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# The incidence rate of cancer in patients with schizophrenia: A meta-analysis of cohort studies☆

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ABSTRACT

*Background:* Numerous studies report that cancer prevalence in patients with schizophrenia might be different from the general population, but findings remain controversial.
*Aim:* Our updated meta-analysis of cohort studies aims to analyze the data from cohort studies concerning the incidence risk of overall cancer and some site-specific cancers in patients with schizophrenia.
*Method:* We performed a systemic search through electronic databases. Cohort studies evaluating and describing the cancer incidence among patients with schizophrenia were included. Pooled risk ratios (RRs) were calculated for assessing the incidence risk of cancer.
*Results:* There were 16 cohort studies included in this meta-analysis, which combined a total of 480,356 participants with schizophrenia and 41,999 cases of cancer. Results showed that there was a slight significant decreased overall risk ratio of cancer incidence among patients with schizophrenia (RR = 0.90, 95% CI 0.81–0.99). When stratified by cancer site and gender, there were significant decreased incidence risk rates of colorectal cancer (RR = 0.82, 95% CI 0.69–0.98) and prostate cancer (RR = 0.55, 95% CI 0.42–0.71) in those patients, moreover, the incidence rate of colorectal cancer decreased significantly in male patients (RR = 0.89, 95% CI 0.81–0.98), and the incidence rate of lung cancer increased significantly in female patients (RR = 1.12, 95% CI 1.01–1.25).
*Conclusions:* The incidence risk of some cancers was reduced in patients with schizophrenia. Gender and type of cancer were two important confounding factors contributed to the heterogeneity that required adjustment in our cancer incidence meta-analysis.



## 1. Introduction

The incidence of cancer in patients with schizophrenia compared to the general population has been a controversial topic since the Board of Control of the Commissioners in Lunacy for England and Wales first noted the possibility of a lower incidence of cancer among psychiatric patients in 1909 (Commissioners in Lunacy for England and Wales, 1909). Some subsequent studies found lower cancer rates among inpatients with schizophrenia compared to general population (Katz et al., 1967; Baldwin, 1979; Mortensen, 1989). More recently, researchers postulated the hospital environment may protect inpatients from exposure to certain cancer risk factors and selected schizophrenic patients living in the community to investigate cancer prevalence; however, results have not been consistent. Some studies reported a lower incidence of cancers in patients with schizophrenia (Ji et al., 2012; Chou et al., 2011; Goldacre et al., 2005). Others studies found higher cancer incidence or risk in schizophrenia patients (G.M. Lin et al., 2013a, 2013b; C.Y. Lin et al., 2013b; Lichtermann et al., 2001). Studies looking at specific cancers have also yielded conflicting results. For breast cancer, studies have reported higher (Hippisley-Cox et al., 2007; Dalton et al., 2005) equivalent (Goldacre et al., 2005; Oksbjerg et al., 2003; Lawrence et al., 2000), and lower (Barak et al., 2005) rates in patients with schizophrenia compared with general populations. The significant inconsistency in cancer incidence rates reported among patients with schizophrenia has been an interesting phenomenon in epidemiology.

☆ All authors participated in designing the study. HL and XY conducted searches and extracted data. HL and JL analyzed the data and wrote the first draft of the manuscript. XB, YZ and CL provided critical revisions of manuscript and approved final version.

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Many potential confounding factors may explain this observed inconsistency, such as sex, ethnicity, genetic background, environmental exposure and antipsychotic medications. Some studies suggest that the genetic or familial factors that contribute to schizophrenia's development might protect against the development of some cancers; the possible protective factors include a tumor suppressor gene p53 and enhanced natural killer cell activity (Yovel et al., 2000; Catts and Catts, 2000; Wang et al., 2010). In addition, medications such as haloperidol and chlorpromazine, used to treat schizophrenia, may inhibit cell viability thus having an anti-cancer effect, or may enhance the effect of some antitumor drugs (Kim et al., 2012; Yde et al., 2009).

Some evidence suggests that antipsychotics may increase the risk of breast cancer by elevating prolactin levels (Wang et al., 2002). In addition to these factors, differences in patient characteristics and research methods could also contribute to the inconsistency. For instance, the male-female ratios in study populations may influence the gender-related cancer incidences that can further confound the assessments of overall cancer incidence. In most clinical studies, researchers mainly used matched case-control, retrospective or prospective cohort studies to assess the cancer incidence rate among patients with schizophrenia. While retrospective case-control studies are more easily conducted than cohort studies, their power to assess causal relationships is weaker and more subjective.

Therefore, this meta-analysis of cohort studies aims to investigate the prevalence of cancer in population with schizophrenia through the analysis of data from cohort studies concerning the incidence risks of overall cancer and some site-specific cancers in the population with schizophrenia.

## 2. Methods

### 2.1. Search strategy

This meta-analysis was conducted according to the guidelines suggested by the Meta-analysis of observational studies in epidemiology (Stroup et al., 2000). Two researchers (HL and XY) independently searched the literature. Studies published between 2000 and 2014 were identified using the MEDLINE, EMBASE, Cochrane Library, Sino Med, and PsycInfo databases. The search terms included “psychotic”, “schizophrenic”, “schizophrenia”, “carcinoma”, “tumor”, “cancer”, and “neoplasm”, combined with “cohort studies” and “follow-up studies”. The reference lists of the more relevant articles screened were checked to search for studies that might not have been captured in our first literature search.

### 2.2. Inclusion/exclusion criteria

We imported all manuscripts obtained into EndNote X7 software, then used it to withdrew duplicate articles and then screened titles and abstracts to remove those that did not appear to be relevant, such as editorials, single case-study reports, reviews, animal studies, and articles on therapeutic approaches to antipsychotic drugs. To be selected for this meta-analysis, studies had to meet the following criteria: (a) a measure of cancer incidence rates [relative risks (RRs) with 95% confidence interval (CIs)] in patients with schizophrenia was reported; (b) the study had a population-based retrospective or prospective cohort design; studies with retrospective case-control or cross-sectional designs were excluded for the reasons mentioned earlier; (c) the study involved inpatient, outpatient or mixed samples of patients as the cohort population with no history of cancer but clear diagnoses of schizophrenia, for example, using the International Classification of Diseases (ICD) or other methods to confirm both the schizophrenia and cancer diagnoses; and (d) the study did not only investigate cancer rates among specific patient populations, such as patients using antipsychotic drugs. Two authors (HL and XY) reviewed the relevant full-text articles independently. The disagreements on study selections were resolved by consensus with another author (XB). The study selection procedure followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Moher et al., 2010).

### 2.3. Data extraction

Two authors (HL and XY) extracted the data from the included studies for the meta-analysis. We extracted the following information from each study: the first author's last name; publication year; country of the cohort; study design; mean age of the population; follow-up period; number of cases and size of the cohort; assessments of schizophrenia and cancer; types of cancer; and measures of association and 95% CI or standard error (SE). We contacted authors to ask for integrated data when the published paper did not provide the data we needed.

### 2.4. Quality assessment

Although quality assessments in meta-analyses of experimental studies can be reliably conducted, their use in observational research is controversial, and there is no clear consensus on rating methods (Juni et al., 1999). In this meta-analysis, we assessed the quality of each included study using a customized version of the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist for

**Table 1**
Methodological quality assessment of included studies: modified STROBE checklist.

| Study | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 3 | 1 | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 25 |
| Lawrence et al., 2000 | 1 | 1 | 1 | 1 | 1 | 0.5 | 1 | 1 | 1 | 0.5 | 2 | 1 | 3 | 1 | 1 | 1 | 1 | 0.5 | 0.5 | 1 | 21 |
| Lichtermann et al., 2001 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0.75 | 1 | 1 | 1 | 0.5 | 1 | 1 | 1 | 1 | 1 | 20.25 |
| Oksbjerg et al., 2003 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 0.5 | 1 | 1 | 1 | 0.5 | 1 | 1 | 1 | 1 | 20 |
| Barak et al., 2005 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0.5 | 1 | 1.5 | 1 | 2.5 | 1 | 0.5 | 0.5 | 1 | 1 | 1 | 1 | 20.5 |
| Dalton et al., 2005 | 2 | 1 | 1 | 0.5 | 1 | 1 | 1 | 1 | 1 | 1 | 3 | 1 | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 0.5 | 24 |
| Goldacre et al., 2005 | 2 | 1 | 1 | 1 | 1 | 1 | 0.5 | 1 | 0 | 1 | 3 | 1 | 1.5 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 21 |
| Grinshpoon et al., 2005 | 1 | 1 | 1 | 0.5 | 1 | 1 | 1 | 1 | 0 | 1 | 3 | 1 | 2.5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 22 |
| Barak et al., 2008 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 2.5 | 1 | 1 | 1 | 0.5 | 1 | 1 | 1 | 1 | 1 | 20 |
| Chou et al., 2011 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 3 | 1 | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 24 |
| Truyers et al., 2011 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 3 | 1 | 3 | 0.5 | 1 | 1 | 1 | 1 | 1 | 1 | 24.5 |
| Ji et al., 2012 | 2 | 1 | 1 | 0.5 | 1 | 1 | 1 | 1 | 1 | 1 | 3 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 23.5 |
| Whitley et al., 2012 | 1 | 1 | 1 | 1 | 0.5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 20.5 |
| Kisely et al., 2013 | 1 | 1 | 1 | 0.5 | 1 | 1 | 1 | 1 | 1 | 1 | 3 | 0.5 | 2.5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 22.5 |
| G.M. Lin et al., 2013a | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2.5 | 1 | 2.5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 24 |
| Osborn et al., 2013 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 3 | 1 | 2.5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 24.5 |
| Raviv et al., 2014 | 1 | 1 | 1 | 0.5 | 1 | 1 | 0.5 | 1 | 0 | 1 | 1.5 | 1 | 1 | 1 | 0.5 | 1 | 1 | 1 | 1 | 1 | 18 |

The modified STROBE checklist criteria: (1) title and abstract; (2) background/rationale; (3) objectives; (4) study design; (5) setting; (6) participants; (7) variables; (8) data sources/measurement; (9) bias; (11) quantitative variables; (12) statistical methods; (13) reporting of participants; (14) descriptive data; (15) outcome data; (16) main results; (17) other analyses; (18) key results; (19) limitations; (20) interpretation and (21) generalisability.

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