Iran J Psychiatry 2024; 19: 4: 441-452

Review Article ***https://doi.org/10.18502/ijps.v19i4.16559***

Investigating the Relationship between Schizophrenia and Incidence Risk of Breast Cancer: A Systematic Review and Meta-Analysis of Cohort Studies

Seyyed Muhammad Mahdi Mahdavinoor[1], Saeed Kargar-Soleimanabad[2], Amir-Hassan Bordbari[2], Aghil Mollaei[3], Leila Seddigh[4], Sorour Sarihi[5,6], Reihaneh FirooziKhojastefar[7], Raziye Dehbozorgi[8,9], Sara Farhang[10,11*]

Abstract

Objective: Schizophrenia seems to have a complex association with various types of cancer, exerting a protective effect against some cancers while being a risk factor against some others. Therefore, we intended to conduct an updated systematic review and meta-analysis in order to examine the relationship between schizophrenia and the risk of breast cancer incidence.
Method: We did a systematic search of databases, namely Web of Science, Scopus, Embase, PubMed, and PsycINFO up to August 15, 2024. Screening and data extraction were performed independently. Data was analyzed using Stata16 software. We used the random effect model to pool the results, while the heterogeneity between studies was calculated using Cochran's Q test and (I^2) index.
Results: We found 15 studies, among which 12 were included in this meta-analysis. The results indicated that the risk of breast cancer development is significantly increased in women with schizophrenia (SIR: 1.43, 95% CI: 1.08-1.85, P < 0.01; IRR: 1.19, 95% CI: 1.13-1.26, P < 0.01). Subgroup analysis revealed significant differences in the incidence of breast cancer rates among women with schizophrenia based on geographic location and duration of follow-up.
Conclusion: The results indicate that schizophrenia increases the risk of developing breast cancer. Therefore, taking preventive measures concerning breast cancer among women with schizophrenia is crucial. Additionally, regular screening programs should be implemented to ensure early diagnosis and treatment in case breast cancer is detected.

Key words: *Breast Cancer; Epidemiology; Meta-Analysis; Risk Factor; Schizophrenia*

1. Student Research Committee, Faculty of Allied Medical Sciences, Mazandaran University of Medical Sciences, Sari, Iran.
2. Student Research Committee, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
3. Student Research Committee, Faculty of Health, Mazandaran University of Medical Sciences, Sari, Iran.
4. Department of Community Medicine, Tehran University of Medical Sciences, Tehran, Iran.
5. Department of Human Nutrition and Hospitality Management, The University of Alabama, Tuscaloosa, Alabama, USA.
6. Department of Nutritional Sciences, University of Connecticut, Storrs, CT 06269, USA.
7. Department of Psychiatry, Roozbeh Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
8. Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran.
9. Community Based Psychiatric Care Research Center, School of Nursing and Midwifery, Shiraz University of Medical Sciences, Shiraz, Iran.
10. University of Groningen, University Medical Center Groningen, University Center for Psychiatry, Rob Giel Research Center, Groningen, The Netherlands.
11. Research Center of Psychiatry and Behavioral Sciences, Tabriz University of Medical Sciences, Tabriz, Iran.

***Corresponding Author:**
Address: University of Groningen, University Medical Center Groningen, University Center for Psychiatry, Rob Giel Research Center, Groningen, The Netherlands., Postal Code: Postbus 30001 9700 RB Groningen Nederlands.
Tel: 31-68 7950690, Email: s.farhang@umcg.nl

Article Information:
Received Date: 2024/05/10, Revised Date: 2024/08/31, Accepted Date: 2024/09/09

Schizophrenia, which is a severe, complex and chronic psychiatric disorder, affects about 24,000,000 individuals all over the world. It is observed in all human societies as well as at different socio-economic levels, and it is different with respect to prognosis and clinical symptoms (1, 2). Schizophrenia is considered an important health issue due to its high burden given the large number of affected people, the difficulties that arise for patients and their families along with high expenses imposed on health care systems and society (3-5). The main goal of treatment is to control the negative and positive symptoms for enabling patients to function normally as much as possible (6).

Despite regular arrangement with psychiatric services, the physical health of those with schizophrenia has been neglected by health care providers or the patients per se (7). Schizophrenia patients are at greater risk for some diseases compared to the general population, including diabetes (8), Parkinson's disease (9) and epilepsy (9). Conversely, these patients might be more resistant to some other diseases, such as liver (10) and prostate cancer (11, 12); however, there are many inconsistent reports in this regard. As an example, there are contradictory reports about the incidence of cardiovascular diseases (9, 13) and colorectal cancer (7, 14). This might be explained by genetic differences, environmental factors such as life style, and the interaction between these two factors. Another important issue is missed diagnosis. Results of a cohort study conducted in Sweden revealed that patients with schizophrenia had remarkably higher premature mortality rates along with underdiagnosed cancer and heart diseases as the main causes (15). This underlines the importance of identifying the diseases that should be screened in these patients.

Comorbidity of breast cancer with schizophrenia is an issue of ongoing debate. The use of antipsychotic medications as the main treatment for these patients make this research question more interesting. The studies conducted so far have reached different results (16). In other words, a number of studies have reported that schizophrenia could be a protective factor against breast cancer, and some others reported the opposite (16-18). However, the most important report to date is perhaps a meta-analysis of cohort studies until August 2017, which reported that women afflicted with schizophrenia are at an increased risk of breast cancer (19). Considering the shortcomings of this valuable study (that will be discussed later), we decided to conduct an updated systematic review and meta-analysis to assess the possible relationship between schizophrenia with the risk of breast cancer incidence. The results of this research can be worthwhile in planning to improve the quality of life as well as life expectancy of people with schizophrenia.

Materials and Methods

Study Design

We developed and presented a systematic review and meta-analysis in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (20) for the study design, screening, search strategy, data extraction and reporting. The protocol of this study was registered with International Registration of Systematic reviews under the following registration number: CRD42022347014 .

Strategy of Search for Detecting Related Studies

We performed both manual and electronic searching. A systematic search of international databases like PsycINFO, PubMed, Embase, Web of Science, and Scopus was done until August 15, 2024. We also used Google Scholar (search engine) to distinguish grey literature in this field. The search strategy encompassed the following MeSH terms and keywords: [(Breast OR Mammary) AND (Cancer* OR Neoplasm* OR Tumor* OR Malignancy* OR Carcinoma* OR Gland*) AND ("Dementia Praecox" OR "Schizophre*" OR "psychos*")].

We searched each database without restrictions regarding the year of publication or region. Given the limitations in resources and linguistic competence of the authors, only articles published in the English language were included in this study. Reference lists of some similar studies was manually searched to detect other appropriate studies that might have been excluded from the initial search of literature.

Risk of Bias (Quality) Assessment

The quality of included studies was independently assessed by two authors using Newcastle-Ottawa Scale (NOS) checklist. NOS range spans from 1 (lowest quality) to 10 (highest quality) stars, which evaluates studies in terms of group selection, comparability of groups, and determination of the desired outcome. The discrepancies were solved through consensus .

Inclusion Criteria

The following studies were included: (1) All types of cohort studies; (2) Studies in the form of full-length articles published in peer-reviewed English journals; (3) Studies that involved adult women and men; (4) Studies that used a general population without the diagnosis of schizophrenia as a control group; (5) Studies that documented the prevalence of breast cancer on follow-up; and (6) Studies that reported the standardized incidence ratios (SIRs) or incidence rate ratios (IRRs).

Exclusion Criteria

Studies with the following criteria were excluded: (1) Clinical trials, comments, abstracts of conferences, case series, any type of reviews, case controls letters, animal studies, case reports, in vitro and cross-sectional studies; (2) Duplicate publications; (3) Qualitative studies; and (4) Studies that reported breast cancer–related mortality instead of its incidence.

If the studies had overlapping participants, reports with longer follow-up duration and larger sample size were included in this study.

Screening and Data Extraction

Two reviewers independently selected the papers. Then, these two reviewers extracted the data independently. In each stage, differences between the two reviewers were solved by consensus. In addition, the inconsistencies were resolved by a third author if needed. Data extraction checklist included the publication year, name of the first author, number of patients afflicted with schizophrenia, the region of study, mean age, number and gender of patients with breast cancer, type of sampling, response rate, control population (general or other), patient characteristics, follow-up duration, SIR (95% CI), and confirmation of cancer cases .

Strategy for Data Synthesis

In this research, standardized incidence ratios (SIRs) and incidence rate ratios (IRRs) were extracted with a 95% confidence interval. The heterogeneity between the studies was measured by Cochran's Q test and (I^2) index. If I2 index indicated the heterogeneity of studies ($I^2 > 0.50$, $P < 0.05$), we did use the random effect model, otherwise the effect of the fixed model was used. Subgroup analysis and sensitivity analysis were our solutions for dealing with heterogeneity between studies. We used a funnel plot along with Begg and Egger tests in order to check possible publication bias. Data was analyzed using Stata16 software.

Results

Literature Search

After searching different databases and removing the duplicates, 2,496 articles were identified. Two reviewers checked the abstracts and titles of the included studies independently. The reviewer identified 150 articles for a full-text review. After the full texts were separately checked by the two reviewers, 136 articles were excluded because of not meeting the inclusion criteria.

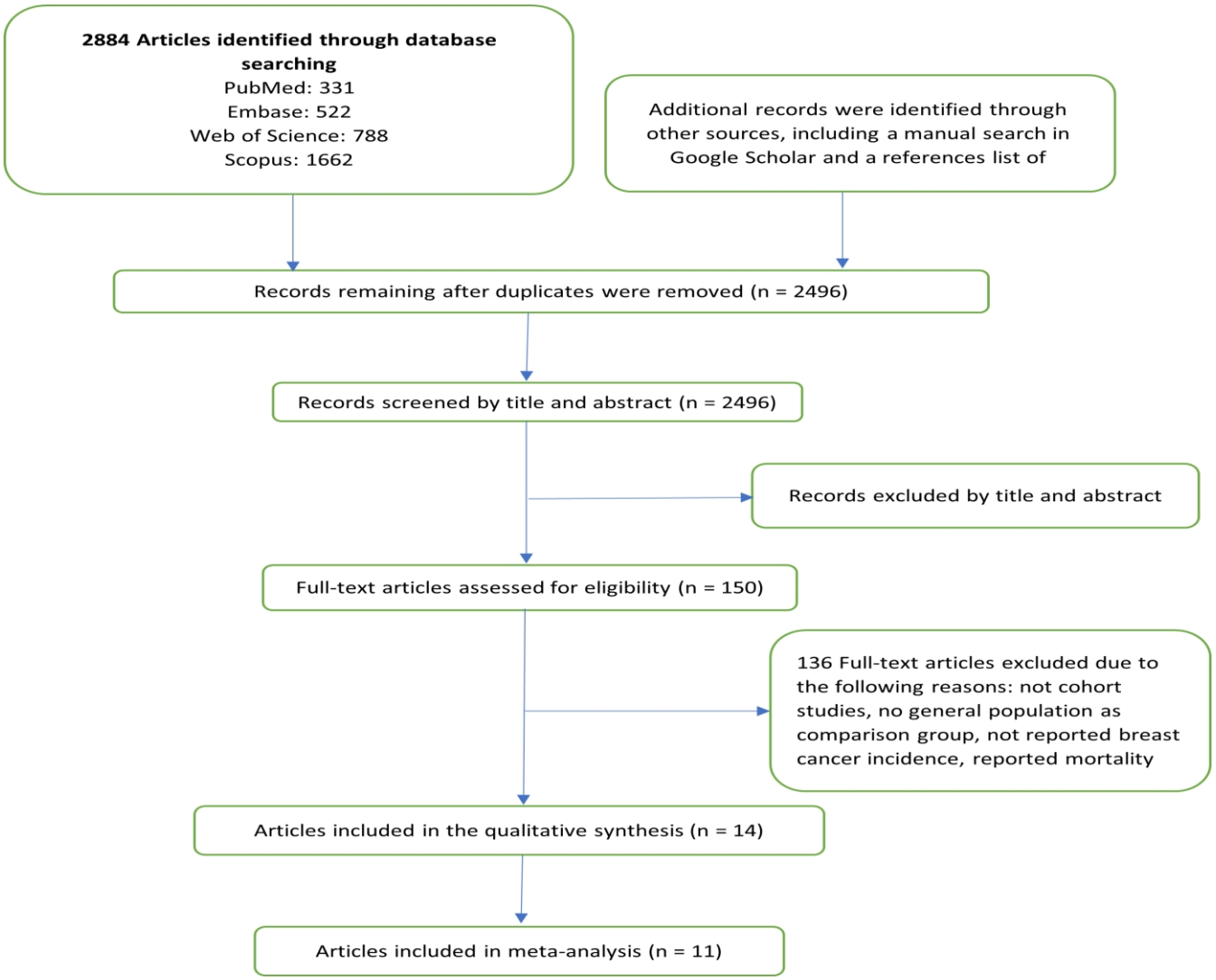

Figure 1. PRISMA Flowchart for the Study Selection Process to Review the Relationship between Schizophrenia and the Risk of Breast Cancer Incidence

Finally, 14 articles were included in qualitative synthesis. One of the articles contained data from two cohort studies, so we extracted the information of 15 studies. 12 studies were included in the meta-analysis. The searching and removing process of studies not meeting the inclusion criteria are shown in Figure 1.

Study Characteristics

Finally, 14 articles (18, 21-33) were included in the study. One of the articles had information coming from two cohort studies (18); therefore, we extracted information from 15 cohort studies. Among them, three studies mentioned IRRs (21, 23, 32) and the other mentioned SIRs. Our analysis explored a total of 502,161 individuals with schizophrenia, comprising of 237,645 men and 155,483 women. The gender of 109,033 individuals was not specified in the articles. Moreover, studies were conducted in different countries from the three continents of Europe, America, and Asia. In addition, in this research, we examined cases of male and female breast cancer separately (Table 1).

Methodological Quality

In this study, we considered a score ≥ 7 to be of good quality. Consequently, any study with a score of ≤ 7 was considered to be of fair quality. Among the included studies, eight studies were of high quality and five studies were of reasonable quality. In this research, we did not exclude any study due to quality. The quality ratings of each article are shown separately in Table 2.

Schizophrenia and Breast Cancer Incidence Risk

The present systematic review and meta-analysis included 15 studies from 1989 to 2023. We used 12 studies in the analysis, the results of which indicated that the risk of breast cancer is significantly increased in women with schizophrenia (SIR: 1.43, 95% CI: 1.08-1.85, P < 0.01; IRR: 1.19, 95% CI: 1.13-1.26, P < 0.01) (Figures 2 and 3). We used subgroup analysis for SIR due to the high heterogeneity value (I^2: 96.23%). In the following, to check the robustness of findings, we performed a sensitivity analysis with the leave-one-out method, where the final results of the model did not show any significant changes. In other words, the variation of SIRs ranged from 1.28 to 1.52, all of which yielded a P < 0.05.

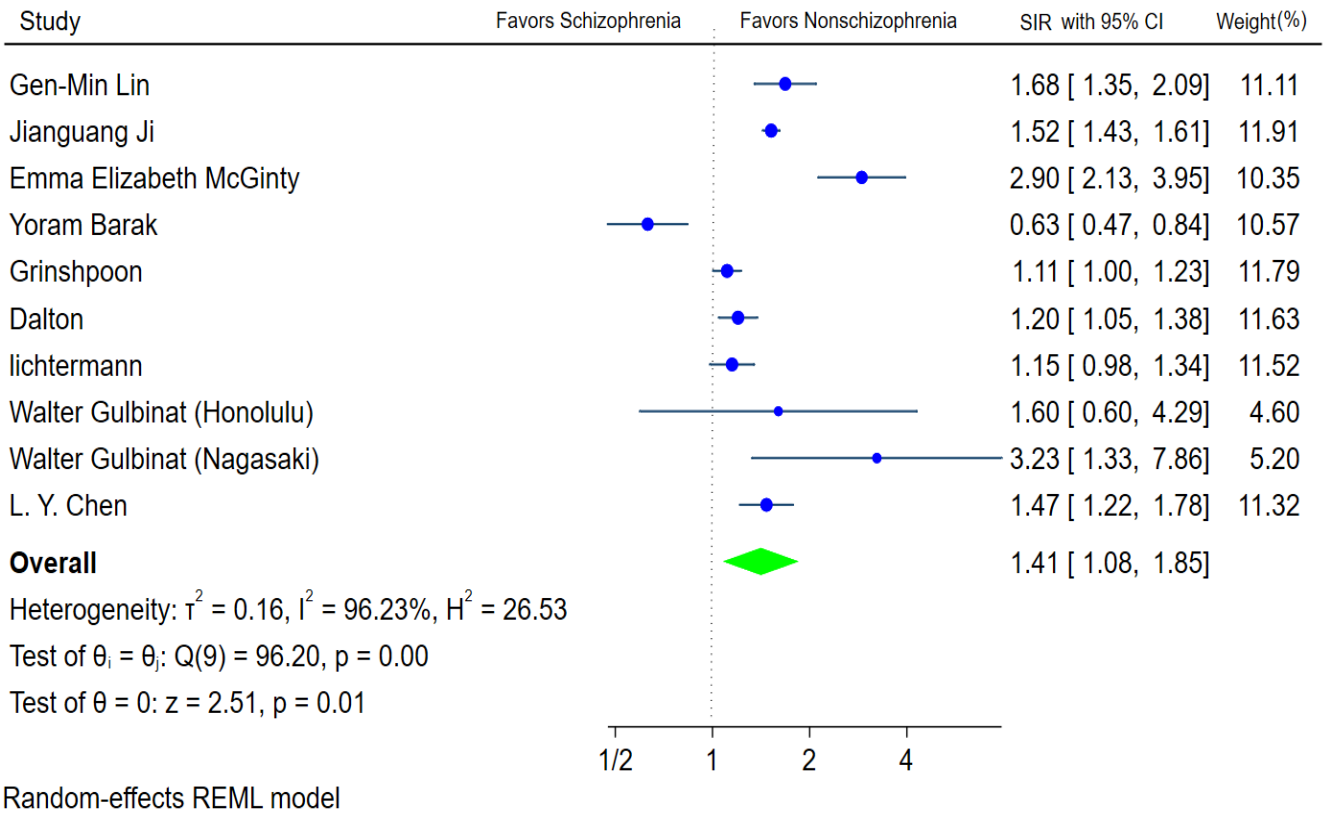

Figure 2. Incidence of Breast Cancer in Women with Schizophrenia Based on the Standardized Incidence Ratio

Table 1. Data Extraction Checklist for Review of the Relationship between Schizophrenia the Risk of Breast Cancer Incidence

Author (Year)	Patient characteristics	Number of patients with schizophrenia (Male, Female)	Comparison population	Follow-up	Confirmation of cancer cases	Number of cancer cases (Male, Female)	Effect Size of both genders (95% CI)	Effect Size of male (95% CI)	Effect Size of female (95% CI)	Country
Pettersson (2020)	National Patient Register (ICD-8 and ICD-9)	111306 (52044, 59262)	General population	1990-2013	Three nationwide registers: the Cancer Register, the National Patient Register, and the Cause of Death Register (The ICD-7) and (ICD-9 and ICD-10 codes)	2189 (NR, 2189)			IRRs: 1.19 (1.12, 1.26)	Sweden
Osborn (2013)	Patients diagnosed with schizophrenia in the Health Improvement Network (THIN) primary care database	6845 (NR, NR)	General population	1990-2008	Medical records in UK primary care visits	NR (NR, NR)	IRR: 1.03 (0.73, 1.46)		IRR: 1.31 (0.93, 1.85)	UK
Lin (2013)	Patients diagnosed with schizophrenia in National Health Insurance	71317 (38020, 33297)	General population	1997-2009	Catastrophic illness database (The ICD-9-CM codes)	215 (NR, 215)			SIR: 1.68 (1.35, 2.09)	Taiwan
Ji (2013)	Patients with schizophrenia were identified according to the seventh, eighth, ninth and tenth revisions of the International Classification of Diseases (ICD)	59233 (32204, 27029)	General population	1965-2008	Swedish Cancer Registry database	1042 (8, 1034)	SIR: 1.47 (1.38, 1.56)	SIR: 1.84 (0.78, 3.63)	SIR: 1.52 (1.43, 1.61)	Sweden
McGinty (2012)	Patients diagnosed with schizophrenia in the Maryland Medicaid database	2315 (1196, 1119)	General population	1994-2004	Surveillance Epidemiology and End Results (SEER) program. Diagnoses were identified with ICD-9 codes.	42 (NR, 42)			SIR: 2.9 (2.1, 3.9)	USA
Barak (2008)	Abarbanel Mental Health Center	2011 (NR, 2011)	General population	1960-2005	Israeli National Cancer Registry	51 (NR, 51)			SIR: 0.63 (0.47, 083)	Israel
Grinshpoon (2005)	All Jewish–Israelis who were admitted to any facility, both psychiatric hospitals and psychiatric wards of general hospitals,	33372 (NR, NR)	General population	1962-2001	Israeli National Cancer Registry	370 (NR, NR)			SIR: 1.11 (1, 1.22)	Israel

Author (Year)	Patient characteristics	Number of patients with schizophrenia (Male, Female)	Comparison population	Follow -up	Confirmation of cancer cases	Number of cancer cases (Male, Female)	Effect Size of both genders (95% CI)	Effect Size of male (95% CI)	Effect Size of female (95% CI)	Country
Goldacre (2005)	Oxford Record Linkage Study)out-patients as well as day cases and in-patients.	9649 (NR, NR)	General population	1963-1999	The Oxford Record Linkage Study.	80 (NR, NR)	SIR: 1.01 (0.8, 1.26)			England
Dalton (2005)	The Danish Psychiatric Central Register (data on admissions to psychiatric hospitals and psychiatric wards in general hospitals)	22766 (13023, 9743)	General population	1969-1993	the Danish Cancer Registry	216 (1, 215)		SIR: 1 (1.01, 5.54)	SIR: 1.2 (1.05, 1.38)	Denmark
Lichtermann (2001)	Hospital Discharge Register and Disability Pension Register	26996 (15578, 11418)	General population	1971-1996	the Finnish cancer registry	152 (NR, 152)			SIR: 1.15 (0.98, 1.34)	Finland
Mortensen (1989)	Inpatients in the Danish psychiatric hospital with the diagnosis of schizophrenia	6152 (2956, 3196)	General population	1957-1984	Danish Cancer Registry	127 (2, 125)	IRR: 1.19 (NR)	IRR: 1.85 (NR)	IRR: 1.19 (NR)	Denmark
Gulbinat (1992)	Psychiatric case register of the department of mental health (all inpatient and outpatient reported by eight community mental health center in Honolulu)	6977 (4198, 2779)	General population	1962-1980	NR	NR (NR, NR)			SIR: 1.6 (0.52, 3.74)	USA
Gulbinat (1992)	Registries of all psychiatric institution in Nagasaki, the registry of the Nagasaki Mental health center	3017 (1717, 1388)	General population	1960-1978	city of the Nagasaki medical association tumor statistical committee	NR (NR, NR)			SIR: 3.23 (1.16, 6.87)	Japan
Chen (2018)	Psychiatric Inpatient Medical Claims database(ICD-9-CM codes)	32731 (17971, 14760)	General population	2000–2008	The catastrophic illness database(ICD-9-CM codes)	105 (NR, 105)			SIR: 1.47 (1.22, 1.78)	Taiwan
Cheng (2023)	Taiwan National Health Insurance Research Database	107481 (58738, 48743)	General population	2000–2019	Taiwan Cancer Registry (ICD-9-CM codes)	484 (NR, NR)	SIR: 0.92 (0.85, 1.01)			Taiwan

Table 2. Newcastle-Ottawa Scale Quality Assessment of Included Articles in Review of the Relationship between Schizophrenia the Risk of Breast Cancer Incidence

Domain and Topic												
Author	Year	Selection				Comparability		outcome			Total	Study quality
		Adequacy of follow-up of cohorts	Was follow-up long enough for outcomes to occur?	Assessment of outcome	Comparability: additional factors	Comparability: age and sex	Outcome was not present at study start	Ascertainment of exposure	Selection of the non-exposed cohort	Representativeness of the exposed cohort		
Pettersson (21)	2020	*	-	*	*	-	*	*	*	*	7	Good
Osborn (23)	2013	*	*	*	*	*	*	*	*	*	9	Good
Lin (24)	2013	*	-	*	*	-	-	*	*	-	6	Fair
Ji (25)	2013	*	*	*	-	*	*	*	*	*	8	Good
McGinty (26)	2012	*	-	*	-	*	-	*	*	-	5	Fair
Barak (27)	2008	*	-	*	-	*	-	*	*	-	5	Fair
Grinshpoon (28)	2005	*	-	*	*	*	-	*	*	-	6	Fair
Goldacre (29)	2005	*	-	*	-	*	*	*	*	-	6	Fair
Dalton (30)	2005	*	-	*	*	*	*	*	*	*	8	Good
Lichtermann (31)	2001	*	-	*	*	*	-	*	*	*	7	Good
Gulbinat (18)	1992	*	*	*	*	*	*	*	*	-	8	Good
Mortensen (32)	1989	*	-	*	*	*	*	*	*	-	7	Good
Chen (22)	2018	*	*	*	*	-	*	*	*	-	7	Good
Cheng (33)	2023	*	*	*	*	*	-	*	*	*	8	Good

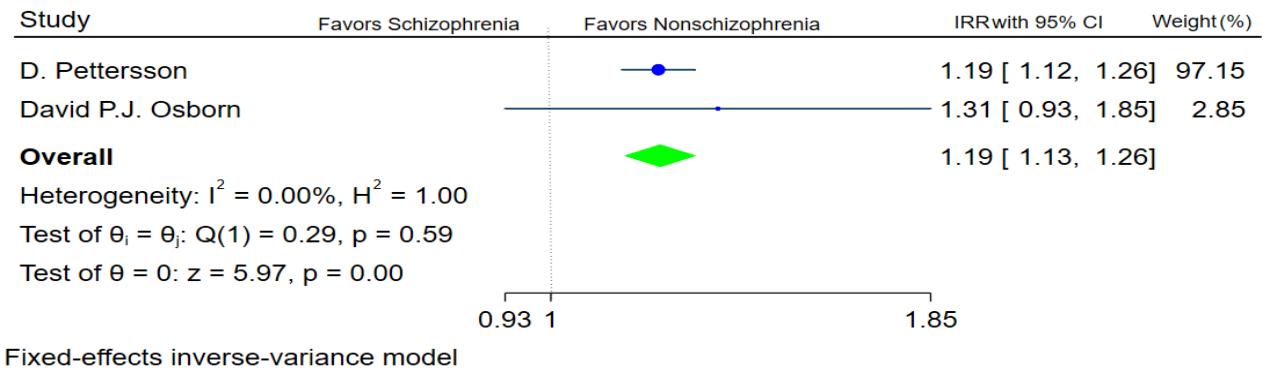

Figure 3. Incidence of Breast Cancer in Women with Schizophrenia Based on the Incidence Rate Ratio

Results of Subgroup Analysis

The results of subgroup analysis based on geographic location (Figure 4) indicated a significant difference between incidence rates of breast cancer among women with schizophrenia in three continents (P = 0.02), such that SIR was 1.30 (95% CI: 1.08-1.95) in Europe, 1.30 (95% CI: 0.84-2.03) in Asia, and in America this effect size reached an impressive value of 2.61(1.67-4.07). To be sure, the difference in the results is likely to be a function of the small number of studies conducted in America (n = 2).

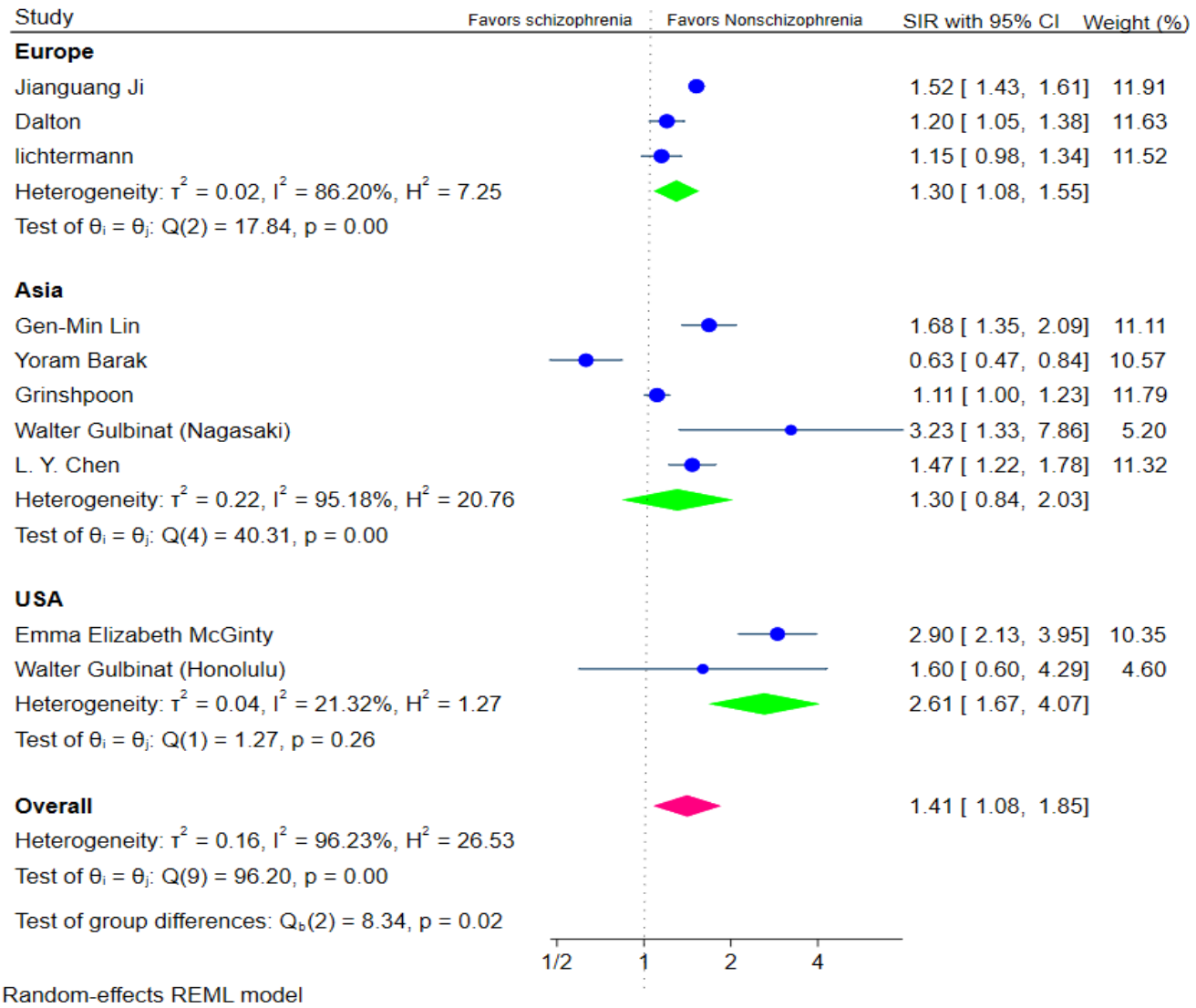

Figure 4. Incidence of Breast Cancer in Women with Schizophrenia Based on Geographic Location

Subgroup analysis based on the duration of follow-ups (less or more than 20 years), as shown in Figure 5, also revealed a significant difference in SIR among studies having less than 20 years of follow-up compared to those with more than 20 years of follow-up ($P < 0.01$). In studies that were followed up for less than 20 years, SIR was 1.96 (95% CI: 1.42-272), while in those that were followed up for more than 20 years, SIR was 1.10 (95% CI: 0.85-1.43).

A subgroup analysis was also performed based on the number of women with schizophrenia (Figure 6). This analysis showed that SIR was 1.69 (95% CI: 0.76-3.78) in studies in which the population of women with schizophrenia was < 10,000. However, in studies in which the population of women with schizophrenia was > 10,000, SIR was 1.33 (95% CI: 1.16-1.52). There was no significant difference in SIR between the two groups ($P = 0.56$).

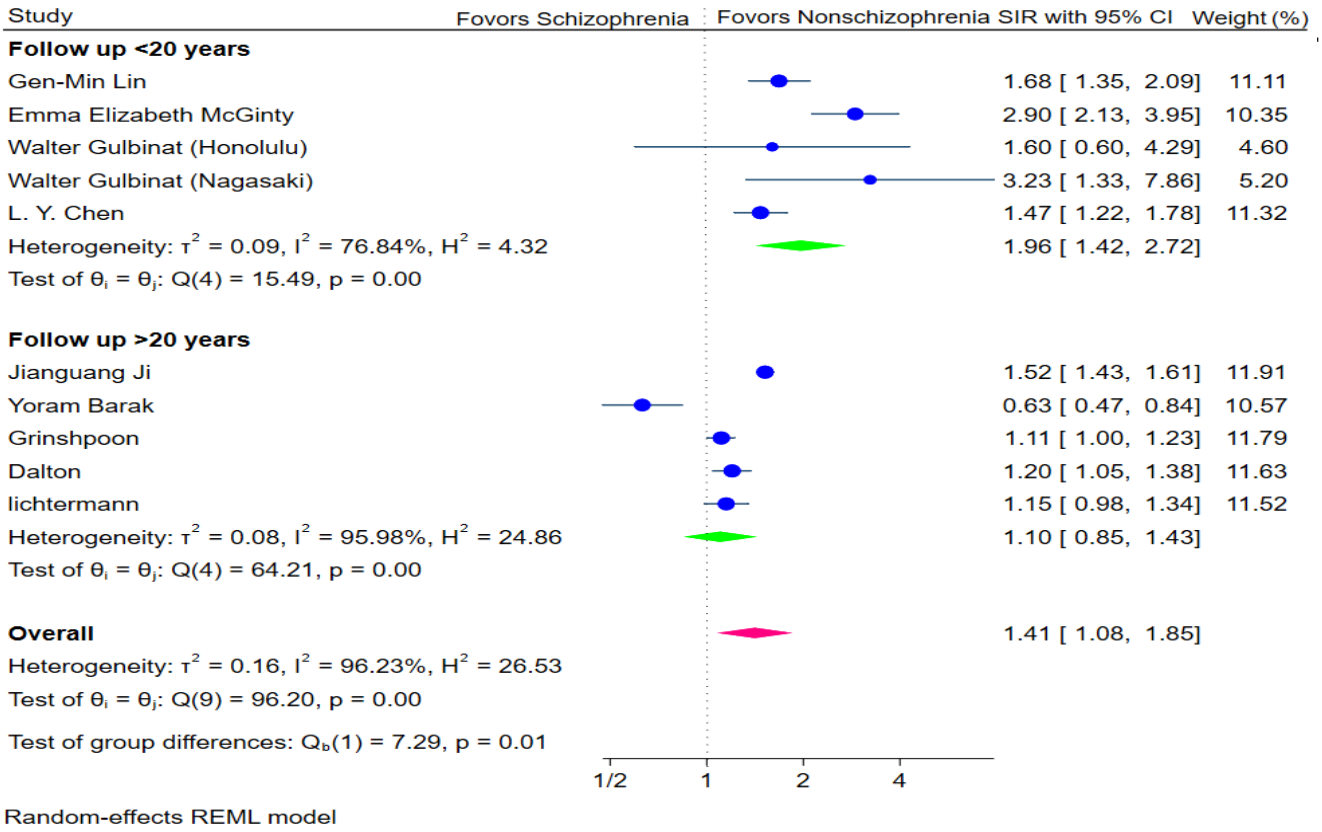

Figure 5. Incidence of Breast Cancer in Women with Schizophrenia Based on the Follow-up Duration

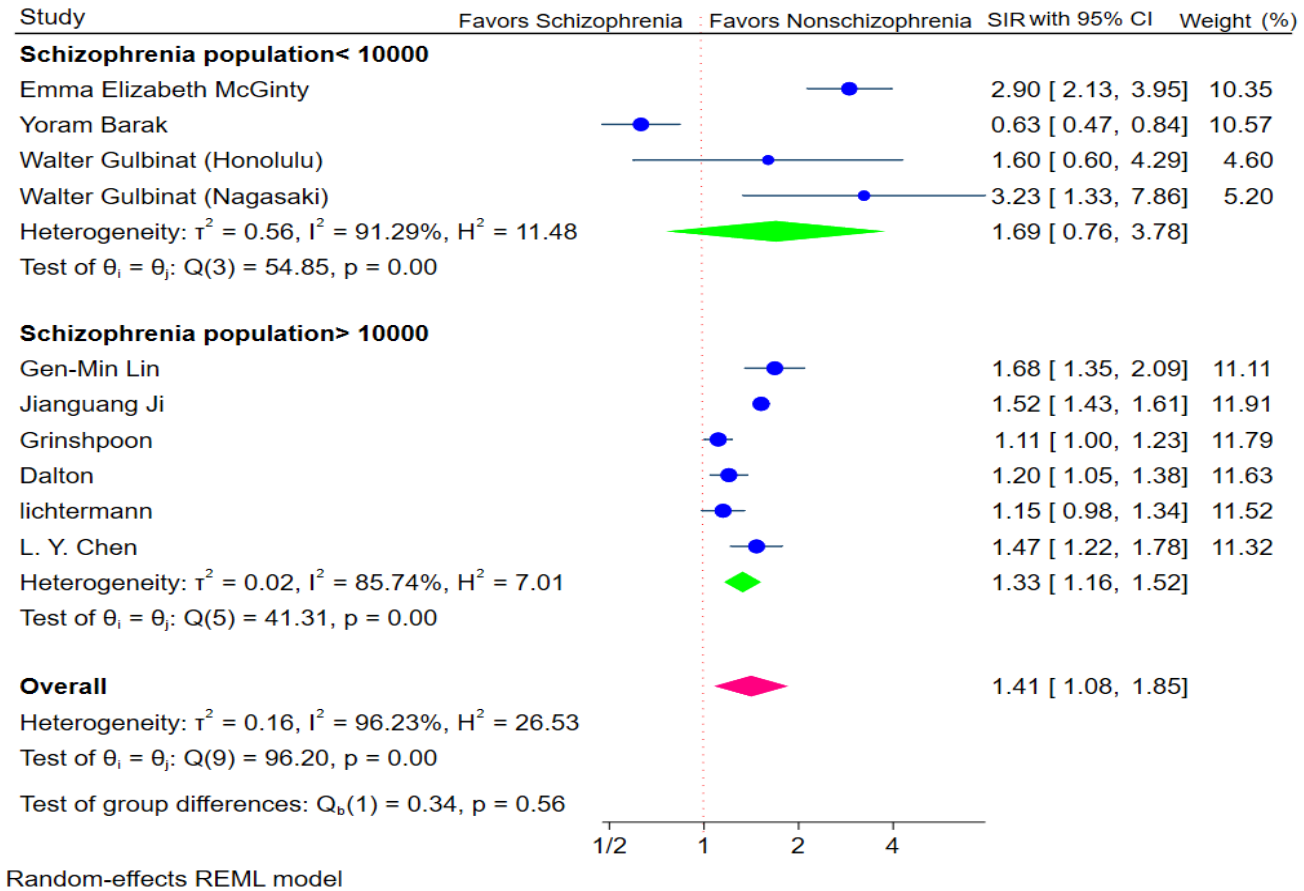

Figure 6. Incidence of Breast Cancer in Women with Schizophrenia Based on the Number of Patients

Publication Bias

The funnel plot was symmetrical in checking for publication bias, which proved the absence of publication bias and was supported by Egger regression test and Begg's non-parametric test (P = 0.224 and P = 0.720, respectively) (Figure 7).

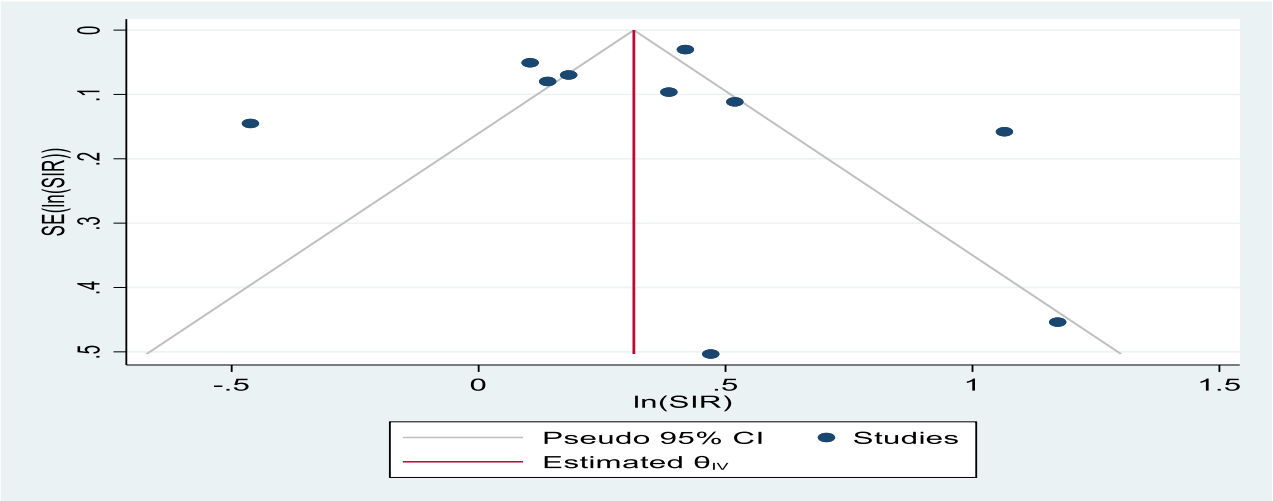

Figure 7. Funnel Plot for the Meta-Analysis of the Incidence of Beast Cancer in Women with Schizophrenia

Discussion

By conducting a meta-analysis of 12 cohort studies, we found in this systematic review that women with schizophrenia were at a greater risk of breast cancer (SIR: 1.43, 95% CI: 1.08-1.85, p < 0.01; IRR: 1.19, 95% CI: 1.13-1.26, P < 0.01). The result of this research can shed some light on the relationship between schizophrenia with breast cancer incidence risk. Along with previous reports, our findings indicate that prevention and screening programs are necessary for women with schizophrenia.

Although our result was previously reported by an earlier meta-analysis study (19), all the shortcomings of that study were addressed in ours. The previous meta-analysis (19) searched only two databases; however, in addition to those databases, we systematically searched three other data bases, including Scopus, PsycINFO and, Web of Science. We also intended to correct a number of errors in reporting (or calculating) such as the number or gender of patients. One of the errors of the previous study that we fixed was that it combined IRR and SIR to perform meta-analysis; however, it is not correct to combine the two for meta-analysis. We also provided a full description about the quality of the studies to depict a vibrant picture. Thus, we believe that sufficient consistency is now provided.

Cancer evolves during several years, and many factors affect the process of cancer. An unhealthy and inactive lifestyle (7) and increasing levels of plasma prolactin are the main factors considered for the higher prevalence of breast cancer among patients with schizophrenia (34). Antipsychotic drugs are still the main treatment for psychotic disorders and might increase the secretion of prolactin, thereby augmenting plasma levels (34). Although the relative risk related associated with high levels of prolactin remains undefined, the best care should include several factors ranging from assessing family history of cancer to regular monitoring of prolactin level as well as screening for breast cancer. The development of new medications with reduced effect on prolactin levels will be a valuable contribution.

One of the main challenges in providing optimal care for these patients is the high possibility of underdiagnosing breast cancer among people with schizophrenia. According to a systematic review and meta-analysis, women afflicted with schizophrenia were less likely to undergo mammography screening than those without schizophrenia, which means they are less likely to be diagnosed (pooled OR = 0.50, 95% confidence interval = 0.38-0.64, P < 0.001) (35). This might be a function of their clinical (mainly negative) symptoms, higher level of stigma, or limited access to health care facilities. Findings of the current study not only highlight the importance of adhering to the guidelines for screening breast cancer in these patients, but also suggest that further studies should probe for additional steps such as a regular measurement of prolactin levels or changing medication prescriptions.

Another finding of this study, revealed by subgroup analysis, indicates significantly lower incidence rate of breast cancer in women with schizophrenia in Asia and Europe compared to that observed in America. This may be due to several factors such as mammography screening of a larger number of people with schizophrenia, resulting in a higher rate of diagnosis). Moreover, a shorter duration of untreated psychosis could lead to longer consumption of antipsychotic

medication, thereby increasing the likelihood of elevated prolactin levels.

In seven studies, the duration of follow-up was more than 20 years. We hypothesized that due to the longer follow-up period, which causes the prolonged use of antipsychotics, the breast cancer incidence is likely to be higher than in those with the follow-up period of less than 20 years. However, subgroup analysis showed exactly the opposite result. As mentioned before, further research should evaluate more details concerning the likely relationship between prolactin levels and breast cancer incidence in these patients.

Limitation

Along with the strengths of this study mentioned earlier in this study, there were also a number of limitations. First, we only reviewed English articles, which could increase publication bias. However, high-quality manuscripts are more probable to be published in English-language journals. Second, this study only looked at the relationship between schizophrenia with the risk of breast cancer incidence. Furthermore, experimental studies are necessary to identify the mechanism of this relationship.

Conclusion

This meta-analysis of 12 cohort studies revealed a higher incidence of breast cancer among patients with schizophrenia. Therefore, implementing preventive measures for breast cancer in women who are afflicted with schizophrenia is a crucial matter. Additionally, regular screening programs should be established to facilitate early diagnosis and treatment of breast cancer.

Conflict of Interest

None.

References

1. Disease GBo. Global Health Data Exchange (GHDE). Global Burden of Disease Study 2019 (GBD 2019). 2019.
2. Aker S, Kahve AC. What do psychiatrists think about renaming schizophrenia in Turkey? Schizophr Res. 2022;248:8-13.
3. Orrico-Sánchez A, López-Lacort M, Muñoz-Quiles C, Sanfélix-Gimeno G, Díez-Domingo J. Epidemiology of schizophrenia and its management over 8-years period using real-world data in Spain. BMC Psychiatry. 2020;20(1):149.
4. Owen MJ, Sawa A, Mortensen PB. Schizophrenia. Lancet. 2016;388(10039):86-97.
5. Shamsaei F, Cheraghi F, Bashirian S. Burden on Family Caregivers Caring for Patients with Schizophrenia. Iran J Psychiatry. 2015;10(4):239-45.
6. Heald A. Physical health in schizophrenia: a challenge for antipsychotic therapy. Eur Psychiatry. 2010;25 Suppl 2:S6-11.
7. McNamee L, Mead G, MacGillivray S, Lawrie SM. Schizophrenia, poor physical health and physical activity: evidence-based interventions are required to reduce major health inequalities. Br J Psychiatry. 2013;203(3):239-41.
8. Vancampfort D, Correll CU, Galling B, Probst M, De Hert M, Ward PB, et al. Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. World Psychiatry. 2016;15(2):166-74.
9. Smith DJ, Langan J, McLean G, Guthrie B, Mercer SW. Schizophrenia is associated with excess multiple physical-health comorbidities but low levels of recorded cardiovascular disease in primary care: cross-sectional study. BMJ Open. 2013;3.(4)
10. Xu D, Chen G, Kong L, Zhang W, Hu L, Chen C, et al. Lower risk of liver cancer in patients with schizophrenia: a systematic review and meta-analysis of cohort studies. Oncotarget. 2017;8(60):102328-35.
11. Raviv G, Laufer M, Baruch Y, Barak Y. Risk of prostate cancer in patients with schizophrenia. Compr Psychiatry. 2014;55(7):1639-42.
12. Torrey EF. Prostate cancer and schizophrenia. Urology. 2006;68(6):1280-3.
13. Veeneman RR, Vermeulen JM, Abdellaoui A, Sanderson E, Wootton RE, Tadros R, et al. Exploring the Relationship Between Schizophrenia and Cardiovascular Disease: A Genetic Correlation and Multivariable Mendelian Randomization Study. Schizophr Bull. 2022;48(2):463-73.
14. Wang Y, Wang L, Li X, Liu B, Zhao Q, Chen P, et al. Polymorphisms of XRCC4 are involved in reduced colorectal cancer risk in Chinese schizophrenia patients. BMC Cancer. 2010;10:523.
15. Crump C, Winkleby MA, Sundquist K, Sundquist J. Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study. Am J Psychiatry. 2013;170(3):324-33.
16. Bushe CJ, Bradley AJ, Wildgust HJ, Hodgson RE. Schizophrenia and breast cancer incidence: a systematic review of clinical studies. Schizophr Res. 2009;114(1-3):6-16.
17. Barak Y, Levy T, Achiron A, Aizenberg D. Breast cancer in women suffering from serious mental illness. Schizophr Res. 2008;102(1-3):249-53.
18. Gulbinat W, Dupont A, Jablensky A, Jensen OM, Marsella A, Nakane Y, et al. Cancer incidence of schizophrenic patients. Results of record linkage studies in three countries. Br J Psychiatry Suppl. 1992(18):75-83.
19. Zhuo C, Triplett PT. Association of Schizophrenia With the Risk of Breast Cancer Incidence: A Meta-analysis. JAMA Psychiatry. 2018;75(4):363-9.
20. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020

explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. Bmj. 2021;372:n160.
21. Pettersson D, Gissler M, Hällgren J, Ösby U, Westman J, Bobo WV. The overall and sex- and age-group specific incidence rates of cancer in people with schizophrenia: a population-based cohort study. Epidemiol Psychiatr Sci. 2020;29:e132.
22. Chen LY, Hung YN, Chen YY, Yang SY, Pan CH, Chen CC, et al. Cancer incidence in young and middle-aged people with schizophrenia: nationwide cohort study in Taiwan, 2000-2010. Epidemiol Psychiatr Sci. 2018;27(2):146-56.
23. Osborn DP, Limburg H, Walters K, Petersen I, King M, Green J, et al. Relative incidence of common cancers in people with severe mental illness. Cohort study in the United Kingdom THIN primary care database. Schizophr Res. 2013;143(1):44-9.
24. Lin GM, Chen YJ, Kuo DJ, Jaiteh LE, Wu YC, Lo TS, et al. Cancer incidence in patients with schizophrenia or bipolar disorder: a nationwide population-based study in Taiwan, 1997-2009. Schizophr Bull. 2013;39(2):407-16.
25. Ji J, Sundquist K, Ning Y, Kendler KS, Sundquist J, Chen X. Incidence of cancer in patients with schizophrenia and their first-degree relatives: a population-based study in Sweden. Schizophr Bull. 2013;39(3):527-36.
26. McGinty EE, Zhang Y, Guallar E, Ford DE, Steinwachs D, Dixon LB, et al. Cancer incidence in a sample of Maryland residents with serious mental illness. Psychiatr Serv. 2012;63(7):714-7.
27. Barak Y, Levy T, Achiron A, Aizenberg D. Breast cancer in women suffering from serious mental illness. Schizophr Res. 2008;102(1-3):249-53.
28. Grinshpoon A, Barchana M, Ponizovsky A, Lipshitz I, Nahon D, Tal O, et al. Cancer in schizophrenia: is the risk higher or lower? Schizophr Res. 2005;73(2-3):333-41.
29. Goldacre MJ, Kurina LM, Wotton CJ, Yeates D, Seagroat V. Schizophrenia and cancer: an epidemiological study. Br J Psychiatry. 2005;187:334-8.
30. Dalton SO, Mellemkjaer L, Thomassen L, Mortensen PB, Johansen C. Risk for cancer in a cohort of patients hospitalized for schizophrenia in Denmark, 1969-1993. Schizophr Res. 2005;75(2-3):315-24.
31. Lichtermann D, Ekelund J, Pukkala E, Tanskanen A, Lönnqvist J. Incidence of cancer among persons with schizophrenia and their relatives. Arch Gen Psychiatry. 2001;58(6):573-8.
32. Mortensen PB. The incidence of cancer in schizophrenic patients. J Epidemiol Community Health. 1989;43(1):43-7.
33. Cheng CS, Chen WY, Chang HM, Pan CH, Su SS, Tsai SY, et al. Unfavorable cancer mortality-to-incidence ratios in patients with schizophrenia: A nationwide cohort study in Taiwan, 2000-2019. Acta Psychiatr Scand. 2023;148(4):347-58.
34. Wang M, Wu X, Chai F, Zhang Y, Jiang J. Plasma prolactin and breast cancer risk: a meta- analysis. Sci Rep. 2016;6:25998.
35. Hwong A, Wang K, Bent S, Mangurian C. Breast Cancer Screening in Women With Schizophrenia: A Systematic Review and Meta-Analysis. Psychiatr Serv. 2020;71(3):263-8.