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Review Paper

Depression and cancer risk: a systematic review and meta-analysis

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ABSTRACT

Objective: To assess the associations between depression and incident cancer risk.
Study design: Systematic review and meta-analysis.
Methods: The Cochrane Library, Web of Science, MEDLINE, and PubMed databases were searched to identify studies. The quality of included studies was assessed using the Newcastle Ottawa Scale. Risk ratios (RRs) were used to measure effect size. A random-effects model was applied to synthesize the associations between depression and cancer risk. A forest plot was produced to visually assess RRs and 95% confidence intervals (CIs). Heterogeneity across studies was assessed using the I-squared statistic. A funnel plot was generated to assess potential publication bias, and Egger's regression was applied to test the symmetry of the funnel plot.
Results: In total, 1,469,179 participants and 89,716 incident cases of cancer from 25 studies were included. Depression was significantly associated with overall cancer risk (RR = 1.15, 95% CI: 1.09–1.22) and with liver cancer (RR = 1.20, 95% CI: 1.01–1.43) and lung cancer (RR = 1.33, 95% CI: 1.04–1.72). Subgroup analysis of studies in North America resulted in a significant summary relative risk (RR = 1.30, 95% CI: 1.15–1.48). No significant associations were found for breast, prostate, or colorectal/colon cancer. The average Newcastle Ottawa score was 7.56 for all included studies.
Conclusion: Our findings showed a small and positive association between depression and the overall occurrence risk of cancer, as well as liver cancer and lung cancer risks. However, multinational and larger sample studies are required to further research and support these associations. Moreover, confounding factors such as cigarette smoking and alcohol use/abuse should be considered in future studies.

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Introduction

Depression and cancer commonly co-occur. As with other psychological problems, such as anxiety,[1] pain[2] and fatigue,[3] most studies[4–6] in cancer patients have focused on the morbidity or mortality attributable to depression risk rather than depression as a risk factor for subsequent cancer. Depression among patients with cancer is not only a concomitant condition but also may be a cause of cancer occurrence.[7] The causes of cancer are complex and are related to genetic factors, unhealthy lifestyles, environmental factors and psychosocial factors, including depression. Since the 1980s, studies have reported that depression is involved in immune function, endocrine function, cancer metastasis, treatment tolerance, and other processes.[8–11] Recently, growing evidence from prospective epidemiological studies has suggested that depression is a risk factor for cancer.[12,13] Some studies[12,14–16] have shown an etiological association, whereas others[13,17–19] have found no association. Reports on the association thus remain controversial and unclear.

These inconsistent and controversial results indicate the need to quantitatively synthesize and interpret the available evidence to provide more explicit information for clinical use and for psychological interventions. To our knowledge, one previous meta-analysis investigated the association between depression and cancer risk and included literature published from 1990 to 2005.[20] Since that review was published, several pertinent studies have emerged.[12–19,21] Therefore, we conducted a systematic review and meta-analysis to summarize the available epidemiologic evidence. We also aimed to clarify the extent of the potential association between depression and cancer risk and to identify the gaps in the existing literature.

Methods

Search strategy

We systematically searched the Cochrane Library, Web of Science, MEDLINE, and PubMed databases for all studies published from January 1, 1990 to September 30, 2016 using search terms related to psychological depression ('depressive disorder' OR 'depress*' OR 'depression') AND ('cancer' OR 'carcinoma' OR 'tumor' OR 'neoplasm') AND outcomes ('incidence' OR 'occurrence' OR 'risk') in combination with each other to find relevant articles. The search was conducted from September 30, 2016 to the last updated search to January 1, 2017. Selected journals and databases from germane published articles were also manually searched and reviewed to supplement the searches. Only publications in English were included in this systematic review.

Inclusion criteria and exclusion criteria

The inclusion criteria were as follows: (i) observational designs and population-based sampling; (ii) depression defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, the International Classification of Disease (ICD) criteria, depression-related scales or physician-diagnosed; (iii) cancer defined by self-reported, physician-diagnosed or the ICD criteria; and (iv) participants without any subtype of cancer at the beginning of the study. The exclusion criteria were the following: (i) reviews and case report studies; (ii) studies without usable data or of low quality; and (iii) animal studies. Additionally, only the most recently published article was included when multiple articles from the same study were available.

Study selection

Two reviewers (ZJP and LYF), independently selected the studies and extracted the data. They initially screened all of the study titles and abstracts and then evaluated the full-text articles. Finally, 25 studies were included in this meta-analysis. Disagreements were resolved by a third investigator (JY). The study selection process is shown in detail in Fig. 1.

Data extraction and quality assessment

We used a standardized table to extract the following information from all of the included articles: first author(s), publication year, country, cancer type, study population, data source, follow-up years, depression measurement tool, definitions of cancer, sample sizes, cases of cancer, adjusted covariates, and adjusted effect sizes with 95% confidence interval (CI) for cancer risk. Adjusted risk estimates were used in this meta-analysis.

The quality of included studies was assessed using the Newcastle Ottawa Scale[22] as recommended by the Cochrane Non-Randomized Studies Methods Working Group. In this scale, each study is evaluated according to eight items categorized into three groups: the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome. Each item was graded with a maximum score of one point, with the exception of comparability, which allowed for two points. The total score ranged from 0 to 9 points, with higher scores indicating higher quality. Quality assessment was performed according to the Newcastle Ottawa Scale by two authors (ZJP and LYF), independently. The two authors discussed the implementation of this assessment tool and agreed on a method of implementation before their independent study assessments. The level of agreement between the two authors was calculated by another author (JY). Regarding the current studies, we considered a study awarded seven or more points to be a high-quality study. Low-quality studies (Newcastle Ottawa score equal to or less than four) were excluded.

Statistical analysis

We used risk ratios (RRs) to measure effect size as an intuitive and commonly used measure in the medical literature. When hazard ratios and incidence risk ratios were reported, we considered them directly as RRs. Because cancer is not very common, we considered reported odds ratios (ORs) equivalent to RRs. A random-effects model was used to synthesize the associations between depression and cancer risk. A forest plot

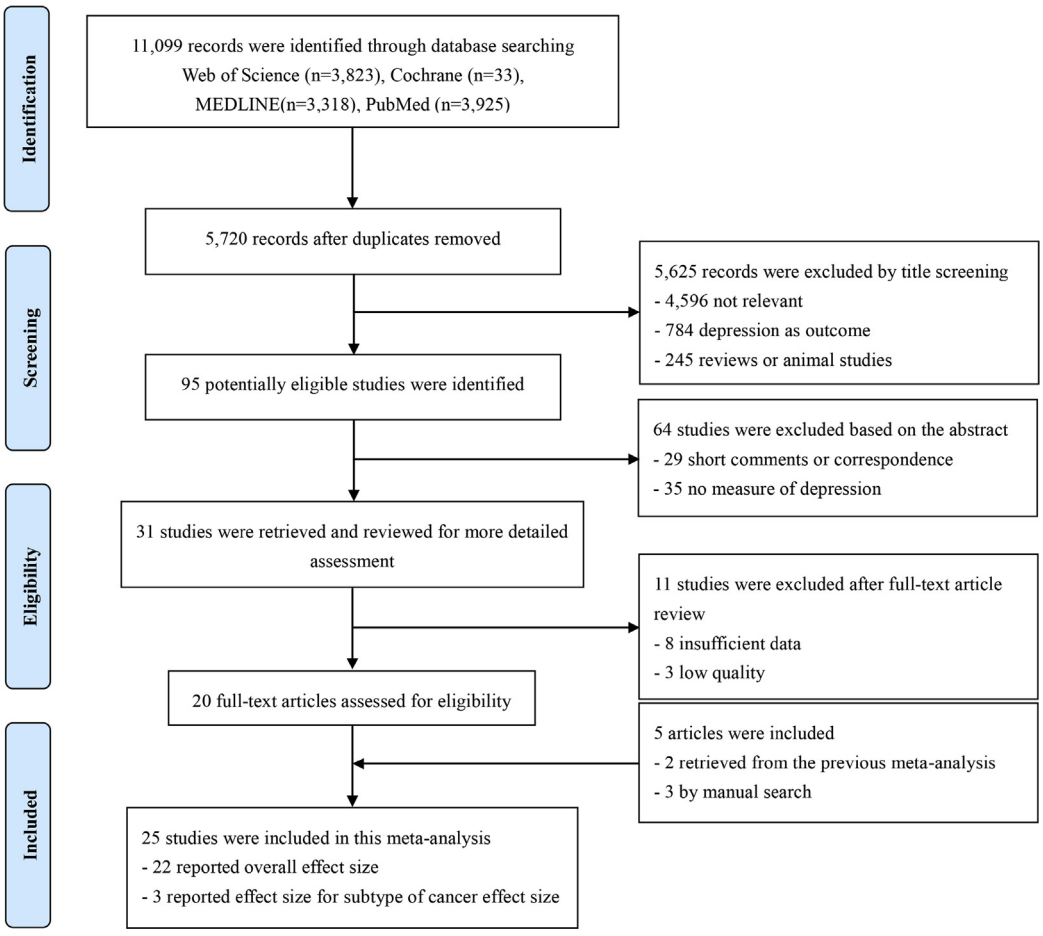

Fig. 1 – Flow chart of the study selection process for this review.

was produced to visually assess the RRs and 95% CIs. Heterogeneity across studies was analyzed using the I-squared (I^2) statistic. I^2 values of 25% or less, 50%, and 75% or more represent low, moderate, and high heterogeneity, respectively.[23] A funnel plot was generated to assess potential publication bias, and Egger's regression was applied to test the symmetry.[24] We used the Duval and Tweedie non-parametric trim-and-fill procedure to further evaluate the possible effect of publication bias.[25] Subgroup analyses were conducted by follow-up years, study site, and subtype of cancer. Statistical analyses were performed using Stata 12.0 (StataCorp, TX, USA). We summarized the extracted data in tables and performed a narrative synthesis of all the included studies. All tests were two-sided, and a *P*-value <0.05 indicated statistically significant outcomes.

Results

Literature search and study characteristics

In total, 11,099 records were identified from the database searches. After screening the titles and abstracts, 31 studies were retrieved and reviewed for further assessment. After reviewing the full-text articles for eligibility, 20 studies were included. Additionally, two studies from the previous meta-analysis were retrieved,[26,27] and three studies were found by manual search.[12,18,28] Thus, 25 studies were finally included in the meta-analysis.[12–19,21,26–41] Three of the 25 studies did not report the effect size for overall cancer.[21,26,29] Fig. 1 shows the flow chart of the study selection process in this meta-analysis. The average Newcastle Ottawa score was 7.56 for all included studies (Table 1).

The 25 studies included a total of 1,469,179 participants (range, 1529 to 601,775) and 89,716 incident cases of cancer (range, 39 to 57,604). The studies were conducted in the USA ($n = 11$), the UK ($n = 2$), the Netherlands ($n = 2$), Taiwan ($n = 3$), Denmark ($n = 1$), Korea ($n = 1$), France ($n = 1$), Finland ($n = 2$), and Australia ($n = 1$), and one was an international study ($n = 1$). The follow-up time of those studies ranged from 5 to 34 years. Adjusted estimates were reported in all studies, and the adjusted variables varied and differed from each other. Table 1 shows the main characteristics of the 25 studies on depression and cancer risk included in this meta-analysis.

Depression in the studies was measured by general practitioner diagnosis, the ICD, eighth revision (ICD-8) or the ICD, ninth revision (ICD-9), the DSM, third edition (DSM-III), the DSM, fourth edition (DSM-IV), the International Classification of Health Problems in Primary Care criteria, the Diagnostic Interview Schedule, the Beck Depression Inventory, the General Well-being schedule, the cheerful vs depressed mood scale (GWB-D), the Present State Examination, the 5-item

Table 1 – Characteristics of included prospective studies on depression and cancer risk.

Author, year	Cancer type and effect size (95% CI)	Follow-up years	Country	Age (years)	Number of cases/sample size	Exposure assessment	Outcome assessment	Adjusted covariates	Quality
Aro et al., 2005[31]	Breast 2.83 (1.26–6.36)[b]	6–9	Finland	48–50	278/10,892	BDI	Cancer registry	Area, parity, education, income, socio-economic status, birth year, family history of cancer, smoking, use of alcohol, physical exercise	8
Goldacre et al., 2007[19]	Overall 1.04 (0.98–1.10) Breast 0.92 (0.80–1.05)[b] Colon 1.05 (0.86–1.26) Liver 1.08 (0.60–1.79) Lung 1.36 (1.19–1.54) Prostate 0.69 (0.47–0.97)[a] Esophagus 1.12 (0.78–1.57) Stomach 0.90 (0.65–1.12)	34	UK	<70	1195/27,818	Physician-diagnosed	ICD-9	Age, sex	7
Lawrence et al., 2000[35]	Overall 1.05 (1.02–1.09)[a] Overall 1.02 (0.98–1.05)[b]	29	Australia	NR	6442/172,932	ICD-8, ICD-9	ICD-8, ICD-10	Age, sex	8
Schuurman et al., 2001[34]	Overall 1.06 (0.71–1.58)	25	Netherlands	≥20	3464/68,366	GP diagnosis ICHPPC-2 criteria	GP-registry	Age, sex	6
Gross et al., 2010[16]	Overall 1.90 (1.20–3.00) Breast 1.15 (0.99–1.34)[b] Colon 0.97 (0.75–1.25) Skin 1.02 (0.78–1.33) Lung 0.97 (0.84–1.12) Prostate 1.03 (0.83–1.29)[a]	24	USA	≥18	334/3177	DIS/DSM-III	Self-reports	Age, self-reported race, sex, marital status at each encounter, smoking status at each encounter, socio-economic status, history of alcohol abuse/dependence	9
Dalton et al., 2002[33]	Overall 1.14 (1.10–1.17) Breast 1.06 (0.98–1.76)[b] Colon 1.16 (1.03–1.30) Liver 1.27 (0.89–1.76) Lung 1.59 (1.47–1.72) Prostate 1.02 (0.84–1.23)[a] Stomach 1.20 (0.99–1.45)	24	Denmark	NR	9922/89,491	ICD-8	ICD-8 or ICD-9	Age, sex, calendar year	7
Chang et al., 2015[29]	Overall ns. Prostate 1.48 (1.38–1.60)[a] Breast 0.92 (0.82–1.02)[b] Cervical 1.12 (0.92–1.36)[b] Endometrial 1.07 (0.77–1.49)[b] Ovarian 1.24 (0.95–1.62)[b]	19	Korea	30–64	57,604/601,775	DSM-IV	Cancer registry	Age, smoking status, alcohol consumption, exercise, BMI, cholesterol, blood sugar, hypertension, cancer family history	8

(*continued on next page*)

Table 1 – (*continued*)

Author, year	Cancer type and effect size (95% CI)	Follow-up years	Country	Age (years)	Number of cases/sample size	Exposure assessment	Outcome assessment	Adjusted covariates	Quality
Friedman, 1994[39]	Overall 1.38 (1.06–1.76)	19	USA	≥19	923/143,574	Physician-diagnosed	Hospitalization records of local surveillance	Sex, examination site	7
Huang et al., 2015[12]	Epithelial ovarian 1.30 (1.05–1.60)	18	USA	30-55/25-42	698/88,093	MHI-5 or physician-diagnosed	Medical records	BMI, physical activity, smoking, intake of caffeine and lactose	7
Archer et al., 2015[13]	Overall 1.03 (0.71–1.49)	17.4	UK	33–55	776/6983	GHQ-30	Cancer registry	Age, sex, socio-economic status, health behaviors, health status, medication, social support	8
Kaplan and Reynolds, 1988[26]	Overall ns.	17	USA	'Adults'	729/6848	HPL	ICD for Oncology (WHO, 1976)	Age, sex	6
Lemogne et al., 2013[21]	Overall ns. Breast 1.01 (0.66–1.55)[b] Prostate 1.07 (0.84–1.38)[a] Colorectal 0.71 (0.43–1.17) Lymphoid and hematopoietic tissues 0.89 (0.52–1.52) Smoking-related 0.91 (0.59–1.42)	15	France	Mean = 45.7	128/3184	CES-D	Self-reports	Age, sex, occupational grade, alcohol, fruit and vegetable consumption, smoking, height, weight, physical activity, health status	7
Vogt et al., 1994[27]	Overall 1.08 (0.77–1.52)	15	USA	≥18	ns./1529	DSM-III	Death certificates and state of vital records	Age, sex, self-reported health status, social class, cigarette smoking status, duration of health plan membership	7
Knekt et al., 1996[38]	Overall 1.22 (0.91–1.63) Lung 3.32 (1.53–7.20)[a] Breast 1.96 (0.88–4.33)[b]	14	Finland	30–95	605/7018	PSE	Cancer registry	Age, sex	8
Hahn and Petitti, 1988[41]	Breast 1.50 (0.90–2.50)[b]	13	USA	All	117/8932	MMPI	Medical records and histology	Age, nulliparity, obesity, prior hysterectomy	7
Liang et al., 2011[18]	Overall 1.03 (0.91–1.15) Breast 1.09 (0.78–1.53)[b] Brain 1.44 (0.55–3.76) Uterus, cervical, ovary, vaginal 1.16 (0.84–1.60)[b] Lung 1.01 (0.65–1.58) Prostate 1.33 (0.79–2.23)[a] Colorectal 0.77 (0.55–1.10) Hematologic malignancy 1.10 (0.64–1.87)	12	Taiwan	All	2892/67,352	ICD-9	ICD-9	Age, sex, urbanization, co-morbidity	8
Linkins and Comstock, 1990[28]	Overall 0.89 (0.59–1.35)	12	USA	>18	169/2264	CES-D	Cancer registry and death certificates	Age, male gender, cigarette smokers	8
O'Neill et al., 2014[14]	Overall 1.30 (1.10–1.60)	10	International	≥18	1499/52,095	DSM-IV	Self reports	Age, gender, person-year and country	7

Lai et al., 2013[17]	Hepatocellular carcinoma 1.20 (0.97–1.49)	10	Taiwan	≥65	114/1815	ICD-9	ICD-9	Age, diabetes mellitus, cirrhosis, other chronic hepatitis, hepatitis B/C infection, alcoholism	7
Heuvel, 1999[36]	Overall 1.32 (0.67–2.61)	10	USA	All	76/2342	GP diagnosis ICHPPC-2 criteria	GP-registry	NR	8
Zonderman et al., 1989[40]	Overall 1.10 (0.90–1.40)	10	USA	25–75	637/6403	CES-D or GWB-D	Hospitalization records and death certificates	Age, sex, marital status, smoking, cancer history, hypertension, serum cholesterol level	8
Kroenke et al., 2005[30]	Colorectal 1.43 (0.97–2.11)[b]	8	USA	46–71	400/81,612	MHI-5	Medical records	Age	9
Penninx et al., 1998[37]	Overall 1.68 (1.04–2.79)	7	USA	71–96	402/4825	CES-D	Hospitalization records and death certificates	Age, sex, race, disability, hospital admissions, alcohol intake, smoking	8
Chen and Lin, 2011[15] Chen and Zhang, 2011[42]	Overall 1.44 (1.07–1.94) Breast 1.25 (0.42–3.76)[b] Hematologic malignancy 1.05 (0.12–9.01) Oral 0.71 (0.21–9.01) Gastrointestinal 1.80 (1.03–3.14) Respiratory 1.83 (0.81–4.13) Genitourinary 1.92 (1.01–3.66)	5	Taiwan	≥18	273/4668	ICD-9	ICD-9	Age group, sex, year of index hospitalization	8
Nyklicek et al., 2003[32]	Breast 0.29 (0.09–0.91)[b]	5	Netherlands	56–62	39/5191	EDS	Cancer registry	Age, family history of breast cancer, parity, BMI, menopausal status, education, history of breastfeeding, oophorectomy, hysterectomy and hypothyroidism, use of estrogens in any form, physical exercise, alcohol	8

GWB-D, General Well-being schedule, cheerful vs depressed mood scale; HPL, Human Population Laboratory-Depression Scale; BDI, Beck Depression Inventory; ICHPPC, International Classification of Health Problems in Primary Care; PSE, Present State Examination; CES-D, Center for Epidemiologic Studies-Depression Scale; MHI-5, 5-item Mental Health Index; EDS, Edinburgh Depression Scale; GHQ, General Health Questionnaire; WHO, World Health Organization; MMPI, Minnesota Multiphasic Personality Inventory; BMI, body mass index; DIS, Diagnostic Interview Schedule; GP, General Practitioner; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Disease; NS, not specified; NR, not reported.

[a] Male study population.

[b] Female study population.

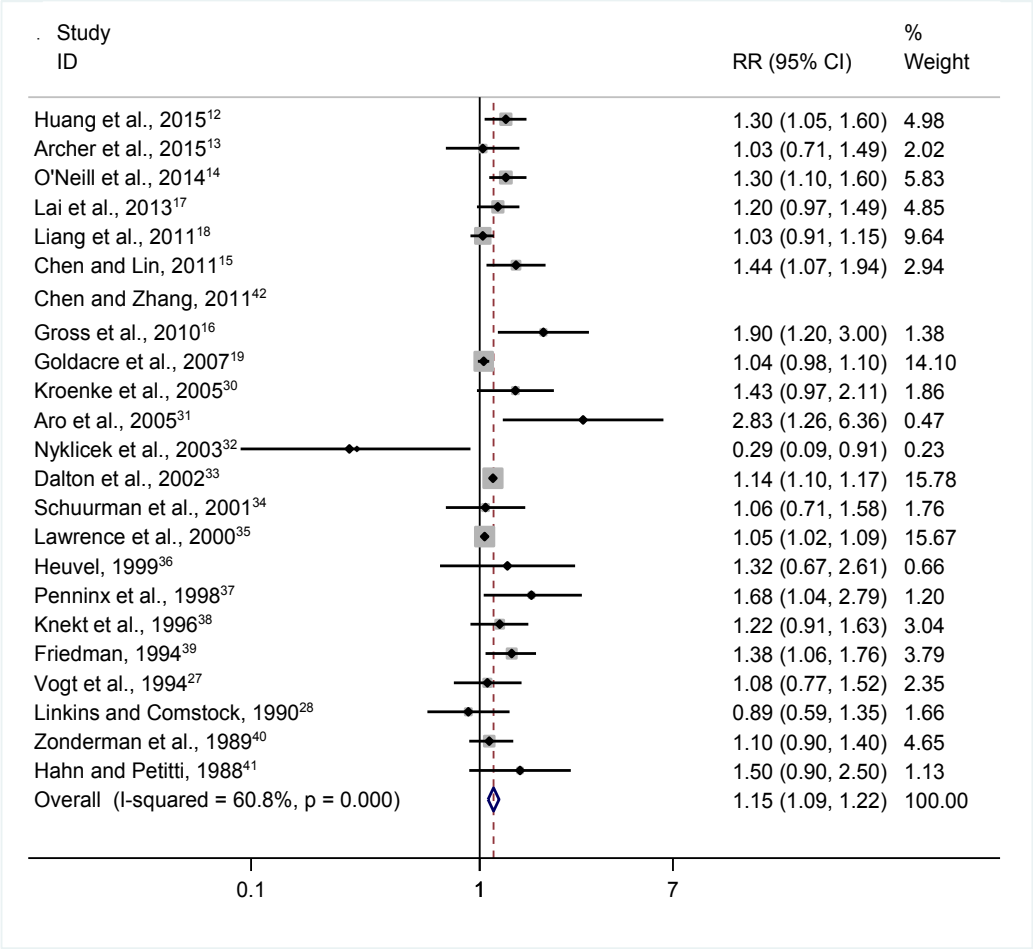

Fig. 2 – Forest plot of depression and cancer risk.

Mental Health Index, the General Health Questionnaire, the Minnesota Multiphasic Personality Inventory, the Human Population Laboratory-Depression Scale, the Center for Epidemiologic Studies-Depression Scale, and the Edinburgh Depression Scale. Cancer was defined by data from cancer registries, medical records, death certificates, histological diagnosis, and hospitalization records from local surveillance. Most studies used DSM-IV to evaluate depression, except for an older study that used DSM-III.[27]

Association between depression and overall cancer risk

The results of this meta-analysis indicated that a small positive association existed between depression and the occurrence risk of overall cancer (RR = 1.15, 95% CI: 1.09–1.22). Heterogeneity between the studies was moderate (I^2 = 60.8%, P = 0.000) (Fig. 2).

Subgroup analyses

Table 2 shows the results of the cancer subgroup analysis. We conducted subgroup analyses by duration of follow-up, study site, and cancer type. For cancer type, depression was associated with liver cancer (RR = 1.20, 95% CI: 1.01–1.43: I^2 = 0.00%) and lung cancer (RR = 1.33, 95% CI: 1.04–1.72: I^2 = 90.50%). No significant association was observed between depression and breast cancer (RR = 1.07, 95% CI: 0.93–1.23: I^2 = 57.30%), prostate cancer (RR = 1.08, 95% CI: 0.86–1.37: I^2 = 86.20%), or colorectal/colon cancer (RR = 1.03, 95% CI: 0.89–1.20: I^2 = 52.70%). For study site, a significant association was observed between depression and studies in North America (RR = 1.28, 95% CI: 1.14–1.48), with minimal heterogeneity in those studies (I^2 = 16.50%). In a subgroup analysis of duration of follow-up, a significant effect was observed in both the more than ten years subgroup (RR = 1.30, 95% CI: 1.11–1.52) and the equal to or less than ten years subgroup (RR = 1.11, 95% CI: 1.05–1.17).

Publication bias and sensitivity analyses

Visual inspection of the funnel plot revealed some asymmetry. However, the Egger test showed no evidence of substantial publication bias (t = 1.86, P = 0.078) according to our significance level (see Fig. 3). A sensitivity analysis using the trim-and-fill method was performed with six imputed studies, producing a symmetrical funnel plot (see Fig. 4). Although the

Table 2 – Subgroup analysis of association between depression and cancer risk.

Subgroup analysis	No. of studies	Estimated effect	95% CI	I^2	P-value
Cancer type[a]					
Breast	11	1.07	0.93–1.23	57.30%	0.009
Colorectal, colon	6	1.03	0.89–1.20	52.70%	0.051
Liver	3	1.20	1.01–1.43	0.00%	0.881
Lung	5	1.33	1.04–1.72	90.50%	0.000
Prostate	6	1.08	0.86–1.37	86.20%	0.000
Duration of follow-up					
≤10	9	1.30	1.11–1.52	61.50%	0.002
>10	13	1.11	1.05–1.17	43.90%	0.075
Study site					
North America	11	1.28	1.14–1.44	16.50%	0.291
Europe	7	1.10	1.00–1.22	67.50%	0.005
Asia	3	1.17	0.97–1.40	59.90%	0.082
International	1	1.30	1.08–1.57	0.00%	0.000
Oceania	1	1.05	1.02–1.09	0.00%	0.000

[a] Number of included studies ≥3.

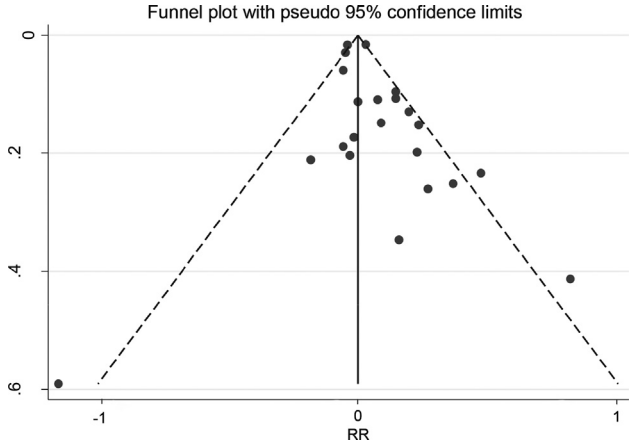

Fig. 3 – Funnel plot of depression and cancer risk. RR = risk ratio.

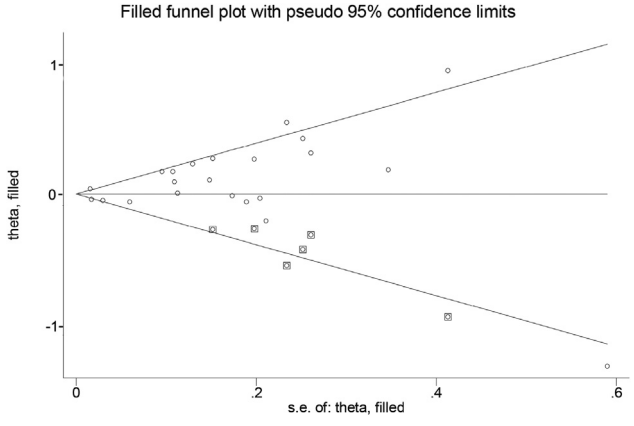

Fig. 4 – Filled funnel plot of depression and cancer after using trim-and-fill method. s.e. = standard error.

pooled RR incorporating the six hypothetical studies was smaller than the original results, it reached significance (RR = 0.11, 95% CI: 0.05–0.17).

Discussion

In this systematic review, we analyzed 25 studies on different types of cancer. The identified epidemiological evidence was highly diverse by subtype of cancer, timing, study location, measures of depression, outcome definition, and control for confounding factors. The studies included individuals with different age ranges and settings, and some studies included only women or men. Recognized categorization criteria such as the ICD and the DSM are based on structured clinical interviews that provide well-validated assessments of depression. In contrast, self-rated symptom scales provide only basic assessments at the time of questionnaire completion.[14,16,21] The previous meta-analysis conducted by Oerlemans et al.[20] investigated the relationship between depression and overall cancer risk in 2007. They did not find a positive result after adjusting for confounders in their pooled summary of relative risk of overall cancer (RR = 1.12, 95% CI: 0.99–1.26: $I^2 \leq 0.001\%$). These inconsistent findings may have resulted from the following factors. The search strategy in Oerlemans' study used the keywords depress* in combination with neoplasm* or cancer to identify studies published in three databases (Medline, Embase, and PsycINFO) from 1990 to 2005. In contrast, five additional articles[28,30,33,35,39] were included in our meta-analysis according to our search strategy using four databases in the corresponding period. Moreover, we also updated our results with eight new studies published from 2006 to 2016.[12–19] Thus, a total of 13 additional articles were included compared to the prior systematic review. Among them, an increasing trend was observed regarding research on the associations of liver,[17,19] lung,[16,18,19] colorectal,[16,18,19,21] and prostate cancer[13,16,18,19,21] with depression in particular.

However, we found very few studies that explored lifestyle cancer risk factors in patients with depression (e.g., smoking status was not assessed in investigations for tobacco-related cancer, such as oral and lung cancer; alcohol use status, hepatitis B/C infection, and chronic hepatitis history were not assessed for liver cancer; and menopausal status was not assessed for breast cancer).[16,17] Notwithstanding this

observation, the tendency of patients with depression to live more unhealthy lifestyles than the general population has been well established.[42] Additionally, other cancer risk factors, such as diet, obesity, physical inactivity, education, and healthcare level, should be considered. Lack of attention to such confounding factors might compromise the results observed in studies of this association. Our finding on the association between depression and subsequent cancer risk is likely to be an underestimate.

Our findings indicated moderate heterogeneity between depression and the occurrence risk of overall cancer ($I^2 = 60.8\%$, $P = 0.000$). We applied subgroup analysis to assess the heterogeneity source. After subgroup analysis, the I^2 values did changed, which indicated that study location and cancer type might influence the overall effect. To our knowledge, minimal heterogeneity may provide a more precise assessment. Two positive trends were observed for cancer subtype, specifically regarding associations between depression and the risk of liver cancer and that of lung cancer. Whereas none of the epidemiological studies indicated a positive association between liver cancer risk and depression, we found that depression as a risk factor might increase the risk of liver cancer. Three included studies investigated depression and liver cancer risk in this study. Among them, the sample sizes of two studies were relatively larger (27,818 and 89,491 individuals, respectively)[19,33] than that of a study from Taiwan (1815 individuals).[17] The sample size of this subgroup was increased by pooling. Moreover, the effect size and the lower limit of CIs of the three studies were all close to one. To our knowledge, given the larger sample size and the stronger evidence from the studies, the combined results of our meta-analysis are more credible and have relatively narrow CIs. Although a significant difference was observed for the association between depression and subsequent liver cancer and lung cancer, further studies are needed to explore these relationships.

Breast cancer is one of the most extensively studied cancer subtypes regarding its relationship with depression. No significant association was observed between depression and breast cancer, prostate cancer or colorectal/colon cancer in our studies. The previous meta-analysis by Oerlemans et al. also identified an association between depression and breast cancer risk by subtype analysis. The subtype analysis included seven studies that involved 111,756 participants and 1601 cases, and no significant association (RR = 1.59, 95% CI: 0.74–3.44) was shown. Our meta-analysis reveals no evidence of an association between depression and subsequent breast cancer risk, which is consistent with the previous meta-analysis. Although human studies and experimental studies reported a relationship between depression and cancer development,[43–45] evidence supporting depression as increasing the risk of breast cancer is insufficient.

To consider the impact of geography on the occurrence of cancer, subgroup analyses by study locations were conducted, which showed a significant difference for North America (RR = 1.28, 95% CI: 1.14–1.44). In this meta-analysis, one study included an 'international' population setting and most studies were from developed countries. We did not identify any studies from developing countries (China, India, or South America). However, cultural factors, socio-economic levels and the state of medical care, which may also influence the association between depression and cancer, differed among the countries. For example, the prevalence of mental disorders, including depression, tends to be lower in Asian countries than in Western countries.[46,47] This finding may reflect an unwillingness to disclose information about personal difficulties and may result in identifying more severe cases and a stronger association with subsequent cancer. The prevalences of liver cancer, lung cancer, and breast cancers in China are not lower than those of other countries.[48,49] Thus, various countries with different prevalences of depression and cancer might have affected our estimate of the effect of depression on cancer risk.

Several mechanisms may be hypothesized regarding the association between depression and subsequent cancer risk.[50–52] A plausible pathway involves the hypothalamic-pituitary-adrenal axis. Stress hormones are released into the plasma when stress is perceived, and plasma cortisol levels increase.[53] Cortisol is also involved in the activation of signaling pathways that control cell growth and regulation of the cell cycle.[54] Alterations in cytokine secretion and regulation are another possible pathway through which exposure to depression may be related to incident cancer risk.[55] Additionally, dysfunctional immune responses, including increased concentrations of cytokines TNF-α and IL-6 have been reported in patients with cancer.[29,56]

The strengths of our study include the comprehensive searches performed across multiple databases and the most robust and current meta-analysis conducted to date. Our results provided evidence of a modest positive association between depression and subsequent liver cancer and lung cancer.

Our study has several limitations that warrant consideration. First, the variables used in the adjusted risk estimates differed among the included studies, which might have resulted in the high heterogeneity among those studies. A meta-analysis of individual participant data is needed, which might decrease the influence of heterogeneity among those studies and might provide a more precise assessment on the effects of depression on cancer risk. Second, we determined the relationship between depression and incident cancer risk only, and other psychological challenges, such as anxiety, pain and fear, were not studied. This omission may have underestimated the risk presented by psychological factors in cancer risk. Third, because only studies that met the inclusion criteria were included in our meta-analysis, the exclusion of other studies may have led to an underestimation of the risk of certain cancers (i.e., stomach, liver, breast and lung cancer) that are associated with high morbidity in China.[48] We also searched three Chinese databases (VIP, Wanfang, and China National Knowledge Infrastructure database) using the same search terms used in this review; however, we found no clear assessments of depression, only reports of depression. Fourth, the definition of depression in most studies was based on questionnaires, which were numerous and differed considerably from one another. This factor might have confounded the definition of depression and its assessment.

In conclusion, our findings showed that a small positive association existed between depression and the overall occurrence risk of cancer and the risks of developing subsequent liver cancer and lung cancer. However, multinational

and larger sample studies are required to further research and support these associations. Moreover, confounding factors such as cigarette smoking and alcohol use/abuse should be considered in future studies.

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Competing interests

None declared.

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