

# Associations between mental illness and cancer: a systematic review and meta-analysis of observational studies

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**Abstract. – OBJECTIVE:** Considering the impact of mental illness and cancer on the society, the relationship between the two diseases should be assessed. This study aimed at determining the association between mental illness and cancer.

**MATERIALS AND METHODS:** The Embase and Medline databases were searched on October 21, 2020. Cohort, case-control, and cross-sectional studies were eligible for study inclusion. The Newcastle-Ottawa scale was used to qualitatively assess the risk of bias. Funnel plots were drawn to evaluate the risks of bias across the included studies.

**RESULTS:** We included 58 studies from 16 countries, incorporating approximately 30 national databases and 25 million individuals. Patients with psychiatric disorders did not show an increased risk of developing cancer. However, patients with cancer had a significantly increased risk of developing mental illness. The survival rates of patients with mental illness according to cancer occurrence and patients with cancer according to mental illness occurrence were significantly decreased.

**CONCLUSIONS:** Clinicians should conduct early screening to ensure that appropriate interventions for mental illness are administered in patients with cancer. Due to the high incidence of death in patients with mental illnesses due to unnatural causes, such as suicide, homicide, and accidents, clinicians should be aware of the importance of the treatment and management of these patients.

*Key Words:*

Mental illness, Cancer, Curvival rate, Meta-analysis.

## Introduction

Cancer is the second most common cause of death worldwide, with approximately 18.1 million new cases and 9.5 million cancer-related deaths in

2018<sup>1</sup>. Cancer diagnosis and treatment can cause physical, mental, and financial burdens to the patients<sup>2</sup>. A recent systematic review<sup>3</sup> reported that mental illnesses in patients with cancer result in additional healthcare cost, ranging from \$2,213 (in 2009) to \$11,009 (in 2003). Early screening and systematic interventions for mental illnesses in patients with cancer are important as a diagnosis of mental illness can lead to poor response and prognosis and, ultimately, low survival rate<sup>4,5</sup>. Considering the impact of these two diseases on the society, the relationship between cancer and mental illness should be assessed.

Several studies<sup>6-10</sup> have attempted to clarify this relationship. However, the risk of developing cancer in patients with mental illnesses remains controversial. Some studies reported an increased risk<sup>6,7</sup>, while others reported low or statistically insignificant risk<sup>8-10</sup>. Contrary to the results regarding the incidence of cancer in patients with mental illness, some studies<sup>11,12</sup> have shown decreased survival rates in patients with mental illnesses due to cancer, which were attributed to physical, psychological, and social burdens in these patients. Because most previous reports focused on the relationship between cancer and two subtypes of mental illness, a comprehensive analysis through an integrated approach is required.

Previous studies<sup>13,14</sup> attempted to elucidate the relationship between cancer and mental illnesses using national registries. Ronaldson et al<sup>13</sup> (2020) analyzed the difference between hospital admission and hospital stay due to mental illness. Davis et al<sup>14</sup> (2020) evaluated the risk of cancer development and cancer-specific mortality in patients with mental illness but included only studies on patients with advanced-stage cancer in the association analysis.

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Therefore, to the best of our knowledge, no studies have assessed the association between cancer and mental illness *in toto*. Thus, this study comprehensively examined the relationship between cancer and mental illness.

## Materials and Methods

### Protocol and Registration

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines<sup>15</sup>. Our research topic was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on November 19, 2020 and approved on December 18, 2020 (registration number: CRD42020221689, CRD42020221687).

### Eligibility Criteria

Cohort, case-control, and cross-sectional studies were eligible for study inclusion. Studies with mathematically unreliable risk values were excluded from the review. We also excluded studies that lacked clearly identified diagnostic criteria. Studies reporting values unrelated to the topic were also excluded.

### Search Strategy

The search was performed in the Embase and Medline databases on October 21, 2020. The search terms were largely classified into three categories (psychiatric disorder, cancer, and effect measures) and combined with the “AND” conjunction. The related search words were discussed by the authors. The detailed search terms were as follows: (cancer OR malignancy, malignant neoplasm OR neoplasm, tumor OR carcinoma OR squamous cell carcinoma OR carcinogenesis OR precancer OR cancer in situ) AND (mental disease OR bipolar disorder OR psychosis OR schizophrenia OR mental deficiency OR mental illness OR major depression OR depression OR posttraumatic stress disorder OR hypomania OR mania OR panic) AND (ratio OR risk OR hazard OR outcome OR prognosis OR mortality OR morbidity OR prevalence OR incidence OR odds ratio OR hazard ratio). Search terms were limited to the title or abstract.

### Study Selection

We searched for articles published between 1966 and 2020. Mathes and Pieper<sup>16</sup> (2017) revealed that, in performing a systematic review, observational studies could be considered cohort studies if rel-

ative risk calculations between different groups are possible. Two authors (KK and YHK) independently conducted the literature search and checked the title and abstract of each study. The same authors reviewed the full-text articles for inclusion. Disagreements were resolved through discussion. The included mental illness types were those with International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) F codes (F01-F99). To avoid selection bias, studies that analyzed only certain subgroups or groups that received specific interventions were excluded.

### Data Extraction

We extracted the title, abstract, journal source, author name, publication year, and publication type during the first screening using a search tool. During the full-text assessments, we obtained additional information on the study design, number of samples, longest follow-up, World Health Organization region, adjusted variables, diagnostic criteria for cancer, and diagnostic criteria for mental illness.

### Summary Measures

Odds ratios (ORs) were used to report the associations between mental illness and cancer. Hazard ratios (HRs) were used to report differences in incidence and survival. We aimed to calculate not only unadjusted but also adjusted values for clinical variables, such as age, sex, race, and medical comorbidities in each study. The adjusted variables are presented in the **Supplementary Table I**. Subgroup analyses were performed according to the detailed classification of cancer and mental illness.

### Risk of Bias in Individual Studies

The Newcastle-Ottawa scale was used to qualitatively assess the risk of bias for the included cohort and case-control studies<sup>17</sup>. Cross-sectional studies were assessed using the adapted version of the Newcastle-Ottawa scale presented by Herzog et al<sup>18</sup> (2013). The assessment tools and results are presented in the **Supplementary Text**. Both authors (KK and YK) independently assessed the risks of bias of the included studies and verified the quality of evidence. Any discrepancies in the assessment were resolved through discussion. Cohort and case-control study scores were converted into three categories of “good,” “fair,” and “poor” according to the Agency for Healthcare Research and Quality (AHRQ) standard. We evaluated the study quality by establishing a criterion similar to the AHRQ standard for cross-sectional studies.

### **Publication Bias Across Studies**

Funnel plots were drawn to evaluate the risks of bias across the included studies based on the ORs and HRs using RevMan 5. Egger's regression test was performed using Stata 13 software to statistically evaluate publication bias.

### **Statistical Analysis**

The values and 95% confidence intervals were extracted from the papers when available. If the OR was not presented, OR and 95% confidence intervals were calculated based on the frequency of the 2×2 contingency table. The pooled OR and HR values for the included studies were calculated using RevMan 5, and forest plots were drawn. The heterogeneity was evaluated according to the classification of  $I^2$  statistics proposed by Higgins et al<sup>19</sup>. The heterogeneity was considered low, moderate, and high for  $I^2$  values of 25%, 50%, and 75%, respectively. If the heterogeneity was >50%, the random-effects method was used; otherwise, the fixed-effects method was used as previously described<sup>20,21</sup>. The most unadjusted values in the included studies were preferentially selected to calculate the pooled unadjusted value, while the most adjusted value in the included studies was preferentially selected to calculate the pooled adjusted value. Cancer-specific survival was preferentially used to calculate the survival rate; otherwise, relapse-free or overall survival was used. Forest plots were drawn to clearly visualize synthesized risk. The  $p$ -value < 0.05 was considered to have a statistical significance.

## **Results**

### **Study Selection and Characteristics**

A total of 21,545 records were searched, and 306 articles were extracted through two screening processes. Finally, 58 studies were included after the full-text assessment. These studies included 42 cohort studies, 12 cross-sectional studies, and four case-control studies. This study included approximately 25 million samples. The characteristics of the included studies are presented in **Supplementary Table I**. The PRISMA flowchart was shown in Figure 1.

### **Synthesis of Results**

#### *Associations between mental illness and cancer*

This analysis included 15 studies (four cohort studies, four case-control studies, and sev-

en cross-sectional studies). The pooled analysis showed an unadjusted OR of 1.85 (1.36-2.52) and an adjusted OR of 1.64 (1.20-2.25) (Figure 2 and **Supplementary Figure 1**). In the subgroup analysis, cancer was significantly associated with major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) but not with Alzheimer's disease (AD) or bipolar disorder (BD) (Table I).

#### *Risk of cancer development in patients with mental illness*

This analysis included 5 cohort studies. The pooled analysis showed an unadjusted HR (uHR) of 1.05 (0.82-1.34) and adjusted HR (aHR) of 1.07 (0.85-1.33) (Figure 3A and **Supplementary Figure 2A**).

#### *Risk of mental illness development in patients with cancer*

This analysis included 10 cohort studies. The pooled analysis showed uHR and aHR of 1.66 (1.30-2.12) and 1.66 (1.28-2.15), respectively (Figure 3B and **Supplementary Figure 2B**). Subgroup analysis showed that MDD in patients with cancer was significant for both uHR and aHR but not significant for AD (Table I). The risk of mental illness development was significantly higher in patients with breast cancer (Table I).

#### *Differences in Survival Rates in Psychiatric Patients According to Cancer Occurrence*

This analysis included 7 cohort studies. The pooled analysis showed an uHR and aHR of 1.32 (1.16-1.51) and 1.38 (1.11-1.70), respectively (Figure 4A and **Supplementary Figure 3A**).

#### *Differences in Survival Rates in Patients with Cancer According to Mental Illness Occurrence*

This analysis included 14 cohort studies. The pooled analysis showed an uHR and aHR of 1.52 (1.28-1.80) and 1.53 (1.30-1.80), respectively (Figure 4B and **Supplementary Figure 3B**). Patients with cancer showed significantly low survival rates due to MDD and schizophrenia but not due to substance use disorder (Table I). Patients with lung cancer and breast cancer showed a significantly low survival rate due to mental illness (Table I).

### **Risk of Bias Within Studies**

Particularly, 40 of 42 cohort studies, 7 of 13 cross-sectional studies, and 2 of 4 case-control studies were rated "good." The detailed assessments are shown in **Supplementary Tables II, III, and IV**.

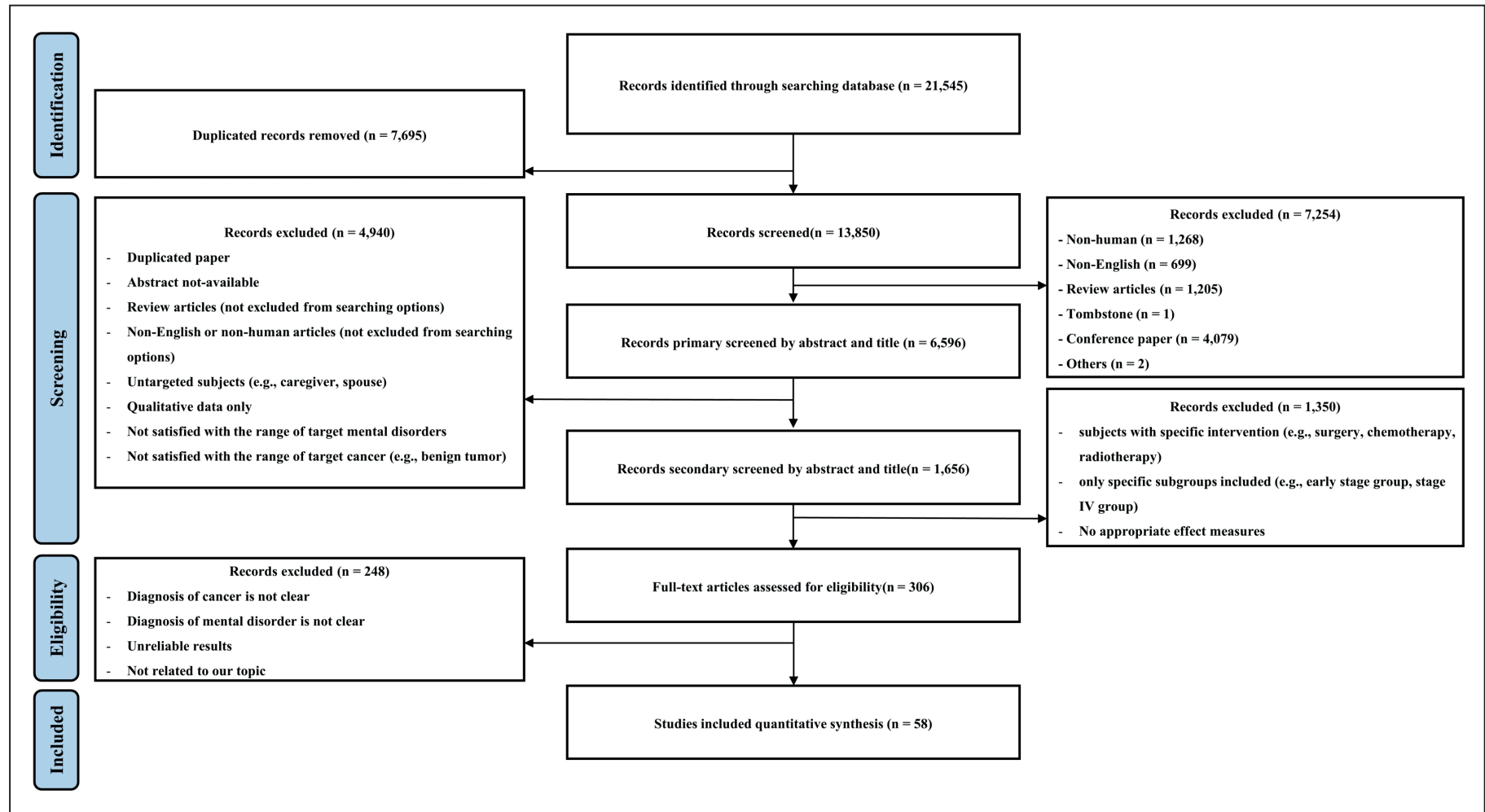


Figure 1. PRISMA flowchart.

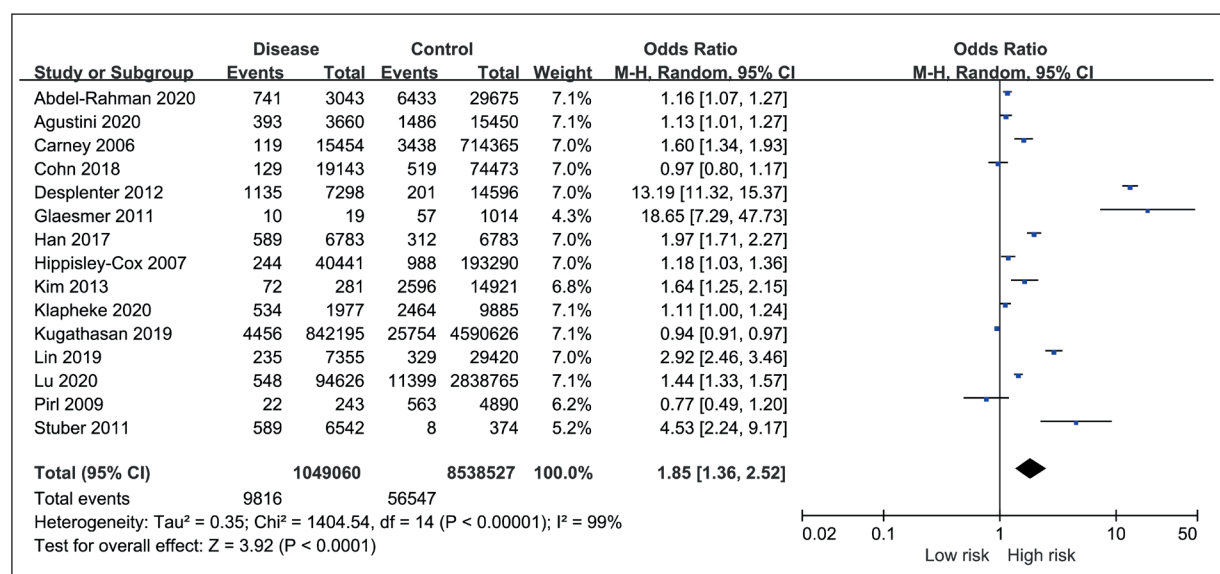


Figure 2. Forest plot of the pooled uOR between any mental illness and any cancer. uOR, unadjusted odds ratio.

### Publication Bias Across Studies

Funnel plots for the OR are presented in [Supplementary Figure 4](#). No significant publication bias was observed according to Egger’s regression test ( $p=0.089$ ).

## Discussion

This study examined the relationship between mental illness and cancer. We analyzed 58 papers from 16 countries, including 30 national databases and 25 million individuals. Our meta-analysis is a novel way to present integrative results featuring all types of cancers and mental illness. We observed a positive association between mental illness and cancer based on an increased OR. The integration of the HR revealed an increased occurrence of mental illness in patients with cancer. Furthermore, we observed low survival rates due to cancer occurrence in patients with mental illness and due to mental illness in patients with cancer.

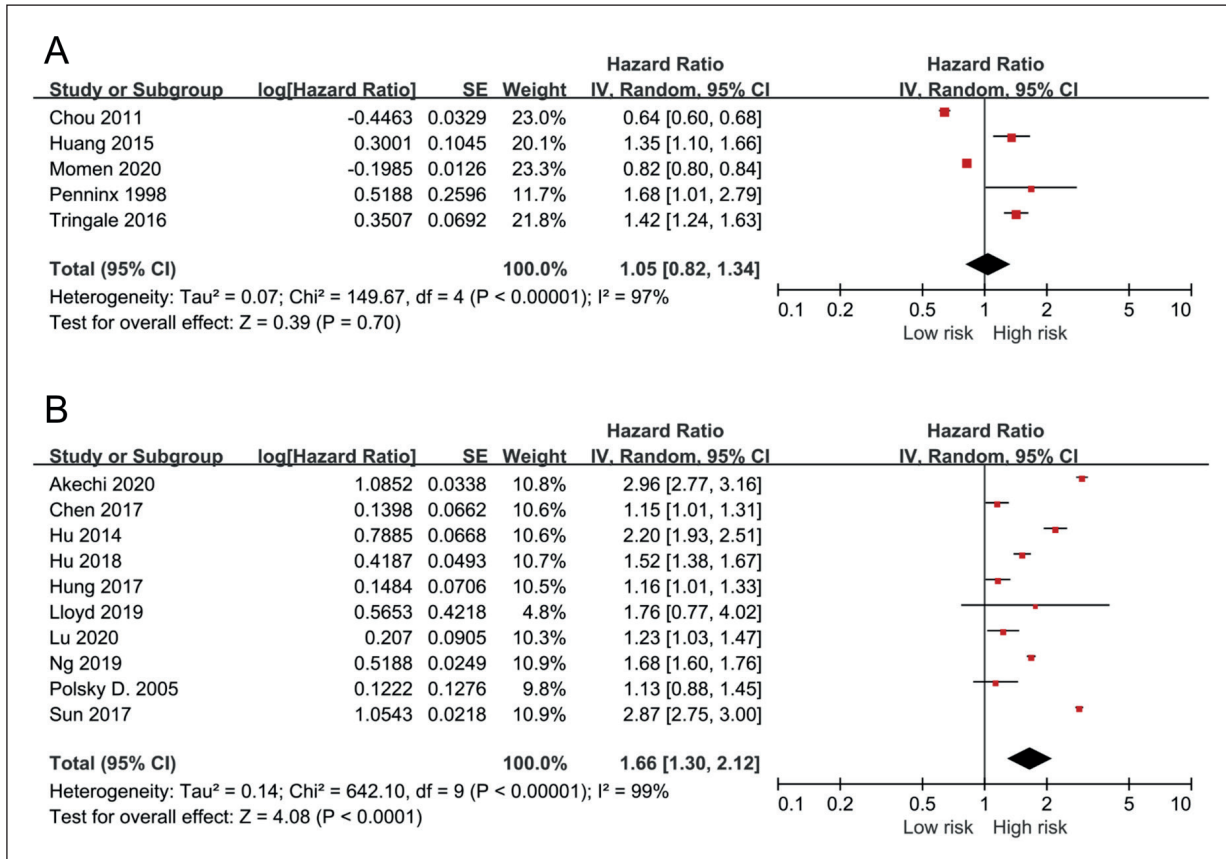
We separately analyzed ORs and HR. The effect measures of OR and HR are often applied interchangeably in the meta-analyses and are statistically integrated into one for relatively rare diseases in general populations<sup>22</sup>. The OR shows the association between two diseases<sup>23</sup>. The HR shows the temporal progression of death or development of a disease within a group<sup>23</sup> and is also a form of risk ratio (RR) independent of the study period<sup>22</sup>. However, their meanings slightly differ and should

be applied according to the study population and design. The included studies in the HR analysis were all cohort studies. We considered that separately analyzing HRs and RRs could lead to various interpretations among investigators.

A cancer diagnosis generates severe psychological distress in individuals and induces nonspecific emotions, including shock, denial, depression, guilt, anxiety, and anger<sup>24,25</sup>. Approximately 5-50% of patients with cancer have emotional distress<sup>26</sup>. These emotional changes can lead to MDD, AD, and adjustment disorders<sup>27</sup>. Moreover, such psychiatric morbidities in patients with cancer could reduce their survival rates by adversely affecting the risk of suicide, adherence to treatment, support from family members, social relationships, and quality of life<sup>28</sup>. Cleeland<sup>29</sup> (2003) suggested that cytokines might provide a biological basis linking cancer to the occurrence of mental symptoms. Reiche et al<sup>30</sup> also established a biological plausibility that depression or stress in patients with cancer affects tumor progression and survival by impairing the immune system *via* dysregulation of the hypothalamic-pituitary-adrenal axis and autonomic nervous system. The OR and HR results in patients with cancer can be used to establish a wider range of logical epidemiological grounds for this claim.

Mood disorders, such as MDD and BD, were significantly associated with cancer, while schizophrenia was not. In fact, the observed cancer risk in patients with schizophrenia was similar to that in the general population, despite the presence of many risk factors (e.g., smoking and obesity)<sup>31</sup>.





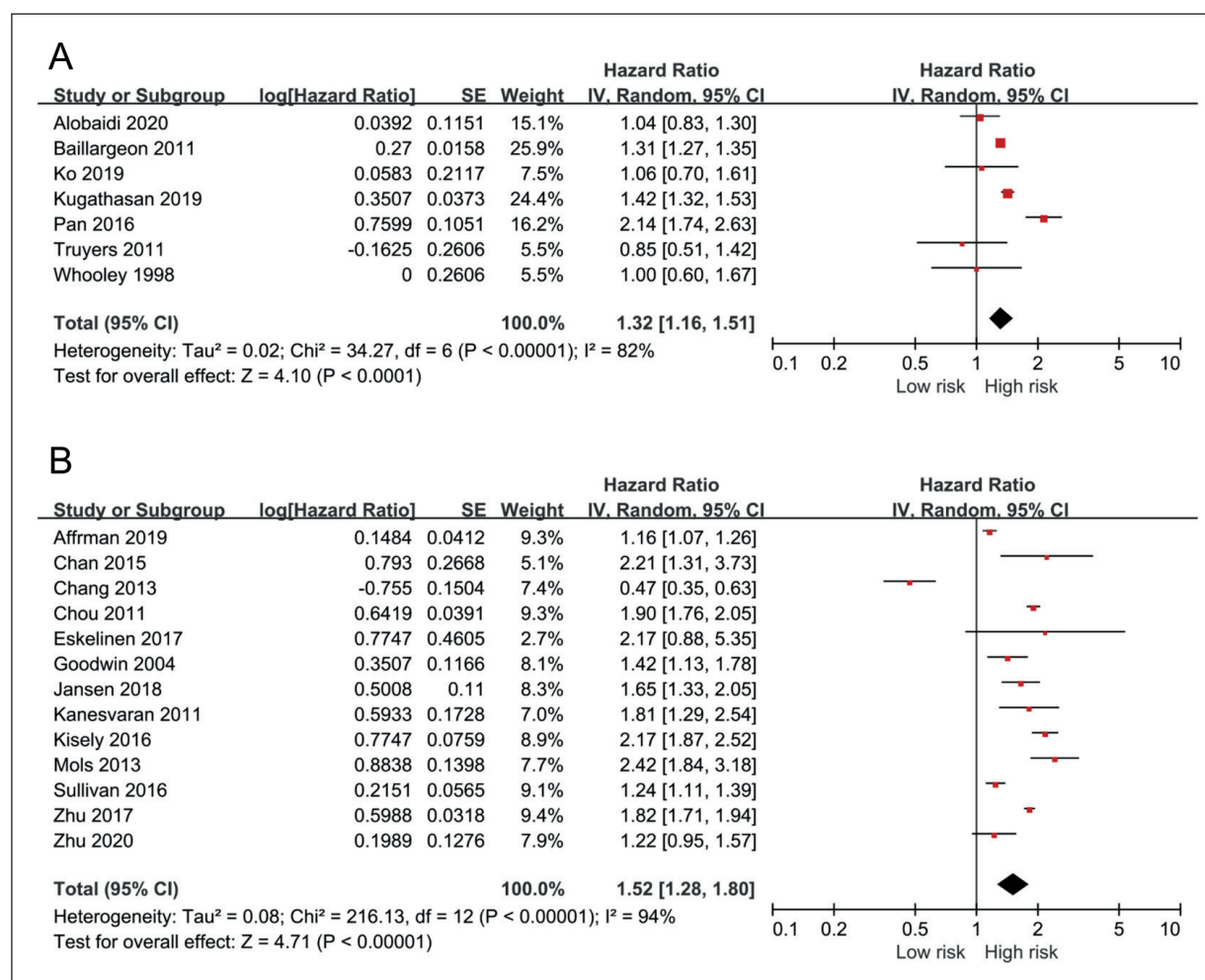
**Figure 3. A,** Forest plot of the pooled uHR for the development of any cancer in any patient with mental illness. **B,** Forest plot of the pooled uHR for the development of any mental illness in patients with any cancer. uHR, unadjusted hazard ratio.

One explanation is that psychiatric drugs have potential anticancer properties<sup>32</sup>. Another explanation is the relatively low screening rate, underdiagnosis, and premature death due to other comorbidities in these patients<sup>33</sup>. Surprisingly, PTSD had a particularly high OR in mood disorders. PTSD occurs when a life-threatening disease, such as a cancer diagnosis or treatment, acts as a traumatic stressor<sup>34</sup>. The prevalence rate of PTSD in patients with cancer was 22%, which was significantly higher than that in the general population<sup>35</sup>. PTSD is likely to be misdiagnosed as MDD or AD, which can lead to other mental illnesses<sup>35</sup>. PTSD also affects social relationships, activities, and return to work<sup>36</sup>. While the accurate diagnosis and treatment of PTSD are essential compared to other mental illnesses, PTSD is not well recognized in patients with cancer<sup>35</sup>. Thus, clinicians should be aware of the importance of early screening and intervention for patients with cancer with various mental illnesses, especially PTSD.

Subgroup analysis according to the cancer type revealed increased occurrence of mental illnesses,

such as MDD and AD, in patients with breast cancer. In patients with breast and lung cancer, the occurrence of mental illnesses negatively affects survival. Each value was not significantly different from the value of the integrated results. No unique rational explanations for the development of psychiatric disorders have been observed for each cancer. Future studies should analyze the associations between various cancer subtypes and mental illnesses.

In this meta-analysis, while the risk of cancer development in patients with mental illnesses was >1, this finding was not statistically significant. Thus, there remain questions regarding the difference in cancer occurrence in patients with mental illnesses. Higher proportions of individuals with mental illnesses have unhealthy lifestyles (smoking, drug or alcohol use, and unsafe sexual activity)<sup>37</sup>. Moreover, some medications used for psychiatric treatment can cause obesity<sup>38</sup>. Since these factors could be risk factors for cancer, it might be reasonable for patients with mental illnesses to have an increased risk of cancer. However, there is currently no clear evidence of increased cancer



**Figure 4.** **A**, Forest plot of the pooled uHR for event-free survival due to any cancer in any patient with mental illness. **B**, Forest plot of the pooled uHR for event-free survival due to any mental illness in patients with any cancer. uHR, unadjusted hazard ratio.

occurrence in patients with mental illnesses<sup>37</sup>. One reasonable explanation for this phenomenon is the low screening rate. Low proportions of patients with mental illnesses underwent colorectal, cervical and prostate cancer screening<sup>39</sup>. Moreover, the more severe the mental illness, the lower the screening rate<sup>40</sup>. Another valid explanation is the longer symptom-to-diagnosis period in individuals with mental illness compared to that in individuals without mental illness<sup>37</sup>. In one study, the symptom-to-diagnosis period was about three times longer in patients with mental illness (90 days) than in those without mental illness (35 days)<sup>41</sup>. The actual risk of cancer development in patients with mental illness might be masked, due to unscreened cases<sup>42</sup>. In the present study, although the risk was >1, this finding was not statistically significant. Considering the aforementioned effects, the actual risk is likely higher. Thus, psychiatrists should

not only try to correct modifiable risk factors but also recognize the importance of cancer screening in individuals with mental illness.

Several studies<sup>11,12</sup> have reported low survival rate in patients with mental illness due to cancer occurrence, as clarified by the results of the present meta-analysis. Although mortality might increase due to physical and psychological burdens influenced by cancer, a history of mental illness could be a risk factor for increased mortality. As mentioned above, the time to diagnosis is prolonged in individuals with mental illness. Delayed examinations can reduce survival rates because cancer is diagnosed at a more advanced stage<sup>43</sup>. Moreover, patients with mental illness are less likely to receive specialized interventions after a cancer diagnosis<sup>37</sup>. Kisely and Crowe<sup>12</sup> reported lower rates of colorectal resection, chemotherapy, and radiotherapy in patients with mental illnesses compared to those

**Table I.** Subgroup analyses between cancer and mental illness.

Subgroup	Number of studies	Number of cohort studies	Unadjusted value	Adjusted value
<b>Associations between cancer and mental illness (OR)</b>				
All cancer types – all psychiatric disorders	15	4	1.85 (1.36-2.52)	1.64 (1.20-2.25)
All cancer types – major depressive disorder	13	2	1.95 (1.33-2.86)	1.95 (1.30-2.94)
All cancer types – anxiety disorder	6	2	2.38 (0.98-5.74)	2.27 (0.86-5.99)
All cancer types – schizophrenia	3	2	1.16 (0.84-1.60)	1.12 (0.80-1.57)
All cancer types – bipolar disorder	4	1	1.39 (1.22-1.58)	1.33 (0.77-2.31)
All cancer types – PTSD	5	1	3.34 (1.63-6.86)	2.41 (1.93-3.01)
<b>Studies examining the risks of cancer in patients with mental illness (HR)</b>				
All cancer types – patients with all mental illnesses	10	10	1.66 (1.30-2.12)	1.66 (1.28-2.15)
Breast cancer – patients with all mental illnesses	3	3	1.85 (1.21-2.82)	1.74 (1.07-2.83)
All cancer types – patients with major depressive disorder	9	9	1.48 (1.17-1.87)	1.47 (1.16-1.87)
All cancer types – patients with anxiety disorder	3	3	1.87 (0.47-4.73)	1.92 (0.71-5.20)
<b>Studies examining the risks of mental illness in patients with cancer (HR)</b>				
All mental illnesses – patients with all cancer types	14	14	1.46 (1.18-1.80)	1.46 (1.24-1.72)
Major depressive disorder – patients with all cancer types	12	12	1.46 (1.21-1.75)	1.42 (1.20-1.68)
Anxiety disorder – patients with all cancer types	3	3	1.43 (1.02-2.02)	1.36 (0.87-2.12)
Schizophrenia – patients with all cancer types	2	2	1.63 (1.11-2.41)	1.63 (1.11-2.41)
Substance use disorder – patients with all cancer types	3	3	1.69 (0.92-3.13)	1.70 (0.92-3.15)
All mental illnesses – patients with lung cancer	3	3	1.34 (1.08-1.65)	1.31 (1.05-1.63)
All mental illnesses – patients with breast cancer	4	4	1.42 (1.25-1.62)	1.45 (1.27-1.66)
Major depressive disorder – patients with breast cancer	5	5	1.47 (1.23-1.75)	1.44 (1.17-1.78)
Anxiety disorder – patients with breast cancer	2	2	1.62 (0.97-2.71)	1.55 (0.86-2.82)

\*PTSD, post-traumatic stress disorder; OR, odds ratio; HR, hazard ratio.

in the general population. As patients with both cancer and mental illness have low survival rate regardless of previous diseases, the oncologists and psychiatrists treating these patients must pay close attention to the signs of either illness.

Despite these explanations, the decrease in survival rate resulting from cancer occurrence in patients with mental illness was lower than our expectations. Depending on the study design, the effect measure and its meaning differed, making it difficult to quantitatively compare the values to those in the general population. In the USA, cancer ranks second in terms of proportional mortality in the general population (23%)<sup>44</sup>. Furthermore, cancer accounts for 21% of deaths in patients with severe mental illness, comparable to the rate in the general population<sup>45</sup>. Western Australia and Ethiopia have relatively low rates of 8.9% and 2.5%, respectively<sup>45</sup>. Suicide, homicide, and accidents account for 5.4-43.8% of deaths in patients with mental illness<sup>45</sup>. Heart diseases are the most common cause of death in patients with mental illness in several countries, including the USA<sup>45</sup>. This phenomenon is attributed to a high smoking rate, drug-induced weight gain, reduced activity, and increased substance (drug) use<sup>46</sup>. Thus, in patients with mental illness, other causes, such as suicide, homicide, and accidents, may

have contributed more to the death rate than cancer, which usually has a chronic course. Therefore, it is necessary to emphasize the importance of mental illness to clinicians, with particular attention to the aforementioned causes of death, including cancer.

The issues surrounding the diagnosis and treatment of patients with both mental illness and cancer include hesitation to diagnose and treat, economic problems, and side effects from the use of multiple drugs to treat both diseases<sup>37,47,48</sup>. Hence, the survival rate might be lower due to the failure to achieve optimal treatment. Healthcare providers must consider these issues in their policy designs.

Our study has several limitations. First, it was not possible to perform a subgroup analysis of variables, such as age, sex, race, and economic status, which are common risk factors for both mental illness and cancer. We also did not adjust for the effects of potential confounders. Second, the results of the subgroup analysis are relatively weak in terms of statistical power due to the small number of included studies in each subgroup. Third, as most included studies were conducted in developed countries, the external validity of these results must be considered when applying them to the general population or developing countries. Finally, since the study design of all included studies were observational, it was difficult to infer causal relation-



ships. We restricted the eligibility of the studies to those published in English only. The search was performed using only the Embase and Medline databases. We did not contact the study authors directly to clarify any information. Despite these shortcomings, our study has several strengths. The total number of 25 million individuals likely provides results with high statistical impact. Since some studies used national registries, the confidence level of the diagnostic criteria is high. Finally, the results were obtained after considering all types of cancer and mental illnesses.

## Conclusions

Despite several limitations, this systematic review and meta-analysis examined the occurrence of cancer, survival, and mental illness based on analyses of ORs and HRs. Clinicians should perform early screening and provide appropriate interventions for mental illness in patients with cancer. The actual risk of cancer development in patients with mental illness may be higher due to undiscovered cases. Owing to the contribution of unnatural causes of death, such as suicide, homicide, and accidents, in patients with mental illness, clinicians should be aware of the importance of the treatment and management of mental illness. This study is important because it provides information to researchers interested in the relationship between cancer and mental illness. Future studies on both cancer and mental illness should also adjust for patient age, sex, and race.

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### Conflict of Interest

The authors declare that they have no conflicts of interest.

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### Ethics Approval

Not applicable.

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### Informed Consent

Not required.

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### Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed in this study.

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### Authors' Contribution

Kihun Kim: Conceptualization, Visualization, Methodology, Investigation, Formal analysis, Data curation, Writing – Original draft preparation. Yun Hak Kim: Conceptualization, Visualization, Project Administration, Funding acquisition, Writing – Reviewing and Editing, Supervision.

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