Original Study

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Meta-analysis of the Correlation Between Schizophrenia and Breast Cancer

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Abstract

In this meta-analysis on correlation between schizophrenia and breast cancer (BC), we found that the incidence of schizophrenia is positively correlated with BC, and the incidence of BC in schizophrenia patients is increased in a certain degree. Because of the effects of potential bias and publication bias, the conclusion needs more high-quality studies to increase the strength of evidence.

Purpose: To determine the correlation between schizophrenia and breast cancer (BC). **Methods:** We searched relevant articles indexed in the PubMed, Embase, and Cochrane Library databases; managed the data in Endnote X7 software; evaluated literature quality by Newcastle-Ottawa quality evaluation criteria; designed tables; and extracted relevant data. The main outcome measure was BC incidence. Effect values were risk ratio and 95% confidence intervals. We used Stata 13.1 software to perform the meta-analysis, choosing a corresponding combination model according to heterogeneity test results and carrying out subgroup analyses in order to better understand the stability of results through sensitivity analysis. **Results:** On the basis of 15 studies that assessed patients in different geographic regions, meta-analysis results showed that BC incidence between the exposure group (patients with schizophrenia) and the control group (nonschizophrenia population or general population) had statistical difference (risk ratio = 1.18; 95% confidence interval, 1.05, 1.32), thus showing that BC incidence in patients with schizophrenia is higher than in the nonschizophrenia or general population. Subgroup analysis indicated that gender and geographic region may be sources of the assessed studies' heterogeneity. **Conclusion:** The incidence of schizophrenia is positively correlated with BC, and the incidence of BC in patients with schizophrenia is increased to a certain degree. Because of the effects of potential and publication bias, this conclusion needs more high-quality studies to increase the strength of evidence.

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Introduction

The health status of psychiatric patients has attracted more and more attention in the past decade; approximately 85% excess mortality is related to natural reasons, and approximately 15% mortality is related to suicide and other nonnatural reasons.[1] So far, most studies on the mortality risk of psychiatric patients have focused on the risk factors of cardiovascular disease but ignore other reasons, such as cancer. Most studies indicate that the heart metabolic rate of psychiatric patients is increased and that the incidence and mortality of cardiovascular diseases are increased significantly. However, there is no consensus on the relationship between mental illness and cancer. Some studies have pointed out that mental illness increases the incidence of cancer.[2-4] Other studies note that mental illness does not increase[5-8] or may even decrease[9] the incidence of cancer. Those differences may be caused by different manifestations of mental illness or by different types of cancer. For example, Huntington chorea is a kind of mental illness; the risk of such patients having digestive tract cancer is lower than that of general population.[10,11] In mental illness, patients with schizophrenia have a lower incidence of prostate cancer and melanoma but are at high risk of breast cancer (BC).[12,13]

BC is the world's second most common type of cancer causing death in women, accounting for about 10.9%.[14] Although several relatively rare specific reasons for BC exist—*BRCA1* and *BRCA2* mutations, history of radiotherapy before puberty, and history of cancer before BC—the etiology of BC otherwise remains largely

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unknown. More and more clinical studies and epidemiologic studies have pointed out that prolactin (PRL) plays a relatively important role in the occurrence and development of BC. In the 1990s, a study constructed transgenic mice overexpressing human growth hormone, including PRL, which can activate the PRL receptor to induce mice to develop BC.[15] Another study showed that the expression level of PRL in human BC cells is higher than that of normal breast tissue.[16] PRL combines with PRL receptor to stimulate the downstream signal pathway, resulting in relevant biological changes of breast epithelial cells, including the promotion of apoptosis and vascularization, as well as the enhancement of tumor-cell proliferation and migration.[17,18]

The process of carcinogenesis of the mammary glands is the same as that of normal breast tissue, which is mainly a process of hormone dependence. Estrogen, progesterone, and even PRL play an important role in the growth and differentiation of mammary gland cells.[17,19] Many antipsychotic drugs can increase serum PRL levels, especially first-generation antipsychotic drugs.[20,21] The plasma concentration of PRL has been found to be significantly increased in 80% to 90% of female subjects.[22] Compared to first-generation antipsychotic drugs, the effect of second-generation antipsychotic drugs' (in addition to risperidone and amisulpride) increasing the plasma PRL level is weak.

The purpose of this study was to explore the correlation between schizophrenia and BC. Meta-analysis can combine and analyze different study results, find key points of dispute through heterogeneity tests and sensitivity analyses, and thereby obtain more abundant information than that presented in the original literature.

Materials and Methods

Inclusion Criteria

To be considered for inclusion in the meta-analysis, the studies had to fulfill the following criteria. The object of the study had to include patients previously diagnosed as having schizophrenia, excluding other mental illness; age and sex were not limited. For intervention measures, the patients in the exposed group had to be patients with schizophrenia, and the control group had to comprise patients without schizophrenia or the general population. For the study outcome, the primary outcome index had to be incidence of BC, and the correlation indexes of schizophrenia and BC had to be risk ratio (RR), odds ratio (OR), standardized incidence ratio (SIR), or hazard ratio (HR). Study types included retrospective or prospective studies published in Chinese or English.

Exclusion Criteria

Studies were excluded for the following reasons: studies had no clear criteria provided for diagnosis and no clear standard of inclusion and exclusion; the studies of outcome measures were of mortality (ie, standardized mortality rate); the studies reported data that were obviously incorrect or incomplete, or were unable to provide the outcome; and the study had been published before.

Retrieval Strategy

We searched authoritative databases, including PubMed, Embase, and the Cochrane Library, for relevant literature published through March 2016. We used the following retrieval terms: breast neoplasm, breast tumor, breast cancer, schizophrenia, schizophrenias, schizophrenic disorders, psychosis.

Literature Screening Method

We introduced our bibliography into Endnote X7 software to check each study. Only literature that met the inclusion criteria was adopted. Subsequently, literature that met the exclusion criteria was excluded. After a preliminary screening, the included studies were read carefully to confirm that they had complete information for data consolidation.

Evaluation of Literature Quality

Internalization studies were carried out via quality evaluation according to the Newcastle-Ottawa quality evaluation standard (NOS). NOS uses the semiquantitative principle of a star system to evaluate literature quality; the best score is 9 stars.[23] The minimum follow-up time of the exposure group was set for 8 years, according to incidence characteristics of BC.[14]

Data Extraction

We designed a data extraction form. Extraction contents included the internalization study's first author, year of publication, geographic area of study, study object and design, population of exposure and control groups, expected outcome, number of subjects in the exposure and control groups, effect indexes, and correction factors of effect indexes.

All processes of literature screening, quality evaluation, and data extraction were carried out by two evaluators. Disagreement was resolved by discussion or by assistance from a third researcher.

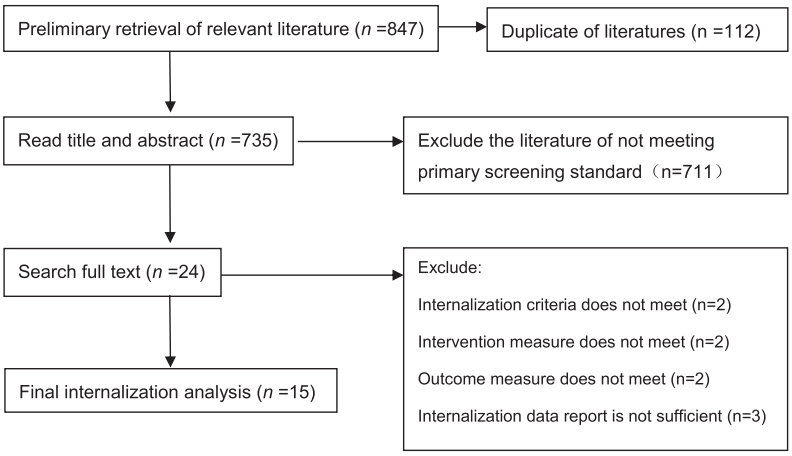
Indexes of Primary Outcome

We created a correlation index of schizophrenia and BC, RR, OR, HR, and SIR, as well as the corresponding confidence interval (CI), including upper and lower limits. SIR refers to the ratio between exposure population incidence and expected incidence. RR refers to the ratio of risk between the exposure group (measure index is cumulative incidence or incidence density) and the control group. The implication of OR is similar to RR, which means how many times the risk between exposure group and nonexposure group. HR refers to the ratio of risk function between the exposure population and the control population; although this is similar to RR, HR includes time factor—in other words, HR is RR including a time effect.

Statistical Analysis

Statistical analysis was conducted by Stata 13.1 software (StataCorp, College Station, TX). The primary outcomes of interest for our study were the indicators associated with schizophrenia and BC, which was calculated as RR, OR, HR, and SIR with their corresponding 95% CIs, including upper and lower limits. Because the absolute risk of BC or schizophrenia is low, the 4 measures of association are expected to yield similar estimates of RR. Consequently, we presented all RR estimates pooled together, as appropriate, so that comprehensiveness of analysis and maximization of statistical power were ensured. We assumed that the logarithm of RR was normally distributed. The particular asymptotic error would not affect the statistical result. Summary RRs with 95% CIs were calculated with the method of DerSimonian and Laird by use of the assumptions of a random-effects model, which considers

Figure 1 Flowchart of Literature Screening and Internalization



both within-study and between-study variation.[24-26] Results are shown as subgroup analyses by reference population (sex and geographic area) and literature quality.

The heterogeneity of various studies was tested by chi-square test and measured by I^2 test. If the results of studies assessed by internalization analysis had no statistical heterogeneity ($P > .1$, $I^2 \leq 50\%$), we used the fixed-effect model to combine and analyze data ($P \leq .1$, $I^2 > 50\%$). We carried out subgroup analysis according to sex and geographic area to determine the source of clinical heterogeneity. The random-effects model was used to combine and analyze data if we could not determine the source of statistical heterogeneity. The funnel plot and Egger test were used to examine publication bias.

Results

Literature Retrieval and Screening

Search results are provided in Figure 1. A total of 847 articles were potentially relevant according to our initial search terms; 112 of them were excluded because they were duplicated. In strict accordance with our inclusion and exclusion criteria, we excluded another 720 studies of the remaining 735. A total of 15 studies published between 2001 and 2013 were finally included in the present meta-analysis.[3-5,26-37]

Literature Quality and Publication Bias

We evaluated literature inclusion by NOS. The quality score of the included 15 articles was 5 to 8 stars. There was no evidence of funnel plot asymmetry or Egger test results significant for publication bias (Figure 2). We therefore believe that there was no publication bias ($P = .555$).

Internalization Literature

The data provided by the various studies included in our meta-analysis are shown in Table 1. These data mainly included year, geographic area, study design, object selection, follow-up time, characteristics of exposure and control populations, main effect index, correction factors of the effect index, and confounding factors of the exposure and control groups. All internalization studies were of retrospective design. The geographic areas mainly included Europe, Asia, Oceania, and North America, including 7 articles in Europe (including Finland, Denmark, Sweden, and the United Kingdom),[3,21,27,29,30,32,36] 6 articles in Asia (including Israel and Taiwan),[28,31,33-35,37] and one article each in North America[4] and Australia.[5]

Correlation Between Schizophrenia and BC

The 15 internalization articles described exposure groups that included patients with schizophrenia, and control groups that included patients without schizophrenia or a general population living in the same area as the exposure group. Based on meta-analysis, the studies have statistical heterogeneity ($P < .001$, $I^2 = 88.6\%$). We chose a random-effects model to combine them. Results show that BC incidence between the exposure and control groups differs (RR = 1.18; 95% CI, 1.05, 1.32). Our data suggest that patients with schizophrenia are significantly associated with a

Figure 2 Funnel Plot for Breast Cancer Incidence Rates in Patients With Schizophrenia

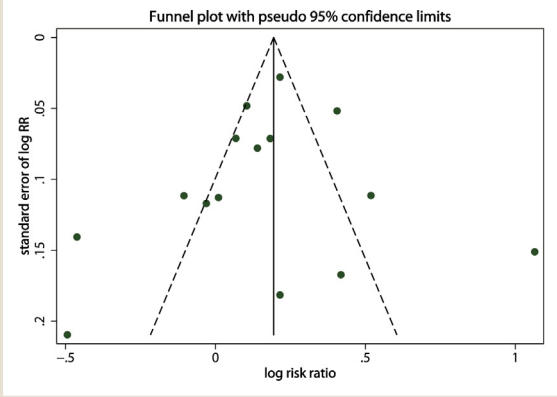


Table 1 Basic Situation of Internalization Study

Internalization Study	Study Design	Study Area	Study Object	Follow-up Time	Exposure Population	Breast Cancer No. in Exposure Group	Control Population	Breast Cancer No. in Control Group	Effect Index	Correction Factors	Confounding Factors
Lichtermann 2001[3]	Retrospective	Finland	Women born 1940-1969 in Finland hospitals and medical insurance system, and diagnosed with schizophrenia in 1969-1991	1971-1996	11,418	152	11,418	132	Female SIR = 1.15 (0.98, 1.34)		
Lawrence 2001[5]	Retrospective	Western Australia	Female patients with mental illness registered in Western Australia health management database in 1966-1998, who still alive before 1980	1982-1998	329	85	3978	1089	Female SIR = 0.97 (0.78, 1.22)		Other mental illness, neurologic disorders
Oksbjerg Dalton 2003[27]	Retrospective	Denmark	Women born 1935-1973 and registered in Denmark Population Registry, still alive after 1970	1943-1997	7541	74	1,328,772	18,044	Female RRa = 0.97 (0.76, 1.20); RRb = 0.90 (0.71, 1.12) Have birth history RRa = 0.77 (0.53, 1.07); RRb = 0.75 (0.52, 1.04) Have no birth history RRa = 1.05 (0.76, 1.41)	(a) Age and follow-up time (b) Age, follow-up time, age of giving birth to first child and child number	Birth history
Grinshpoon 2005[28]	Retrospective	Israel (Jews)	Men and women aged 18-45 y in Israel medical insurance system record and diagnosed to be in compliance with ICD-10 F20 psychosis	1962-2001	33,372	370	33,372	333.34 General population	Total female SIR = 1.11 (1.00, 1.22) Afro-Asia SIR = 1.37 (1.12, 1.63) Europe and North America SIR = 1.08 (0.91, 1.25) Jewish SIR = 1.03 (0.84, 1.23)		Age

Table 1 Continued

Internalization Study	Study Design	Study Area	Study Object	Follow-up Time	Exposure Population	Breast Cancer No. in Exposure Group	Control Population	Breast Cancer No. in Control Group	Effect Index	Correction Factors	Confounding Factors
Dalton 2005[29]	Retrospective	Denmark	Men and women aged >15 y, registered in Denmark mental illness registry in 1969-1993, including psychiatric hospital and psychiatric ward of general hospital, no history of cancer or hospital admission before this time, with average age of 42 y (people aged <45 y accounting for 59%)	1969-1995	22,766	216	22,766	179	Female SIR = 1.20 (1.05, 1.38) Male SIR = 1 (1.00, 0.01)		Drugs for schizophrenia
Goldacre 2005[30]	Retrospective	UK	All patients with schizophrenia in National Health Service Center in 1963-1999, after 1994, including men and women of community cases, age not restricted, average age 40 y, average follow-up time 12.6 y (people aged <45 y accounting for 64%)	1963-1999	9649	80	600,000	2659	Male and female RR = 1.01 (0.80, 1.26)	Sex, age, follow-up time	Medical level
Barak 2005[31]	Retrospective	Israel	Jewish patients with schizophrenia registered in Abarbane Mental Health Center in 1993-2003, average age 49 ± 14.7 y	1993-2003	1247	22	1247	37.4	Female SIR = 0.61 (0.39, 0.92)		
Hippisley-Cox 2007[32]	Retrospective (nested case-control study)	UK	Medical data before August 1, 2005, from QRESEARCH database, sex and age not restricted, average age of exposure group 67 y and control group 68 y	1995-2005	139	49	571	153	Male and female OR = 1.52 (1.10, 2.11)	Smoking, obesity, social and economic status, chromic medical history, antipsychotic drugs	Other mental illness, (bipolar disorder)
Barak 2008[33]	Retrospective	Israel	Jewish women aged >18 y with mental disorders registered in Israel Abarbane Mental Health Center online system	1960-2205	2011	51	2011	81	Female SIR = 0.63 (0.47, 0.83)		Other mental illness

Table 1 Continued

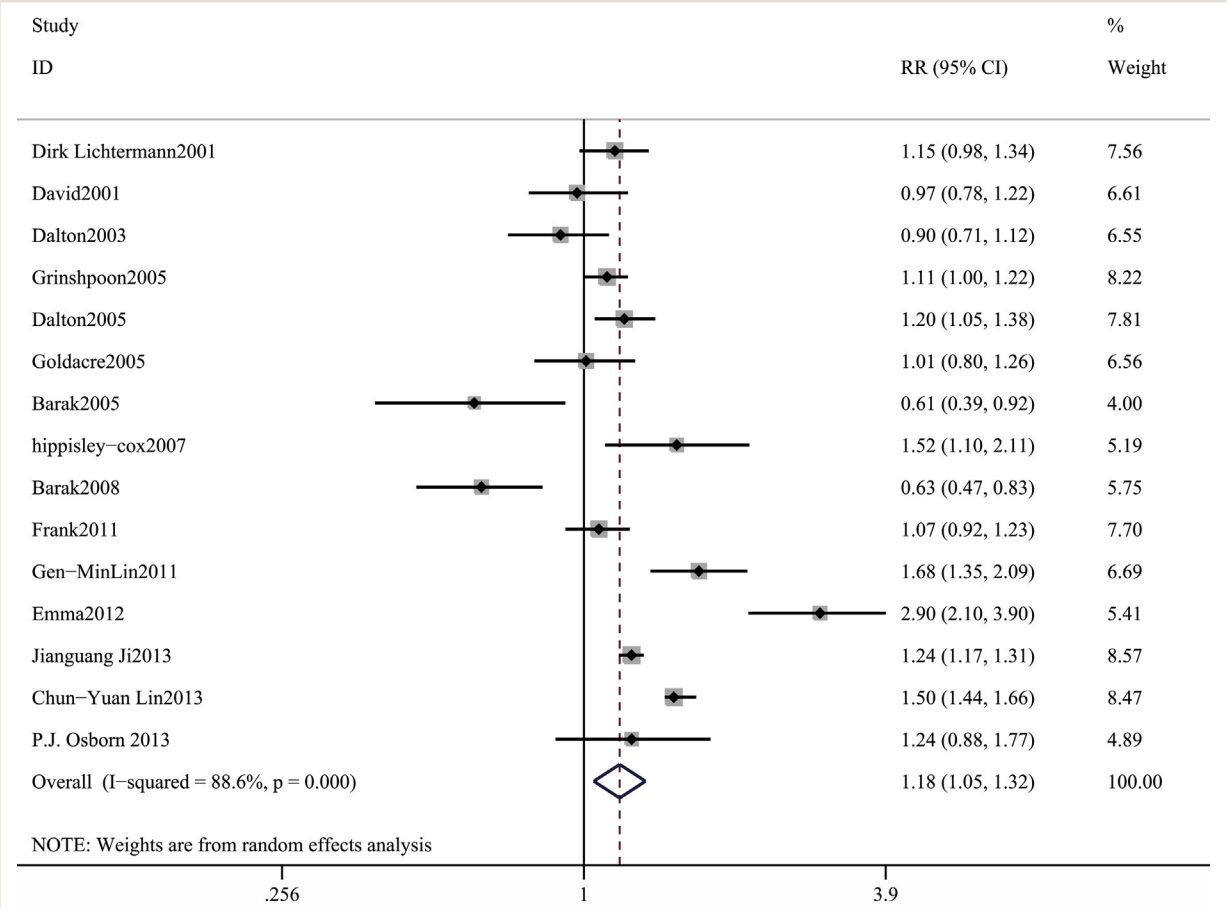
Internalization Study	Study Design	Study Area	Study Object	Follow-up Time	Exposure Population	Breast Cancer No. in Exposure Group	Control Population	Breast Cancer No. in Control Group	Effect Index	Correction Factors	Confounding Factors
Chou 2011[34]	Retrospective	Taiwan	Object determined in 1999 from NHIRD, including men and women, average age 40 y	2000-2009	249,248	1145	702701 women and 1 man	5294	Male and female HR = 1.07 (0.92, 1.23) Female HR = 1.06 (0.92, 1.23) Male HR = 3.0 (0.19, 48.19)	Age, sex, income level, complication, urbanization level	
Lin 2011[35]	Retrospective	Taiwan	Women determined in 1995-1996 from NHIRD, average age 38.9 ± 14.2 y	1997-2009	33,297	215	33,297	128	Female SIR = 1.68 (1.35, 2.09) Age >50 y SIR = 1.75 (1.24, 2.47) Age <50 y SIR = 1.64 (1.24, 2.17)		Other mental illness, (bipolar disorder)
McGinty 2012[4]	Retrospective	North America	Women aged 21-62 y in social life subsidy system July 1992-July 1993; object is Baltimore urban residents or eastern rural residents of Maryland, average age 41.5 ± 10.2 y	1996-2004	1119	42	1119	14	Female SIR = 2.9 (2.1, 3.9)		
Ji 2013[36]	Retrospective	Sweden	Men and women in Swedish hospital discharge registry system (1965-2004) and hospital outpatient (1998-2004), average age ≥50 y accounting for 30.5%	1965-2008	32,204 men, 27,029 women	10 men, 1315 women	59,233	1066	Female SIR = 1.24 (1.17, 1.31) Male SIR = 1.62 (0.77, 3.00)		

Table 1 Continued

Internalization Study	Study Design	Study Area	Study Object	Follow-up Time	Exposure Population	Breast Cancer No. in Exposure Group	Control Population	Breast Cancer No. in Control Group	Effect Index	Correction Factors	Confounding Factors
Lin 2013[37]	Retrospective	Taiwan	Schizophrenic women recorded in disease registration and recording system March 1, 1995, to December 31, 2007, aged >20 y and no history of cancer before this time; those with average age ≥50 y accounted for 78.08%; average age of group 39.03 ± 12.81 y	1995-2007 Follow-up median period is 7.58 y	46,447 women	341	46,447	228	Female SIR = 1.50 (1.44, 1.66) Age 20-29 y SIR = 4.53 (3.80, 7.16) Age 30-39 y SIR = 1.88 (1.75, 2.33) Age 40-49 y SIR = 1.27 (1.19, 1.52) Age 50-59 y SIR = 1.55 (1.44, 1.92) Age 60-69 y SIR = 1.70 (1.50, 2.37)		Age
Osborn 2013[8]	Retrospective	UK	Male and female residents aged >18 y recorded in electronic medical database, January 1990 to December 2008, with >6 months' follow-up	From entry to queue time to end of 2008	20,632		Nonschizophrenic population matched with exposure group in age and sex = 116,152		Male and female: Female IRRa = 1.37 (0.97, 1.94); IRRb = 1.38 (0.98, 1.96); IRRc = 1.24 (0.88, 1.77) Male IRRa = 1.38 (0.97, 1.95); IRRb = 1.39 (0.98, 1.97); IRRc = 1.36 (0.96, 1.93)	(a) Age, sex, follow-up time, economic status (b) Age, sex, follow-up time, economic status, smoking (c) Age, sex, follow-up time, economic status, smoking, BMI ≥30 kg/m^2	Other mental illness, severe mental disorder, bipolar disorder

Abbreviations: BMI = body mass index; HR = hazard ratio; IRR = incidence rate ratio; OR = odds ratio; RR = risk ratio; SIR = standardized incidence ratio.

Figure 3 Forest Plots for Random-Effects Meta-analysis of Breast Cancer Incidence Rates in Patients With Schizophrenia



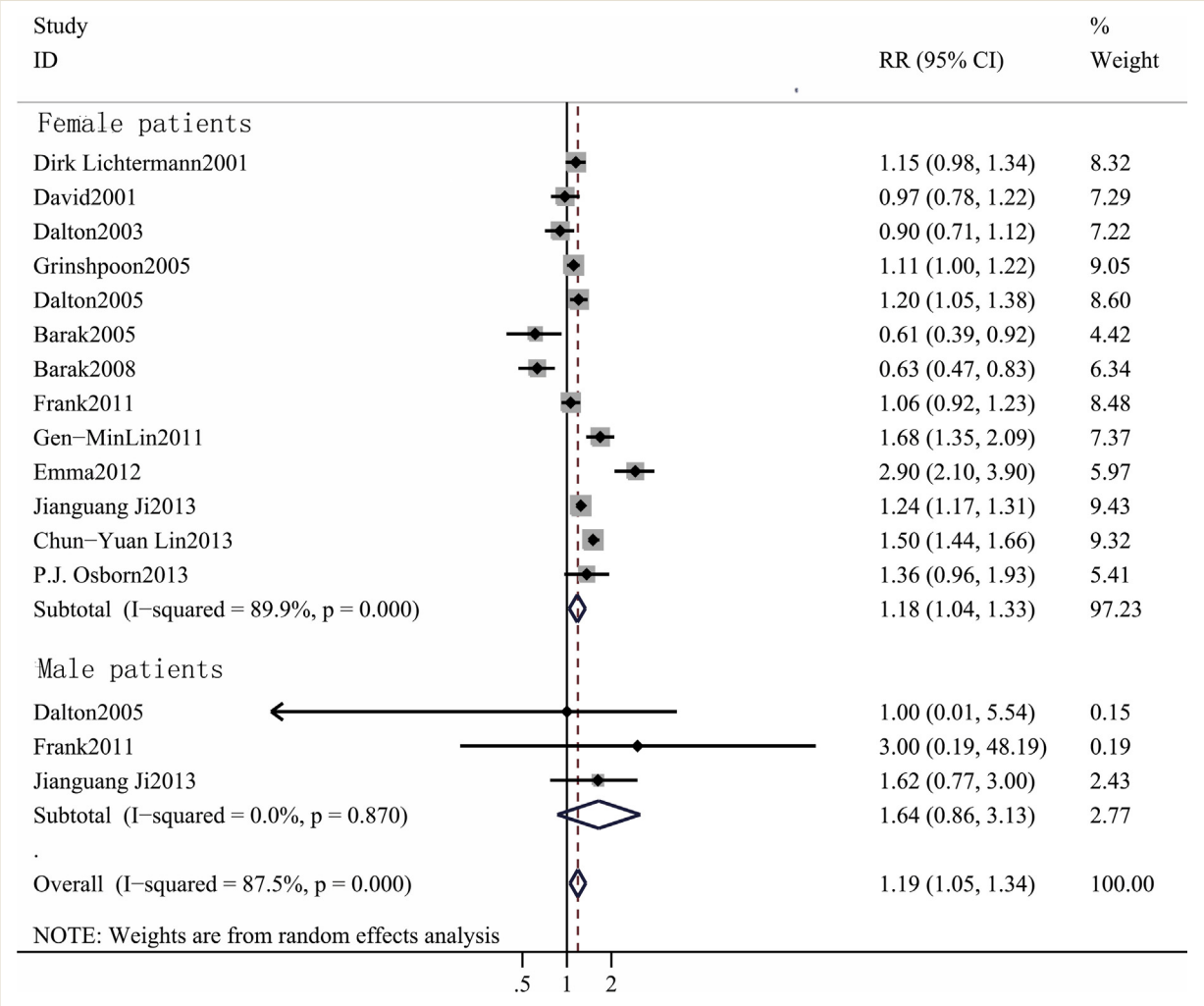
higher risk of BC compared to those without schizophrenia (Figure 3).

The morbidity rate of BC is relevant to sex: it mostly happens in female subjects. For this reason, for effect-size merging, we selected studies that assessed women, thereby excluding two studies.[30,32] Meta-analysis revealed that statistical heterogeneity occurred among each research group ($P < .001$, $I^2 = 89.9\%$), so we selected the random-effects model for merging. The subgroup analysis was carried out on patients according to sex. Thirteen articles addressed female patients. The RR value after combination was 1.18 (95% CI, 1.04, 1.33). The morbidity rate of female BC patients with or without schizophrenia had statistical significance (RR = 1.18; 95% CI, 1.04, 1.33; $P = .013$). Indeed, schizophrenia can be regarded as a dangerous BC morbidity factor among women. Three articles included male patients. The RR value after combination was 1.64 (95% CI, 0.86, 3.13). The different morbidity of the male patients with or without schizophrenia did not have statistical significance (RR = 1.64; 95% CI, 0.86, 3.13; $P = .259$). It showed that schizophrenia could not be regarded as a dangerous BC morbidity factor among male subjects (Figure 4). The subgroup analysis results therefore indicate that sex may be one of the sources of study heterogeneity.

The study object was the population in different geographic areas and comprising different races, according to areas for which subgroup analysis could be performed. Seven articles described European populations (including Finland, Denmark, Sweden, and the United Kingdom)[3,21,27,29,30,32,36]; based on meta-analysis, the studies had no statistical heterogeneity ($P = .064$, $I^2 = 49.7\%$). A random-effects model was chosen to combine these studies. Results found that the incidence of BC between the exposure and control groups was different (RR = 1.16; 95% CI, 1.06, 1.28). Six articles described Asian populations (including Israel and Taiwan)[28,31,33-35,37]; based on meta-analysis, the studies had statistical heterogeneity ($P < .001$, $I^2 = 93.3\%$). A random-effects model was chosen to combine these studies. Results found that incidence of BC between the exposure and control groups had no statistical significance (RR = 1.07; 95% CI, 0.85, 1.35; Figure 4).

Groups from different geographic regions and of different races were regarded as objects of research, and subgroup analysis was implemented according to region. Europeans were involved in 7 articles (including Finland, Denmark, Sweden, and the United Kingdom)[3,21,27,29,30,32,36]; meta-analysis revealed that there was no statistical heterogeneity among research groups ($P = .064$, $I^2 = 49.7\%$). The subgroup analysis was carried out on patients

Figure 4 Forest Plots for Random-Effects Sub–Meta-analysis of Breast Cancer Incidence Rates in Different Sexes of Patients With Schizophrenia



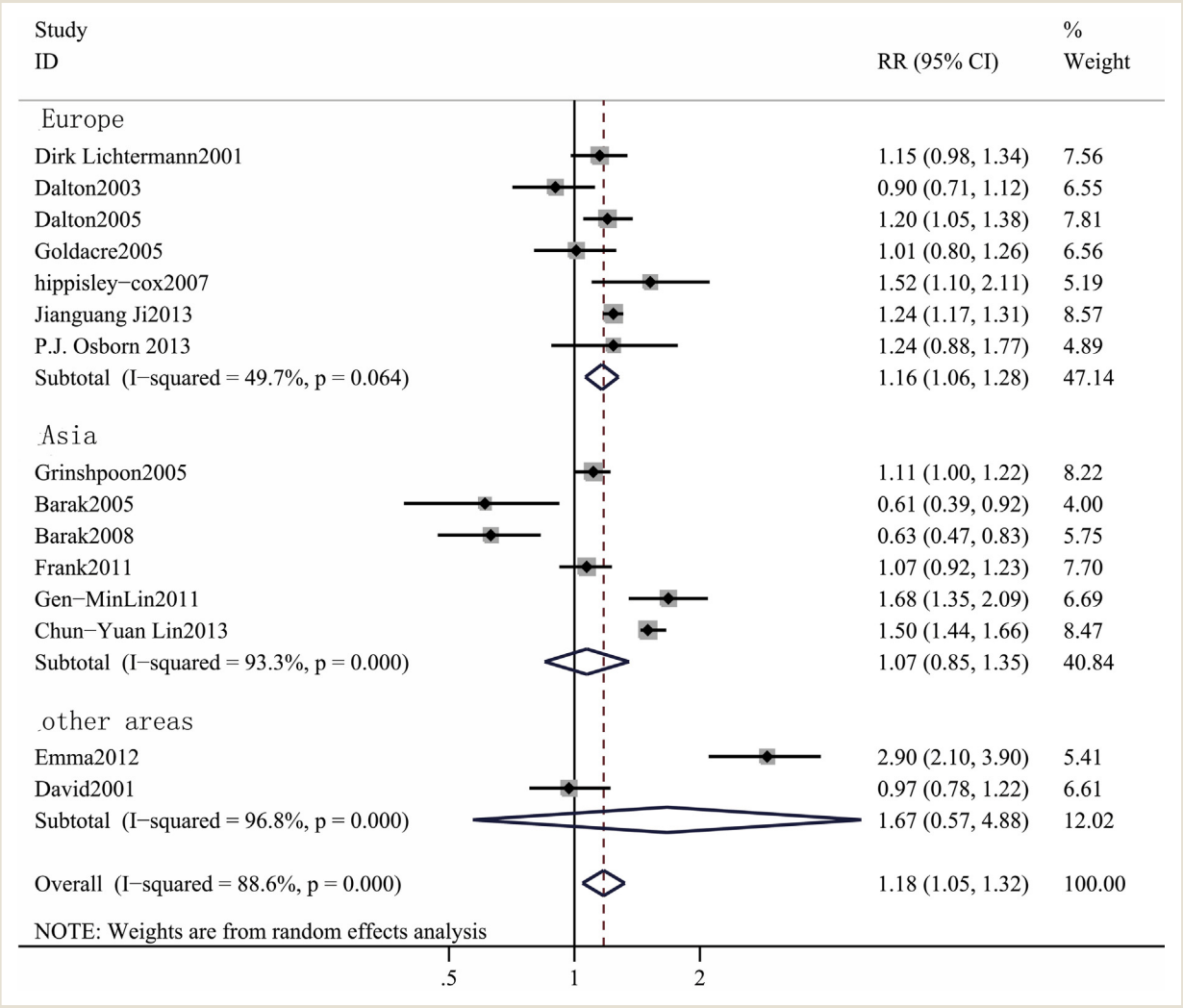
according to different geographic regions, and the random-effects model was selected for combination. The RR value after combination was 1.16 (95% CI, 1.06, 1.28). In Europe, the different morbidity rate of the BC of the patients with or without schizophrenia had statistical significance ($P = .001$). This indicates that schizophrenia could be regarded as a dangerous morbidity factor of BC among Europeans. In Asia, there were 6 related literature reports (including Israel and Taiwan)[28,31,33-35,37]; meta-analysis showed that there was statistical heterogeneity among research groups ($P < .001$, $I^2 = 93.3\%$). The random-effects model was selected for combination. In Asia, the different morbidity rates of BC in patients with or without schizophrenia did not have statistical significance (RR = 1.07; 95% CI, 0.85, 1.35; $P = .564$). At present, schizophrenia ought not be regarded as a dangerous morbidity of BC among Asian people. For other regions, there was a single literature report each for Australia and North America. Combined results indicate that the different morbidities of BC in patients with or without schizophrenia did not have statistical significance (RR = 1.67; 95% CI, 0.0.57, 4.88; $P = .350$; Figure 5). Schizophrenia therefore ought not be regarded as a dangerous morbidity factor of BC.

On the basis of the geographic region subgroup analysis results, region may be a source of article heterogeneity.

Table 2 presents subanalyses by quality of literature within the subgroup of study quality score as evaluated by NOS. The quality scores of the 15 articles included in this meta-analysis ranged from 5 to 8 stars, divided into 3 groups. Four studies had a score of 8[21,32-35]; 5 studies had a score of 7[4,5,29,30,37]; and 6 studies had a score of < 7.[3,27,28,31,33,36] Meta-analysis showed no significant differences in the incidence of BC among research groups when the quality score was equal to 8 and less than 7 (respectively, RR = 1.10; 95% CI, 0.97, 1.26; and RR = 1.09; 95% CI, 0.76, 1.58), while we found significant differences in the incidence of BC among research groups (RR = 1.36; 95% CI, 1.06, 1.75) when the quality score was equal to 7 (Figure 6).

In short, sex, geographic region, and literature quality may be sources of article heterogeneity.

Figure 5 Forest Plots for Random-Effects Meta-analysis of Breast Cancer Incidence Rates in Different Geographic Areas in Patients With Schizophrenia



Discussion

Results of Correlation Analysis

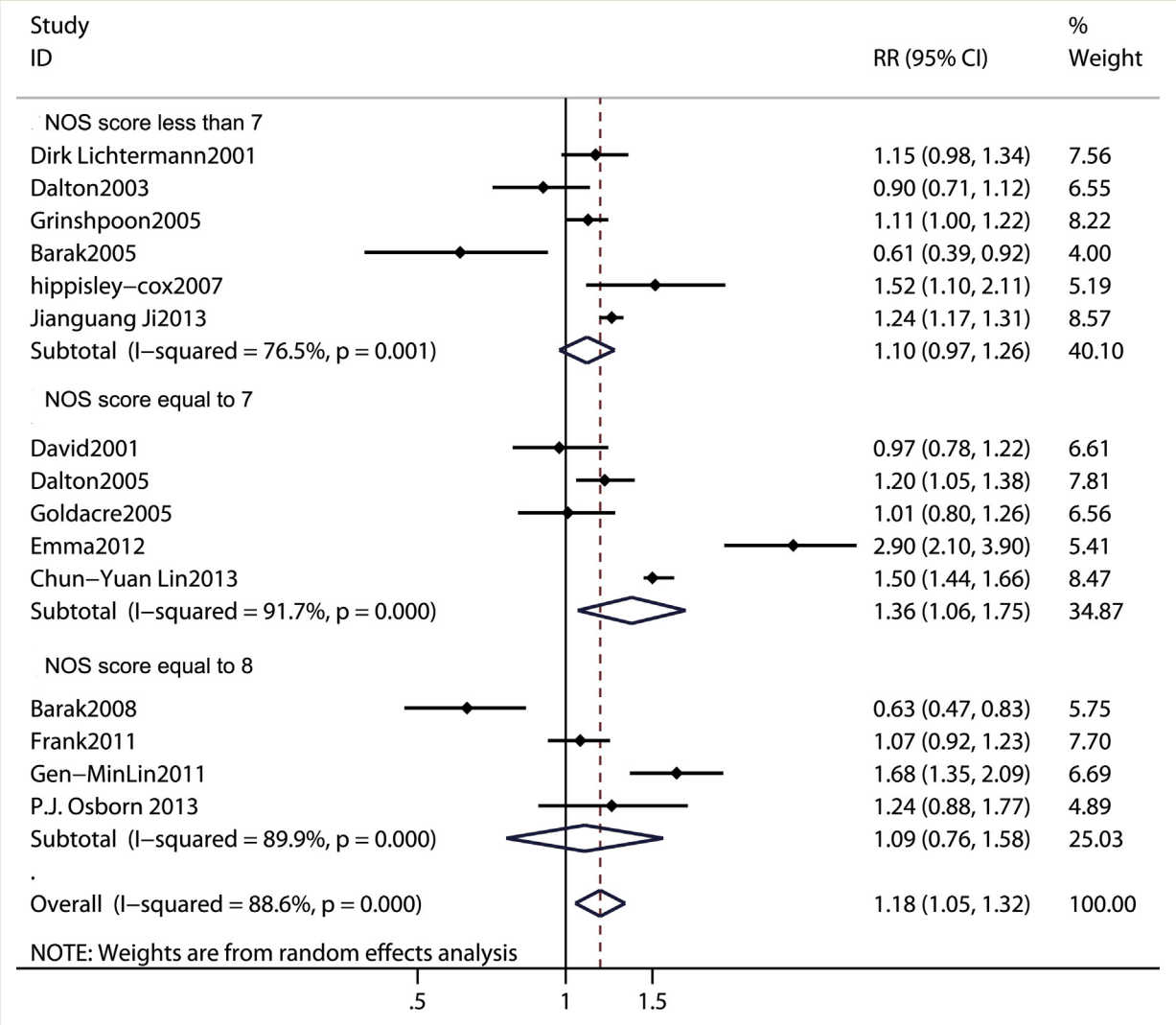
At present, there is no consensus on BC incidence in patients with schizophrenia. Indeed, the results of the studies included in this meta-analysis are not consistent. In the 15 articles included in this meta-analysis, several studies showed that the risk of patients with schizophrenia having BC is higher than the general population,[4,28,29,32,35-37] but others found that the risk of patients with schizophrenia having BC is decreased.[31,33] Other studies, however, show that there is no correlation between schizophrenia and BC.[3-5,29,33,35] When we combined and comprehensively analyzed the articles, we found that the incidence of BC between the exposure and control groups was different (RR = 1.18; 95% CI, 1.05, 1.32), thereby indicating that the risk of patients with schizophrenia having BC is higher than that of patients without schizophrenia or the general population.

There are many reasons for BC, including obesity. One meta-analysis that included 282,000 subjects showed that the risk of having BC is increased with an increase in body mass index (BMI). The risk of people with BMI > 30 kg/m^2 having BC is 1.3 to 2 times that of people of normal weight, and obesity can significantly increase the risk of women having BC.[38] In particular, the incidence of BC in postmenopausal women is positively correlated with body weight and BMI.[39] Obesity promotes biosynthesis of estrogen, and estrogen binding globulin level is decreased. BC is hormone dependent, and excessive serum estrogen will cause abnormal proliferation and transformation of BC cells.[40] Adiponectin and leptin secreted by adipose tissue may mediate the process of obesity, promoting occurrence and development of BC. In addition, obesity can lead to the occurrence of chronic inflammation; a large number of inflammatory factors and various cells in the body can form a tumor microenvironment that promotes the occurrence and

Table 2 Quality Evaluation Table of Internalization Study

Internalization Study	Selection of Study Population				Comparability Between Groups	Outcome Measurement			Score
	How Representative of Exposure Group	Selection Method of Nonexposure Group	Determination Method of Exposure Factors	No Outcome Measure Observed at Start of Study	Comparability Between Exposure Group and Nonexposure Group Should Be Considered for Design and Statistics	Research Whether Evaluation of Results Is Sufficient	Whether Follow-up Time Is Long Enough After Outcome Is Given	Whether Follow-up of Exposure Group and Nonexposure Is Sufficient	
Lichtermann 2001[3]	X	X	X			X	Not mentioned	X	5
Lawrence 2001[5]	X	X	X		X (Other mental illness, neurologic disorders)	X	Not mentioned	X	7
Oksbjerg Dalton 2003[27]	X	X	X		X (Birth history)	X	Not mentioned	X	6
Grinshpoon 2005[28]	X	X	X		X (Age)	X	Not mentioned	X	6
Dalton 2005[29]	X	X	X	X (Excluded cases in first year of follow-up time)	X (Antipsychotic drugs)	X	Not mentioned	X	7
Goldacre 2005[30]	X	X	X		X (Medical level)	X	X (Follow-up median period of 12.6 y)	X	7
Barak 2005[31]	X	X	X			X	Not mentioned	X	5
Barak 2008[33]	X	X	X		X (Other mental illness)	X	Not mentioned	X	6
Hippisley-Cox 2007[32]	X	X	X	X (Excluded cases in first year of follow-up time)	X (Other mental illness, bipolar disorder)	X	Not mentioned	X	8
Chou 2011[34]	X	X	X	X	X (Age)	X	X (Follow-up median period of 9 y)	X	8
Lin 2011[35]	X	X	X	X	X (Other mental illness, age)	X	X (Follow-up median period of 12 y)	X	8
McGinty 2012[4]	X	X	X	X		X	X (Follow-up median period of 8 y)	X	7
Ji 2013[36]	X	X	X		X (Age)	X	Not mentioned	X	6
Lin 2013[37]	X	X	X	X (Excluded cases of 6 mo before follow-up time)	X (Age)	X	(Follow-up median period of 7.59 y)	X	7
Osborn 2013[8]	X	X	X	X (Excluded cases of 6 mo before follow-up time)	X (Other mental illness, age)	X	(Follow-up median period of 6.5 y)	X	8

Figure 6 Forest Plots for Random-Effects Meta-analysis of Breast Cancer Incidence Rates by Newcastle-Ottawa Quality Evaluation Standard Score



development of BC cells.[41] Patients with schizophrenia have a high incidence of obesity as a result of uncontrolled diet, lack of exercise, and receipt of antipsychotic drugs, among other factors.[42]

Diabetes, which may be related to obesity and antipsychotic drugs, is also a nonindependent risk factor of patients with schizophrenia having BC. Patients with schizophrenia often have symptoms of type 2 diabetes. Forty percent of patients with schizophrenia have a family history of type 2 diabetes, and indeed the incidence of patients with schizophrenia having type 2 diabetes is significantly higher than that of general population.[43,44] Many studies show that the incidence of patients with diabetes having BC is higher than that of general population, and the mortality rate is also higher than that of general population.[45]

At present, early screening is one of the most effective methods to prevent BC; however, regular and formal screening is difficult to achieve for patients with schizophrenia. A study by Jensen et al[46] on the participation rate of BC screening in women with schizophrenia found that it is common for them to never or rarely participate in BC screening.

Hyperprolactinemia is considered to be one of main reasons why patients with schizophrenia are at a high risk of BC. Prolactin is a protein hormone secreted by anterior pituitary and is an important neuroendocrine factor; it also plays an important role in the growth and differentiation of mammary gland cells.[21] Büschlen et al[47] and Druyts et al[48] found that there are pathologic changes in the hypothalamus−pituitary−gonadal axis of patients with schizophrenia; the inhibition function of dopamine is decreased and serum PRL level is increased. Antipsychotic drugs may also cause an increase in serum PRL. Drugs that result in a high frequency of hyperprolactinemia are chlorpromazine and risperidone; ziprasidone and aripiprazole have no significant effect on female PRL.[49] At present, there is enough evidence to show that hyperprolactinemia is

related to an increasing risk of BC.[50] Studies show that childbirth and lactation are protective factors of BC, which are mainly related to hormone (mainly estrogen and progesterone) level changes during pregnancy and lactation.[51] Fewer female patients with schizophrenia establish a family than women in the general population. In addition, regarding lactation, in the past, clinicians did not recommend that patients with schizophrenia breast-feed.

An unhealthy lifestyle is a high risk factor for BC. For example, patients with schizophrenia tend to smoke; indeed, one study found that smoking increases the risk of BC incidence.[52] The mechanism may be that some substances in tobacco smoke have a direct or indirect reversible or irreversible effect on the occurrence and development of BC.[53] Many patients with schizophrenia engage in substance abuse, especially alcohol abuse.[54] Epidemiologic studies show that drinking alcoholic beverages can increase the risk of BC. In addition, some experimental studies have confirmed that drinking can promote the growth and metastasis of existing tumors.[55-57] As a result of the sedative effect, a relatively closed living environment, behavioral withdrawal, partial loss of life skills, and lack of activity, among other reasons, patients with schizophrenia lack adequate exercise. A relatively sedentary lifestyle is one of the risk factors of BC. Ligibel et al[58] found that exercise is a protective factor for metastasis and prognosis of early BC.

Outcome Bias

This meta-analysis quantitatively analyzed the study data of 15 studies. All the studies included study subjects from crowd-based population or medical registries. The outcome of follow-up study is incidence, which avoids the confounding effect of mortality on study results. Some patients with cancer died from other diseases, such as cardiovascular disease or respiratory failure, which may be related on a medical level. As Figure 2 indicates, a large heterogeneity exists among the included studies. In particular, 2 articles about patients in Israel showed that schizophrenia is a protective factor of BC.[31,33] This may be related to different methods of patient inclusion. Both articles studied patients with schizophrenia registered in the online system of the Abarbane Mental Health Center; these patients received regular and systematic treatment. The exposure group included hospitalized patients with schizophrenia; risk factors of BC such as obesity, diabetes, smoking, and alcohol abuse were effectively controlled for. The control group was the general population. Therefore, we can ascertain that the cancer incidence of the exposure group is lower than that of control group, which shows that cancer incidence in patients with schizophrenia is higher than that of the general population, and which may be caused by environmental rather than genetic factors. The incidence of cancer (such as BC) can be decreased as long as effective 3-level prevention disease management can be provided to patients with schizophrenia.

Overall, the quality of internalization study evidence was high. The main problem was that in the included literature, only 4 studies had a median follow-up period of > 8 years.[4,30,34,35] The rest had follow-up periods of < 8 years or the period was not mentioned. Too short a follow-up time will cause the expected outcome measure of the object to be incompletely observed, resulting in a lower than actual incidence rate. Two articles excluded cancer cases in the first year of follow-up,[29,33] 2 articles excluded cancer cases in the first 6 months before follow-up,[21,37] and the other articles did not mention whether cancer cases were excluded. We therefore still cannot determine whether the object of study had an expected outcome in the initial study. In the comparison process of patients with schizophrenia with patients without schizophrenia or the general population, we found that the most important confounding factor was other mental illness or receipt of antipsychotic drugs. In addition, sex, age, and follow-up time were also important confounding factors. McGinty et al[4] studied but did not control for confounding factors, so they could not ensure the comparability of their exposure and control groups. Such problems as these lead to bias and affect the authenticity of the results.

In summary, schizophrenia is positively correlated with BC incidence, and BC incidence of patients with schizophrenia is increased to a certain degree. Because of the effects of potential bias and publication bias, this conclusion still requires more high-quality studies to increase the strength of evidence.

Clinical Practice Points

- We performed a meta-analysis to explore the correlation between schizophrenia and BC. Meta-analysis can combine and analyze different study results, find the key point of dispute through heterogeneity test and sensitivity analysis, and obtain more abundant information than the original literature.
- On the basis of 15 studies performed in different regions, meta-analysis revealed that BC incidence between the exposure group (schizophrenia patients) and the control group (non-schizophrenia population or general population) had statistical difference, thus indicating that BC incidence in schizophrenia patients is higher than that of the nonschizophrenia population or general population.
- Subgroup analysis indicated that gender and region may a source of article heterogeneity.
- The incidence of schizophrenia is positively correlated with BC, and the incidence of BC in schizophrenia patients is increased to a certain degree.
- Because of the effects of potential bias and publication bias, this conclusion needs more high-quality studies to increase the strength of evidence.

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