other hand, utilized instruments that were more than 20% somatic items.

Of the studies that utilized instruments with less than 20% somatic items, 33.3% (1 of 3) found positive and 66.6% (2 of 3) found negative associations between depression and breast cancer. Of the studies that utilized instruments with more than 20% somatic items, 90.9% (10 of 11) found positive associations, while only 9.1% (1 of 11) study found negative associations between depression and breast cancer. This difference suggests that somatic items may result in an overestimation of the association between depression and breast cancer.

Discussion

The purpose of this review was to examine the effects of (a) insufficient time frame and (b) assessment of depression including somatic items on the study of the development of breast cancer. It was expected that an insufficiently long time frame would lead to an underestimation of the association between depression and cancer, while the inclusion of somatic items in the assessment of depression would lead to an overestimation of the association between depression and breast cancer.

Using sample size as a weight, the estimated predictive associations between depression and development of breast cancer incidence is approximately $r = +.025 \pm .027$ (95% Confidence Interval). Thus, the estimated predictive associations are not significant. This estimate is associated with additional uncertainty, however, due to the possibility of the discussed

methodological problems. Therefore, we examined how the proportion of positive (12 studies) and negative effects (3 studies) varied as a function of studies scoring "well" vs. "not well" on two dimensions. These findings were as predicted. Not only did a short time frame appear to underestimate the association, but every study with an appropriate time frame found a positive association between depression and breast cancer incidence. Furthermore, studies utilizing measures of depression with higher percentage of somatic items were more likely to find positive associations than studies with lower percentage of somatic items.

Clearly, the current review has limitations. All studies we identified relied on a single diagnosis or assessment of depressive symptoms. A hypothesis linking depression and breast cancer development presumably implies some element of chronicity; therefore, a one-time assessment of depression with no measure of duration weakens the test of any such hypothesis [15]. Evidence regarding the differential effects of short vs. long-term depression comes from a study evaluating the impact of a single episode of Major Depression, recurrent episodes of Major Depression, and Dysthymia on the development of breast cancer [41]. Single and recurrent episodes of Major Depression did not significantly predict the development of breast cancer in this study; however, Dysthymia did. This is interesting since an episode of Major Depression requires more symptoms, but it can be as short as two weeks. Dysthymia, on the other hand, requires fewer symptoms, but the symptoms need to be present for at least two years. A related issue is the need for more thorough psychological assessment that includes different trait and state-like constructs. Stable constructs like cognitive risk factors of depression may account for more variance in health-related outcomes than do episodic bouts of depressive symptomatology (i.e., episode of Major Depression). For example, rumination, a trait-like cognitive style in which individuals respond to a sad mood by repetitively focusing their attention on their mood

and implications of the mood, does not only prolong depressive mood [52] but is also associated with the immune suppressive hormone cortisol, even after controlling for depressive symptoms [53].

Regarding our methods, one drawback to the weighted vote count approach is that, relative to a more traditional meta-analysis of effect sizes, it has lower statistical power (i.e., confidence intervals arising from a weighted vote count will be wider). A second potential problem is that this procedure uses a fixed effect model, and if that model is inappropriate, the resulting confidence intervals could be spuriously narrow. Future systematic reviews and meta-analyses would benefit from additional studies that allow for a reasonable amount of time between the assessments of depression and cancer. Although it would be resource intensive, a meta-analysis involving individual participant data would be a valuable contribution to this area of research. It would allow reviewers to create conceptually similar groups of effect sizes to better explore both the link between depression and breast cancer as well as the impact of certain methodological choices.

Another direction for future research is to evaluate the impact of other risk factors and regulators on the association between depression and the development of breast cancer. When other potential risk factors and regulators are not identified, measured, and controlled for by appropriate design or statistical techniques, they can bias the results of a study, leading researchers to make erroneous conclusions. Thus, methodological control has a substantial influence on the empirical findings of a study. Certain variables (e.g., smoking), however, are likely to be stronger confounders than other variables (e.g., alcohol consumption). Thus, systematic reviews should categorize potential confounders and then evaluate their impact on the association between depression and development of breast cancer.

Finally, it needs to be considered that all three studies finding negative associations between depression and breast cancer incidence [33, 39, 43] and six studies finding positive associations [40-42, 44, 47, 48] included fewer than 220 individuals that developed breast cancer, while all studies finding positive associations had numbers of individuals developing breast cancer ranging from 229 to 2,892 cases of breast cancer [38, 45, 46, 49-51]. Thus, the small number of breast cancer cases could be another explanation for the negative associations between depression and breast cancer incidence.

In summary, twelve studies included in the review found positive associations between depression and breast cancer incidence while three studies found negative associations. The vote count revealed relations between depression and breast cancer that, while not statistically significant, were large enough to be meaningful at a population level. Perhaps even more important is our observation that the existing literature related to depression and the development of breast cancer revealed significant problems concerning time frame and the measures used to assess depression. The findings related to the predictive associations between depression and breast cancer incidences revealed that (a) studies with inappropriate short time frame underestimate the association and (b) utilizing measures of depression with somatic items overestimate positive associations. Although there is evidence that depression is positively associated with breast cancer incidence, the current literature does not allow for definitive conclusions.

Acknowledgements

The review was not supported by any kind of grant.

The authors declare that they have no conflict of interest.

References

1. American Cancer Society. Cancer Facts & Figures 2010. Available from URL: http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-026238.pdf [accessed September 5, 2011]
2. Greer S. Cancer and the mind. *British Journal of Psychiatry*. 1983;14: 535-543.
3. Snow HL. Cancer and the cancer process. London: Churchill, 1893.
4. Ader R, Cohen N, Felten D. Psychoneuroimmunology: interaction between the nervous system and the immune system. *Lancet*. 1995;345: 99–103.
5. Andersen BL, Farrar WB, Golden-Kreutz D, et al. Stress and immune responses after surgical treatment for regional breast cancer. *Journal of the National Cancer Institute.* 1998;90:30–36.
6. Schleifer SJ, Keller SE, Bartlett, JA, Eckholdt HM, Delaney BR. Immunity in young adults with major depressive disorder. *American Journal of Psychiatry*. 1996;153:477–482.
7. Kiecolt-Glaser JK, Robles TF, Heffner KL, Loving TJ, Glaser R. Psycho-oncology and cancer: psychoneuroimmunology and cancer. *Annals of Oncology*. 2002;13:165–169.
8. Glaser R, Thorn BE, Tarr KL, Kiecolt-Glaser JK, D'Ambrosio SM. Effects of stress on methyltransfease synthesis: an important DNA repair enzyme. *British Journal of Health Psychology*. 1985;4:403-412.
9. Pulaski L, Kania K, Ratajewski M, et al. (2005). Differential regulation of the human MRP2 and MRP3 gene expression by glucocorticoids. *Journal of Steroid Biochemistry and Molecular Biology*. 2005;96:229–234.
10. Su F, Ouyang N, Zhu P, et al. Psychological stress induces chemoresistance in breast cancer by upregulating mdr1. *Biochem Biophys Res Commun*. 2005;329:888–897.

11. Ticher A, Haus E, Ron IG, et al. The pattern of hormonal circadian time structure (acrophase) as an assessor of breast cancer risk. *International Journal of Cancer*. 1996;65:591–593.
12. Butow PN, Hiller JE, Price MA, Thackway SV, Kricker A, Tennant CC. Epidemiological evidence for a relationship between life events, coping style, and personality factors in the development of breast cancer. *Journal of Psychosomatic Research*. 2000;49:169-181.
13. Dalton SO, Boesen EH, Ross L, Schapiro IR, Johansen C. Mind and cancer: Do psychological factors cause cancer? *European Journal of Cancer*. 2002;38:1313-1323.
14. Garssen B. Psychological factors and cancer development: evidence after 30 years of research. *Clinical Psychology Review*. 2004;24:315-338.
15. McGee R, Williams S, Elwood M. Depression and the development of cancer: a meta-analysis. *Social Science & Medicine*. 1994;38:187-192.
16. McKenna MC, Zevon MA, Corn B, & Rounds J. Psychosocial factors and the development of breast cancer: a meta-analysis. *Health Psychology*. 1999;18:520-531.
17. Oerleman MEJ, van den Akker M, Schuurman, AG, Kellen E, Buntinx F. A meta-analysis on depression and subsequent cancer risk. *Clinical Practive and Epidemiology in Mental Health.* 2007;3:29.
18. Spiegel D, Giese-Davis J. Depression and cancer: mechanisms and disease progression. *Biological Psychiatry*. 2003;54:269-282.
19. Friberg S, Mattson S. On the growth rates of human malignant tumors: implications for medical decision making. Journal of Surgical Oncology. 1997;65:284-297.
20. Spratt JS, Meyer JS, Spratt JA. Rates of growth of human solid neoplasms: Part II. *Journal of Surgical Oncology* 1996;61:68–83.

21. Eskelinen M, Ollonen P. Beck Depression Inventory in patients with breast disease and breast cancer: A prospective case-control study. *In Vivo*. 2011;25:111-116.
22. Eskelinen M, Ollonen P. Montgomery-Asberg Depression Rating Scale (MADRS) in healthy study subjects, in patients with breast disease and breast cancer: A prospective case-control study. *Anticancer Research*. 2011;31:1065-1069.
23. Eskelinen M, Ollonen P. Montgomery-Asberg Depression Rating Scale (MADRS) in healthy study subjects, in patients with breast disease and breast cancer: A prospective case-control study. *Anticancer Research*. 2011;31:1065-1069.
24. Eskelinen M, Ollonen P. Measurement of pessimism: Hopelessness Scale in healthy study subjects, in patients with breast disease and breast cancer: A prospective case-control study in Finland. *Anticancer Research*. 2011;31: 4019-4023.
25. Ollonen P, Lehtonen J, Eskelinen M. Anxiety, Depression and the history of psychiatric symptoms in patients with breast disease: A prospective case-control study in Kuopio, Finland. *Anticancer Research*. 2005;25:2527-2534.
26. Dugan W, McDonald MV, Passik SD, Rosenfeld BD, Theobald D, Edgerton S. Use of the Zung Self-Rating Depression Scale in cancer patients: feasibility as a screening tool. *Psycho-Oncology*. 1998;7:483-493.
27. Wedding U, Koch A, Röhrig B et al. Requestioning depression in patients with cancer: contribution of somatic and affective symptoms to Beck's Depression Inventory. *Annals of Oncology*. 2007;18:1875-1881.
28. Endicott J. Measurement of depression in patients with cancer. *Cancer*. 1984;53:2243-2248.
29. Cavaugh S. Diagnosing depression in the hospitalised patient with chronic medical illness. *Journal of Clinical Psychiatry*. 1984;45:13-16.

30. Ryder AG, Yang J, Zhu X, Yao S, Yi J, Heine SJ, Bagby RM. The cultural shaping of depression: Somatic symptoms in China, psychological symptoms in North America? *Journal of Abnormal Psychology*. 2008;117:300-313.
31. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). 4th ed*. Washington, DC: American Psychiatric Association., 1994.
32. Akechi T, Nakano T, Akizuki N, et al. Somatic symptoms for diagnosing major depression in cancer patients. *Psychosomatics*. 2003;44:244-248.
33. Bleiker EM, Hendriks JH, Otten JD, Verbeek AL, van der Ploeg HM. Personality factors and breast cancer risk: a 13-year follow-up. *Journal of the National Cancer Institute*. 2008;100:213-218.
34. Bushman BJ, Wang MC. Vote-counting procedures in meta-analysis. In: Cooper H, Hedges LV, Valentine JC,editors. *The handbook of research synthesis and meta-analysis, 2nd ed*. New York: Russell Sage Foundation, 2009:207-220.
35. Aro AR, de Koning HJ, Schreck M, Hendriksson M, Anttila A, & Pukkala E. Psychological risk factors of incidence of breast cancer: a prospective cohort study in Finland. *Psychological Medicine*. 2005;35:1515-1521.
36. Bleiker EMA, van der Ploeg JHCL, Hendriks HJA. Personality factors and breast cancer development: a prospective longitudinal study. *Journal of the National Cancer Institute*. 1996;88:1478-1482.
37. Penninx BW, Guralnik JM, Pahor M, et al. Chronically depressed mood and cancer risk in older persons. *Journal of the National Cancer Institute*. 1998;90:1888-1893.

38. Goldacre MJ, Wotton CJ, Yeates D, Seagroatt V, Flint J. Cancer in people with depression and anxiety: record-linkage study. *Social Psychiatry and Psychiatric Epidemiology*. 2007;42:683-689.

39. Nykliček I, Louwman WJ, Van Nierop PW, Wijnands CJ, Coebergh JW, Pop VJ. Depression and the lower risk for breast cancer development in middle-aged women: a prospective study. *Psychological Medicine*. 2003;33:1111-1117.

40. Gallo JJ, Armenian HK, Ford DE, Eaton WW, Khachaturian AS. Major depression and cancer: the 13-year follow-up of the Baltimore epidemiologic catchment area sample (United States). *Cancer Causes & Control*. 2000;11:751-758.

41. Gross AL, Gallo JJ, Eaton WW. Depression and cancer risk: 24 years of follow-up of the Baltimore Epidemiologic Catchment Area sample. *Cancer Causes & Control*. 2010;21:191-199.

42. Jacobs JR, Bovasso GB. Early and chronic stress and their relation to breast cancer. *Psychological Medicine*. 2000;30:669-678.

43. Lichtman JH. *Are depressive symptoms, social networks and social support, or self-evaluated health measures predictive of cancer incidence and stage of diagnosis? Evidence from a prospective community based sample of elderly New Haven residents* (Doctoral dissertation). Yale University, New Haven, CT., 1996.

44. Hahn RC, Petitti DB. Minnesota Multiphasic Personality Inventory-rated depression and the incidence of breast cancer. *Cancer*. 1988;61:845-848.

45. Hjerl K, Andersen EW, Keiding N et al. Breast cancer risk among women with psychiatric admission with affective or neurotic disorders: a nationwide cohort study in Denmark. *British Journal of Cancer*. 1999;81:907-911.

46. Dalton SO, Mellemkjaer L, Olsen JH, Mortensen PB, Johansen C. Depression and cancer risk: a register-based study of patients hospitalized with affective disorders, Denmark, 1969-1993. *American Journal of Epidemiology*. 2002;155:1088-1095.

47. Kaplan GA., Reynolds P. Depression and cancer mortality and morbidity: prospective evidence from the Alameda County study. *Journal of Behavioral Medicine*. 1988;11:1-13.

48. Knekt P, Raitasalo R, Heliövaara M, et al. Elevated lung cancer risk among persons with depressed mood. *American Journal of Epidemiology*. 1996;144:1096-1103.

49. Chen Y-H, Lin H-C. Increased risk of cancer subsequent to severe depression-A nationwide population-based study. *Journal of Affective Disorders.* 2011;131:200-206.

50. Liang J-A, Sun L-M, Muo C-H, et al. The analysis of depression and subsequent cancer risk in Taiwan. *Cancer Epidemiology, Biomarkers & Prevention.* 2011;20:473-475.

51. Schuurman AG, van den Akker M, Ensinck KTJL et al. *Does depression increase susceptibility for somatic disease?* NWO-report. Maastricht: Research Institute Ex Tra, 2001.

52. Kuehner C, Holzhauer S, Huffziger S. Decreased cortisol response to awakening is associated with cognitive vulnerability to depression in a nonclinical sample of young adults. *Psychoneuroendocrinology.* 2007;32:199-209.

53. Nolen-Hoeksema S, Morrow J. A prospective study of depression and posttraumatic stress symptoms after a natural disaster: The 1989 Loma Prieta earthquake. *Journal of Personality and Social Psychology.* 1991;61:115-121.

Table 1. Summary of studies examining depression and the development of breast cancer included in the analyses

Study Author(s) & Year	Time Frame (in years)	Depression measure	Analytical sample/incidence of breast cancer
Bleiker et al. [33]	13	Zung Rating Scales for Depression	9,705/217[a]
Goldacre et al. [38]	33	ICD 7-10	276,627[c]/229[a]
Nykliček et al. [39]	5	EDI	5,191/58[a]
Gallo et al. [40]	13	DIS	1,213/25[a]
Gross et al. [41]	24	DIS	3,481/50[a]
Jacobs & Bovasso [42]	15	DIS	1,213/39[a]
Lichtman [43]	6	CES-D	1,458/26[a]
Hahn & Petitti [44]	15 to 18	MMPI-1	8,932/117[a]
Hjerl et al. [45]	24	ICD 8	66,648/1,270[a]
Dalton, Mellemkjaer et al. [46]	24	ICD 8	89,491/1,391[b]
Kaplan & Reynolds [47]	17	HPL	6,848/77[b]
Knekt et al. [48]	14	GHQ	3,773/210[a]
Chen & Lin [49]	5	ICD 9	4,668/273[b]
Liang et al. [50]	8	ICD 9	75,771/2,892[b]
Schuurman et al. [51]	25	ICHPPC-2	68,366/728[b]

Note: MMPI-1 = Minnesota Multiphasic Personality Inventory -1st edition, HPL = Human Population Laboratory, CES-D = Center for Epidemiological Studies-Depression, GHQ = General Health Questionnaire, ICD = International Classification of Diseases, DIS = Diagnostic Interview Schedule, EDI = Edinburgh Depression Inventory, ICHPPC-2 = International Classification of Health Problems in Primary Care, [a] = females only, [b] = females and males, [c] = Goldacre et al. report an overall sample size of n = 553,254 and to calculate the analyses with breast cancer with female participants only. However, they do not report the number females in their sample. Thus, for the purpose of the weighted vote count, we estimated the sample would include 50% female participants.

Table 2. Breast cancer studies with confounding variables and direction of their findings

Study Author(s)	Time Frame (in years)	Assessment (Somatic Items)	Effect size and 95% CI (most adjusted model)	Direction of Association between depression and breast cancer
Bleiker et al. [33]	13	10 out of 20	0.75 (0.52-1.07)[b]	Negative
Goldacre et al. [38]	33	2 out of 6	0.92 (0.80-1.05)[c]	Positive
Nykliček et al. [39]	5	1 out of 10	0.29 (0.09-0.92)[b]	Negative
Gallo et al. [40]	13	4 out of 8	3.8 (0.5-3.4)[d]	Positive
Gross et al. [41]	24	4 out of 8	1.87(1.16-3.01)[a]	Positive
Jacobs & Bovasso [42]	15	4 out of 8	17.2 (3.76-78.08)[b]	Positive
Lichtman [43]	6	3 out of 20	0.9 (NR)[b]	Negative
Hahn & Petitti [44]	15 to 18	14 out of 57	1.5 (0.9-2.5)[d]	Positive
Hjerl et al. [45]	24	2 out of 6	1.02 (0.97-1.08)[e]	Positive
Dalton, Mellemkjaer et al. [46]	24	2 out of 6	1.06 (0.98-1.15)[e]	Positive
Kaplan & Reynolds [47]	17	4 out of 18	1.13 (NR)[d]	Positive
Knekt et al. [48]	14	0 out of 18	1.65 (0.60-4.58)[d]	Positive
Chen & Lin [49]	5	2 out of 6	1.25 (0.42-3.76)[a]	Positive
Liang et al. [50]	8	2 out of 6	1.09 (0.78-1.53)[a]	Positive

Schuurman et al. [51]	25	1 out of 6	1.06 (0.71-1.58)[a]	Positive

Note: [a] = hazard ratio; [b] = odds ratio; [c] = rate ratio; [d] = relative risk; [e] = standardized incidence ratio; (NR) = confidence interval not reported; Positive = positive association between depression and cancer; Negative = negative association between depression and cancer.

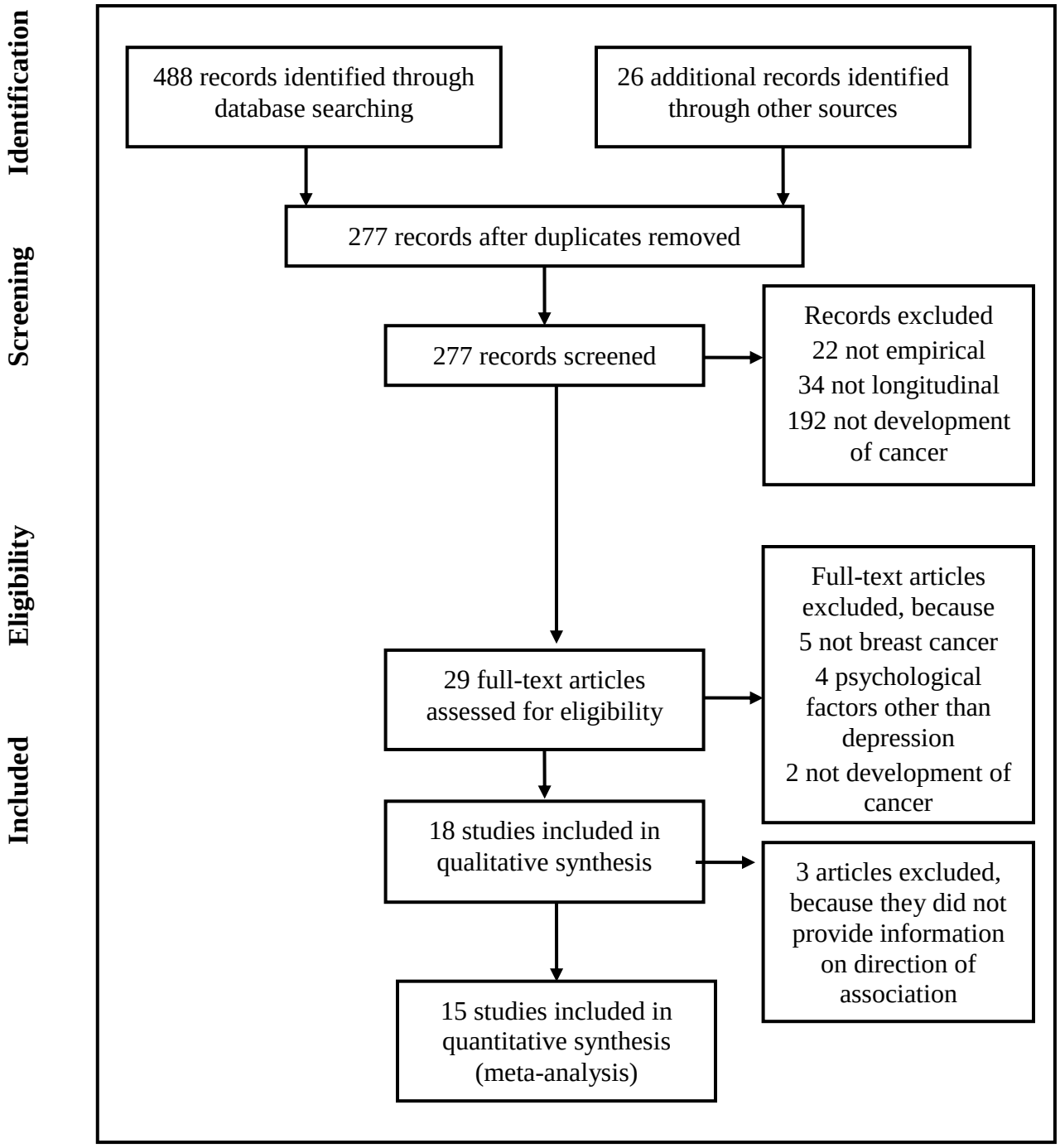

Figure 1: Flowchart for the literature screening process.