

## RESEARCH ARTICLE

# Depression and the Risk of Breast Cancer: A Meta-Analysis of Cohort Studies

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### Abstract

**Background:** Whether depression causes increased risk of the development of breast cancer has long been debated. We conducted an updated meta-analysis of cohort studies to assess the association between depression and risk of breast cancer. **Materials and Methods:** Relevant literature was searched from Medline, Embase, Web of Science (up to April 2014) as well as manual searches of reference lists of selected publications. Cohort studies on the association between depression and breast cancer were included. Data abstraction and quality assessment were conducted independently by two authors. Random-effect model was used to compute the pooled risk estimate. Visual inspection of a funnel plot, Begg rank correlation test and Egger linear regression test were used to evaluate the publication bias. **Results:** We identified eleven cohort studies (182,241 participants, 2,353 cases) with a follow-up duration ranging from 5 to 38 years. The pooled adjusted RR was 1.13(95% CI: 0.94 to 1.36;  $I^2=67.2\%$ ,  $p=0.001$ ). The association between the risk of breast cancer and depression was consistent across subgroups. Visual inspection of funnel plot and Begg's and Egger's tests indicated no evidence of publication bias. Regarding limitations, a one-time assessment of depression with no measure of duration weakens the test of hypothesis. In addition, 8 different scales were used for the measurement of depression, potentially adding to the multiple conceptual problems concerned with the definition of depression. **Conclusions:** Available epidemiological evidence is insufficient to support a positive association between depression and breast cancer.

**Keywords:** Depression - breast cancer - meta-analysis

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### Introduction

Depression is highly prevalent in the general population, and it is estimated that 5.8% of men and 9.5% of women will experience a depressive episode in a 12-month period. The lifetime incidence of depression has been estimated at more than 16% in the general population (World Health Organization, 2001; Kessler et al., 2003; World Health Organization, 2008). Breast cancer is by far the most common cancer in women (International Agency for Research on Cancer, 2008), the global burden of breast cancer measured by incidence and mortality is substantial and on the increase (Benson et al., 2012). There are an estimated 1.5 million cases diagnosed annually and almost 0.5 million died from this disease, representing 14% of female cancer deaths in the worldwide (Jemal et al., 2011; Benson et al., 2012). Many factors have been shown to be associated with the occurrence of breast cancer, such as having a first degree relative with breast cancer, bearing the first child at a late age, alcohol consumption and long term use of menopausal estrogen replacement therapy (Kampert et al., 1988; Gail et al., 1989; Slattery et al., 1993). However, it has long been debated that whether

depression is an increased risk of the development of breast cancer. Depression may affect the endocrine and immune function (Kowal et al., 1955; Miller et al., 1993), which may have influence on cancer initiation and progression, including breast cancer. Importantly, women themselves widely believed that depression was a risk factor in the development of their breast cancer (Mitchell et al., 1995). However epidemiology evidences on the association between depression and breast cancer incidence are mixed and inconclusive.

A great many of studies have assessed the association between depression and subsequent risks of breast cancer. A previous meta-analysis (Oerlemans et al., 2007) focusing on breast cancer pooled results from 7 prospective studies published before 2003 as a secondary analysis and reported a pooled relative risk estimated of 1.59 (95% confidence intervals, 0.74-3.44). Since then some cohort studies have been published, which provide stronger evidence of the association between depression and breast cancer. Therefore, we conducted a meta-analysis of cohort studies to describe the association between depression and risk of breast cancer.

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## Materials and Methods

### Search strategy

We conducted a systematic literature search (up to April 2014) of Medline, Embase, Web of Science for studies describing the association between depression and breast cancer. We used the following terms “*depression*” or “*depressive disorder*” or “*major depressive disorder*” or “*depressive symptoms*” and “*breast cancer*” or “*breast carcinoma*” combined with “*cohort study*” or “*prospective study*” or “*follow-up study*” or “*longitudinal study*”. In addition, studies from reference lists of all relevant publications and reviews were searched to identify potential pertinent studies.

### Study selection

Studies meeting the following criteria would be included in this meta-analysis: *i*) the study was a cohort design (prospective cohort or historical cohort); *ii*) the exposure was depression symptoms or depressive disorder which were measured by self-reported scales or structured clinical interview or clinician diagnosis; *iii*) the endpoint was diagnosis or report of breast cancer, all participants were free of any subtypes of cancer at the beginning of the study; *iv*) the study reported the RR or hazard risk (HR) with corresponding 95% CIs for the association between depression and breast cancer; and *v*) study was published in English. If multiple independent published reports were from a same cohort, only the latest one was included. Study selection was independently performed by two authors (S.H.L and D.X.X) and conflicts were resolved through discussion with the third reviewer (L.Z.X).

### Data extraction

We extracted the following information from each retrieved article: name of the first author, year of publication, study location, characteristics of study population at baseline, duration of follow-ups, sample size, numbers of cases, depression and breast cancer measurements, adjusted effect estimate and corresponding 95% CIs, and variables used in multivariable analysis.

Quality assessment was performed according to the Newcastle-Ottawa quality assessment scale for cohort studies (Wells et al., 2006) by two investigators (S.H.L and D.X.X). This scale allocates a maximum of nine points for quality of selection (0-4 points), comparability (0-2 points), exposure and outcome of study participants (0-3 points). The two authors discussed the implementation of this assessment tool and agreed on a method of implementation before their independent assessments of studies. The level of agreement between the two reviewers was calculated by another investigator (L.Z.X).

### Statistical analysis

The RRs were used as the common measure of association across studies, and the hazard ratios (HRs) were considered equivalent to RRs. Forest plot was produced to visually assess the RRs and corresponding 95% CIs across studies. Statistical heterogeneity across studies was estimated by  $I^2$  statistic.  $I^2$  values of 25%, 50%, 75% are regarded as cut-off points for low, moderate and

high degrees of heterogeneity, respectively (Higgins et al., 2003). The RRs were pooled using the fixed-effect model if no or low heterogeneity was detected, or random-effect model otherwise (DerSimonian et al., 1986). In sensitivity analyses, we conducted leave-one-out analysis (Wallace et al., 2009) for each study to examine the magnitude of influence of each study on pooled risk estimates. Subgroup analyses for study location, number of participants and cases, follow-up time, exposure measurement, smoking or alcohol drinking and study quality were conducted to examine the robustness of the primary results. Visual inspection of a funnel plot and Begg rank correlation test, Egger linear regression test (Begg et al., 1994; Egger et al., 1997) were used to evaluate the potential publication bias. The Duval and Tweedie nonparametric trim-and-fill procedure (Duval et al., 2000) was used to further assess the possible effect of publication bias. All statistical analyses were performed with STATA version 11.0 (StataCorp, College Station, Texas, USA). All tests were two sided with a significance level of 0.05.

## Results

### Eligible studies

Totally 1705 articles were identified from the Medline, Embase, Web of Science. After the first round of screening based on titles and abstracts with aforementioned criteria, 1682 articles were excluded. Examining the articles remained in more details, nine articles (Hahn et al., 1988; Jacobs et al., 2000; Dalton et al., 2002; Nyklicek et al., 2003; Goldacre et al., 2007; Gross et al., 2010; Chen et al., 2011; Liang et al., 2011; Lemogne et al., 2013) met the inclusion criteria. The detailed reasons for exclusion were shown in Figure 1. Besides, one article (Schuurman et al., 2001) was found from the previous meta-analysis (Oerlemans et al., 2007) and one (Knekt et al., 1996) was identified by searching the reference lists. In total, eleven articles were included in this meta-analysis.

### Study characteristics

Characteristics of the eleven articles were showed in Table 1. These studies were published between 1988 and 2013. The sample size of studies varied from 1,533 to 57,320, with a total of 182,241, and the number of breast cancer cases ranged from 20 to 728, with a total of 2,353. With regard to study location, three studies were conducted in the USA, two studies in Taiwan, two in Netherlands, one in France, one in the UK, one in Denmark, and one in Finland. In four of eleven studies, depression was measured by self-reported scales which were the Center for Epidemiologic Studies Depression Scale (CES-D), General Health Questionnaire (GHQ), Minnesota Multiphasic Personality Inventory (MMPI), and Edinburgh Depression Scale (EDS). Two studies used the Diagnostic Interview Schedule (DIS) and one used International Classification of Health Problems in Primary Care (ICHPPC) to define depression. The other four studies defined depression according to the International Classification of Disease, Ninth Revision, Clinical Modification or International Classification of Disease, Eighth Revision, Clinical Modification (ICD-9-CM or

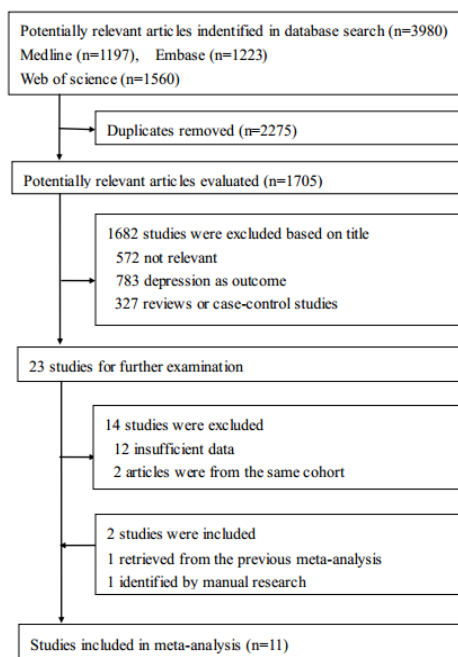
**Table 1. Characters of Included Studies of an Association of Depression with Breast Cancer Risk**

References	Study location	No. of participants	Cases	Follow-up years	Age	Depression measures	Breast cancer measures	Adjusted Effect estimate and 95%CI	Adjusted factors	Study quality
Lemogne et al., 2013	Franch	3184	128	15	mean 45.7	CES-D	self-report	1.01 (0.66-1.55)	age, cupational grade, alcohol consumption, smoking, fruit and vegetable consumption, height, weight, physical activity, health status	7
Ji-An et al, 2011	Taiwan	45819	325	8	NA	ICD-9-CM	Register database	1.09 (0.78-1.53)	age, urbanization, comorbidity	7
Yi-Hua et al, 2011	Taiwan	1836	20	5	≥18	ICD-9-CM	register database	1.25 (0.42-3.76)	age	7
Alden et al, 2010	USA	1945	50	24	mean 46	DIS-diagnosed MDD	self-reports and National Death Index (NDI)	4.4 (1.08-17.6)	age, race, marital status, smoking, parity, alcohol, socioeconomic status	8
Goldacre, et al, 2007	UK	17701	229	38	NA	ICD-9-CM	medical records and death certificates	0.92 (0.80-1.05)	age	6
Nyklicek, et al, 2003	The Netherlands	5191	58	5	mean 50	10-item EDS≥11	register database	0.29 (0.09-0.91)	family history of breast cancer, parity, age at first parity above 30, body mass index, menopausal status, education, breastfeeding, physical exercise, alcohol, menopause, oophorectomy, hypothyroidism	8
Dalton et al, 2002	Denmark	57320	601	12.5	mean 49.7	ICD-8-CM	death certificate	1.04 (0.97-1.11)	age, calendar-year-specific incidence rates	8
Schuurman et al, 2001	The Netherlands	35007	728	25	NA	ICHPPC-2	NA	1.06 (0.71-1.58)	age, social status	6
Jacobs et al, 2000	USA	1533	40	15	mean 48	DIS-diagnosed MDD	self-report	17.20 (3.67-77.08)	age, smoking, alcohol	6
Knekt et al, 1996	Finland	3773	54	14	≥0	36-item GHQ	medical records	1.96 (0.88-4.33)	age	6
Hahn et al, 1988	USA	8932	120	18	NA	399-item MMPI	medical records	1.50 (0.90-2.50)	age, nulliparity, obesity, hysterectomy	7

\*Abbreviations: ICD, International Classification of disease ; DIS, Diagnostic Interview Schedule; ICHPPC, International Classification of Health Problems in Primary Care; EDS, Ediburgh Depression Scale; CES-D, Center for Epidemiological Studies- Depression; GHQ, General Health Questionnaire; MMPI, Minnesota Multiphasic Personality Inventory; NA, not available.

**Table 2. Subgroup Analysis of Association Between Depression and Breast Cancer Risk**

Subgroup analysis	No.of studies	Estimated effect	95%CI	I <sup>2</sup>	P value
<b>Study location</b>					
Taiwan	2	1.1	0.80-1.52	0.00%	0.815
America	3	4.23	0.97-18.41	81.30%	0.001
Europe	6	1	0.87-1.15	48.30%	0.085
<b>No. of study participants</b>					
≥10000	4	1.02	0.96-1.08	67.20%	0.001
<10000	7	1.62	0.89-2.94	74.30%	0.001
<b>No. of cases</b>					
≥100	6	1.02	0.95-1.10	12.30%	0.336
<100	5	2.07	0.65-6.57	80.20%	0.001
<b>Duration of follow-up</b>					
<10 years	3	0.82	0.39-1.74	67.20%	0.09
≥10 years	8	1.18	0.96-1.46	72.70%	0.001
<b>Measurement of exposure</b>					
Depression diagnosis	7	1.1	0.90-1.35	70.70%	0.002
Depression symptom	4	1.11	0.65-1.89	66.20%	0.031
<b>Control smoking in models</b>					
Yes	4	1.96	0.48-7.99	86.20%	0
No	7	1.04	0.94-1.16	28.10%	0.214
<b>Control alcohol in models</b>					
Yes	4	1.96	0.48-7.99	86.20%	0
No	7	1.04	0.94-1.16	28.10%	0.214



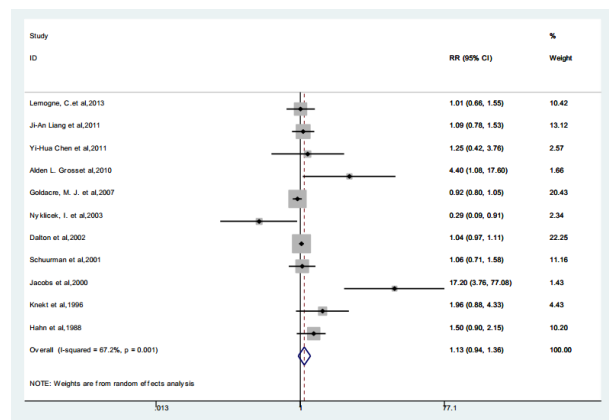
**Figure 1. Flowchart Indicating the Results of the Systematic Review with Inclusions and Exclusions**

ICD-8-CM). The outcome of studies was ascertained by medical records or death certificates in seven studies, by self-report in two studies, and by combining self-report with medical records in the rest two studies. The eleven articles were assessed and were of moderate quality with a mean score of 6.9 (ranging from 6-8).

All the included studies provided adjusted RRs. The major confounding factors adjusted included age, family history of breast cancer, cigarette smoking, alcohol intake, obesity, social status, and complications.

*Association between depression and risk of breast cancer*

The association between depression and breast

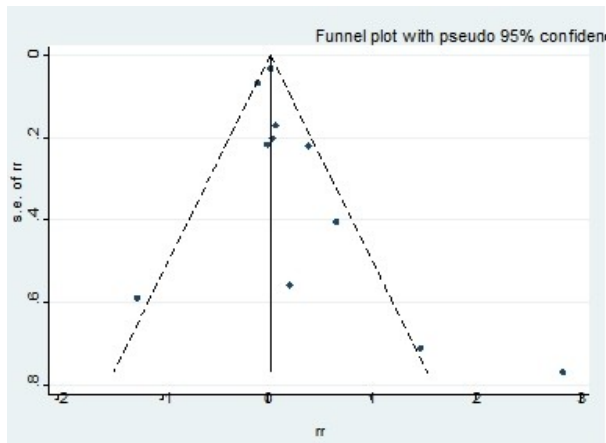


**Figure 2. Forest Plot of Depression and Risk of Breast Cancer**

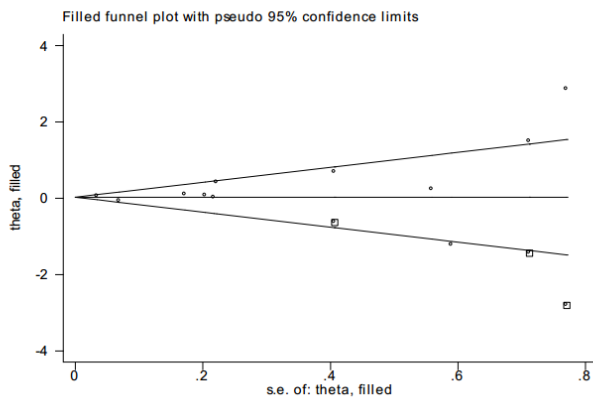
cancer risk was shown in Figure 2. The majority of all the eleven studies indicated a positive trend between depression and breast cancer (RR>1), but only two of them were statistically significant. At the same time one article (Nyklicek et al., 2003) reported that depression could reduce the risk of breast cancer in middle-aged women. With a moderate to high heterogeneity (I<sup>2</sup>=67.2%, p=0.001), the pooled analysis from random-effect model revealed that depression was not associated with breast cancer risk (RR,1.13; 95% CI 0.94 to 1.36).

*Subgroup analyses and sensitivity analyses*

Table 2 showed the results of subgroup analyses. We conducted subgroup analyses by study characteristics, such as study locations, number of study of participants and cases, duration of follow-up, exposure levels and study quality, while the results were not statistically significant. In addition, we conducted subgroup analyses according to the results whether or not adjusted by alcohol consumption or smoking, and neither alcohol consumption nor smoking altered the association.



**Figure 3. Funnel Plot of Depression and Breast Cancer**



**Figure 4. Filled Funnel Plot of Depression and Breast Cancer After Using Trim-and-Fill Method**

Sensitivity analysis by excluding each study one by one showed that Jacobs et al.'s study (Jacobs et al., 2000) and Goldacre et al.'s study (Goldacre et al., 2007) imposed the largest influence on the results. The pooled RRs were 1.24 (95%CI: 0.95-1.61) and 1.06 (95%CI: 0.92-1.22) after excluding the two studies, respectively.

#### Publication bias

Visual inspection of funnel plot revealed some asymmetry (see supplementary Figure 1A). However, the Begg rank correlation test, Egger linear regression test provide no evidence of substantial publication bias (Begg's test  $Z=1.25$ ,  $p=0.213$ ; Egger's test  $t=-0.39$ ,  $p=0.709$ ). A sensitivity analysis using the trim-and-fill method was performed with 3 imputed studies, which produced a symmetrical funnel plot (see supplementary Figure 1B). The pooled RR incorporating the three hypothetical studies was smaller than the original results, but it still did not reach the statistically significant (RR, 1.04; 95% CI, 0.84-1.27).

## Discussion

The study results were derived from eleven cohort studies which reported association between depression and risk of breast cancer. In all, our meta-analysis involved 2,353 cases of breast cancer and 182,241 participants. No significant association between depression and risk of breast cancer was found (RR, 1.13; 95%CI, 0.94 to 1.36)

after adjustment for potential confounders. Furthermore, the association between depression and breast cancer persisted across subgroup analyses.

Taking into account the impact of ethnic and geographic on the incidence of breast cancer, subgroup analyses by locations (European countries vs. USA vs. Taiwan) were conducted but no significant difference was found. As we know, different levels of exposure may have different effects on the study outcome. Therefore, we conducted subgroup analysis by exposure levels (depression symptoms vs. depressive disorder) which showed no statistically significant association between depression and breast cancer risk. Given that a long period was required to develop a detectable tumor, subgroup analysis by the duration of follow-up were conducted and the results were not statistically significant as well, though the RR was elevated in the cohorts of more than 10 years of follow-up. There were studies identified that depression individuals may engage more unhealthy behaviors that predispose them to further onset of cancer, such as smoking, alcohol consumption, lack of physical activity (Son et al., 1997; Strine et al., 2008). But the subgroup analyses according to the results that whether or not adjusted by smoking and alcohol consumption did not find significant association.

A meta-analysis conducted by Marjolein EJ Oerlemans et al. (2007) in 2007 investigated the relationship between depression and overall cancer risk. The previous meta-analysis also identified association between depression and breast cancer as a secondary analysis. The secondary analysis included seven prospective studies which involved 111756 participants and 1601 cases and reported no significant association (RR, 1.59; 95%CI, 0.74-3.44). Our meta-analysis, with four more cohort (Goldacre et al., 2007; Chen et al., 2011; Liang et al., 2011; Lemogne et al., 2013) studies and one update study (Gross et al., 2010), demonstrates no evidence of association between depression and breast cancer, which is consistent with the previous meta-analysis. However, we noticed that the previous review found depression might be a risk factor for breast cancer (RR, 2.5; 95%CI, 1.06-5.91) if study population were followed more than 10 years. In our review, this association in subgroup analysis by follow-up more than 10 years was not proved. To our knowledge, the larger size of participants, the stronger evidence of the study. The combined results of our meta-analyses are more credible with relatively narrow confidence intervals. Considering the limited number of the included studies of the previous meta-analysis, we can not conclude that there is significant association between depression and breast cancer.

Experimental animal studies, human studies and clinical evidence suggest that depression may put an influence on the development of breast cancer through several mechanisms, such as impairing immune function, causing an aberrant activity of the hypothalamic-pituitary-adrenal axis and inhibiting DNA repair mechanisms (Kiecolt-Glaser et al., 2002; Reiche et al., 2005; Soygur et al., 2007). However, epidemiological research evidences did not indicate the presence of such a relationship between depression and breast cancer. The

inconsistency of evidence between experimental studies and epidemiological studies may be explained by two reasons. On the one hand, the strength of experimental evidence may be compromised due to species differences, inconsistent of laboratory conditions and the measurement of biomarker. Some experiments could not be replicated by different investigators. On the other hand, epidemiological studies may have some methodological flaws, such as insufficient follow-up duration, different definitions and measurement of exposure, the size of sample and so on. Overall, evidence supporting that depression increases the risk of breast cancer are insufficient.

There are two strengths in our meta-analysis. Firstly, all studies in the present analyses were cohort studies, which minimized the selection and recall bias. Although our review is an updated meta-analysis, it provides robust and credible conclusion for the association between depression and breast cancer. Secondly, most of studies included in this meta-analysis had average follow-up times more than 10 years. Sufficiently long follow-up duration is necessary because most cancers have a latent period of a few years or even decades (Spratt et al., 1996; Friberg et al., 1997). Thus, our results based on long follow-up duration studies could indicate that the depression might not increase the risk of breast cancer.

Limitations: A few limitations of our meta-analysis should be acknowledged. Firstly, depression was only measured on the basis of a single baseline measure, which was clearly not identical to depression diagnosis. During the follow-up duration, the exposure intensity of subjects would change. Penninx et al (1998) (Penninx et al., 1998) proved that repeated assessment of depressive symptoms yielded positive association with later development of some cancers, in contrast to single measurements. Therefore, a one-time assessment of depression with no measure of duration weakens the test of hypothesis. Secondly, no less than 8 different scales were used for the measurement of depression in the 11 original studies. It may add to the multiple conceptual problems concerned with the definition of depression (Buntinx et al., 2004), which could increase the heterogeneity in our meta-analyses.

In conclusion, available epidemiological evidences are insufficient to support association between depression and the development of breast cancer. Given the high prevalence and morbidity of depression and breast cancer, the results of this meta-analysis not only can act as the clue of the etiology, but can provide the evidence to women who believed that depression could increase the risk of breast cancer.

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