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). Breast cancer is by far the most common cancer in women (International Agency for Research on Cancer, 2008). Breast cancer is by far the most common cancer in women (International Agency for Research on Cancer, 2008). Breast cancer is by far the most common cancer in women (International Agency for Research on Cancer, 2008). Breast cancer is by far the most common cancer in women (International Agency for Research on Cancer, 2008). 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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 (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 $F$ statistic. $F$ 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 (ICHPHC) 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                                                                 |
|--------------------|-------------------------|---------------------|-------|------------------|-----|---------------------|------------------------|-------------------------------------|----------------------------------------------------------------------------------|
| Lemogne et al., 2013 | France                  | 3184                | 128   | 15               | mean 45.7 | CES-D self-report | self-report            | 1.01 (0.66-1.55)                  | age, cupational grade, alcohol consumption, smoking, fruit and vegetable consumption, height, weight, physical activity, health status |
| Ji-An et al., 2011  | Taiwan                  | 45819               | 325   | 8                | NA  | ICD-9-CM register database | 1.09 (0.78-1.53)       | age, urbanization, comorbidity       |
| Yi-Hua et al., 2011 | Taiwan                  | 1836                | 20    | 5                | ≥18 | ICD-9-CM register database | 1.25 (0.42-3.76)       | age                                |
| 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       |
| Goldacre, et al.,2007 | UK                      | 17701               | 229   | 38               | NA  | ICD-9-CM medical records and death certificates | 0.92 (0.80-1.05)       | age                                |
| 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 |
| 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                                      |
| Schurman et al.,2001 | The Netherlands          | 35007               | 728   | 25               | NA  | ICHPPC-2 NA | NA | 1.06 (0.71-1.58)       | age, social status                  |
| Jacobs et al.,2000  | USA                     | 1533                | 40    | 15               | mean 48 | DIS-diagnosed MDD self-report | 17.20 (3.67-77.08)      | age, smoking, alcohol               |
| Knekt et al.,1996   | Finland                 | 3773                | 54    | 14               | ≥0  | 36-item GHQ medical records | 1.96 (0.88-4.33)       | age                                |
| Hahn et al.,1988    | USA                     | 8932                | 120   | 18               | NA  | 399-item MMPI medical records | 1.50 (0.90-2.50)       | age, nulliparity, obesity, hysterectomy                                      |

*Abbreviations: ICD, International Classification of disease; DIS, Diagnostic Interview Schedule; ICHPPC, International Classification of Health Problems in Primary Care; EDS, Edinburgh Depression Scale; CES-D, Center for Epidemiological Studies- Depression; GHQ, General Health Questionnaire; MMPI, Minnesota Multiphasic Personality Inventory; NA, not available.
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 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 ($I^2=67.2\%$, $p=0.001$), 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 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.

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

| Subgroup analysis                      | No. of studies | Estimated effect | 95% CI          | $I^2$ | $p$ value |
|----------------------------------------|---------------|-----------------|-----------------|------|-----------|
| Study location                          |               |                 |                 |      |           |
| 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     |
| No. of study participants              |               |                 |                 |      |           |
| ≥100000                                | 4             | 1.02            | 0.96-1.08       | 67.20%| 0.001     |
| <10000                                 | 7             | 1.62            | 0.89-2.94       | 74.30%| 0.001     |
| No. of cases                           |               |                 |                 |      |           |
| ≥100                                   | 6             | 1.02            | 0.95-1.10       | 12.30%| 0.336     |
| <100                                   | 5             | 2.07            | 0.65-6.57       | 80.20%| 0.001     |
| Duration of follow-up                  |               |                 |                 |      |           |
| <10 years                              | 3             | 0.82            | 0.39-1.74       | 67.20%| 0.049     |
| ≥10 years                              | 8             | 1.18            | 0.96-1.46       | 72.70%| 0.001     |
| Measurement of exposure                |               |                 |                 |      |           |
| 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     |
| Control smoking in models              |               |                 |                 |      |           |
| Yes                                    | 4             | 1.96            | 0.48-7.99       | 86.20%| 0       |
| No                                     | 7             | 1.04            | 0.94-1.16       | 28.10%| 0.214     |
| Control alcohol in models              |               |                 |                 |      |           |
| Yes                                    | 4             | 1.96            | 0.48-7.99       | 86.20%| 0       |
| No                                     | 7             | 1.04            | 0.94-1.16       | 28.10%| 0.214     |
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.

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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