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Review article

Cancer mortality in patients with schizophrenia: systematic review and meta-analysis

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Background
Previous studies have reported conflicting results on the association between schizophrenia and cancer mortality.

Aims
To summarise available evidence and quantify the association between schizophrenia and cancer mortality using meta-analysis.

Method
We systematically searched literature in the PubMed and Embase databases. Risk estimates and 95% confidence intervals reported in individual studies were pooled using the DerSimonian–Laird random-effects model.

Results
We included 19 studies in the meta-analysis. Among them, 15 studies reported standardised mortality ratios (SMRs) comparing patients with schizophrenia with the general population, and the pooled SMR was 1.40 (95% CI 1.29–1.52, $P<0.001$). The other four studies reported hazard ratios (HRs) comparing individuals with schizophrenia with those without schizophrenia; the pooled HR was 1.51 (95% CI 1.13–2.03, $P=0.006$).

Conclusions
Patients with schizophrenia are at a significantly increased risk of cancer mortality compared with the general population or individuals without schizophrenia.

Declaration of interest
None.

Schizophrenia is a serious mental illness that has a profound effect on the patients, their families and society.[1] Despite its low prevalence in populations, schizophrenia is associated with an enormous economic burden worldwide.[2] In the USA, the economic burden of schizophrenia was estimated at 62.7 billion dollars in 2002[3] and 155.7 billion dollars in 2013.[4] Patients with schizophrenia are known to have a significantly higher risk of premature death,[5–7] with nearly 20% shorter life expectancy than the general population.[8] Although unnatural causes of death such as suicide, homicide and accidents partly contribute to the excess mortality of schizophrenia, more patients actually died from natural causes, such as cardiovascular diseases, respiratory diseases and cancers.[9–12] In Sweden, natural causes accounted for 90.9% and 82.3% of all deaths among women and men with schizophrenia respectively.[13] In a previous systematic review of mortality in schizophrenia, the median standardised mortality ratios (SMRs) were 2.58, 2.41 and 7.50 for mortality from all causes, natural causes and unnatural causes respectively, when comparing patients with schizophrenia with the general population.[5]

During recent decades, there has been an immense interest in estimating the risk of cancer mortality after a diagnosis of schizophrenia. Findings from previous studies have been mixed with positive, null and inverse associations between schizophrenia and cancer mortality. Several studies, in particular early studies, reported a lower or similar risk of cancer mortality among patients with schizophrenia compared with the general population. For instance, in a retrospective cohort study (1957–1986) in Denmark, Mortensen & Juel reported a 15% lower risk of cancer mortality in men but a 17% higher risk of cancer mortality in women.[14] Similar results were found in subsequent studies in Japan[15] and West Australia.[16] However, a positive association between schizophrenia and cancer mortality was observed in other studies in a Danish population[17,18] and studies in other populations.[9,10,13,19–27] In a large national cohort in the USA, Olfson *et al*[9] found that adults with schizophrenia had a 1.8-fold chance of dying from cancers compared with adults in the general population. Similarly, paradoxical findings were also reported in literature pertaining to cancer incidence after a diagnosis of schizophrenia.[28–31] Cancers are usually invasive and life-threating; thus, it is important to accurately characterise cancer mortality patterns after a diagnosis of schizophrenia, which may help inform changes in clinical care to reduce cancer-related deaths in patients with schizophrenia. However, because the prevalence of both schizophrenia and cancer mortality are very low, a robust estimate of the association between schizophrenia and cancer mortality may not have been achievable in some previous studies. Therefore, this study was performed to systematically review the currently available evidence regarding cancer mortality in patients with schizophrenia and to quantify the association between schizophrenia and cancer mortality through a comprehensive meta-analysis.

Method

This study was conducted in accordance with the guidelines in the Meta-analysis of Observational Studies in Epidemiology statement.[32]

Literature searches

We searched the PubMed and Embase databases for literature that was published up to 16 October 2016. The search terms were a combination of key words and standard subheading terms relevant to schizophrenia, cancer and mortality. Specifically, we used the following search terms in PubMed: ("Schizophrenia"[Mesh] or "schizophrenia"[tiab] or "schizophrenic"[tiab]) AND ("Neoplasms"[Mesh] or "cancer"[tiab] or "tumor"[tiab]) AND ("Mortality"[Mesh] or "mortality"[tiab] or "death"[tiab]). Similar search terms were constructed and used in the Embase database. Additionally, the references listed in any relevant articles or reviews were screened. No language restrictions were applied for the searches or study inclusion.

Study selection and data extraction

Any published article that reported the risk of cancer mortality in patients with schizophrenia was eligible for inclusion in this systematic review. During the screening steps, we excluded reviews, editorials or protocols that did not include original data. We also excluded studies on animals or cell lines, studies that did not evaluate schizophrenia as an exposure variable, and studies that did not include cancer mortality as an outcome variable. After detailed evaluation, we excluded studies if risk estimates and/or confidence intervals for the association between schizophrenia and cancer mortality were not reported and were unable to be calculated. We also excluded two studies[33,34] in which the results were updated by later reports[10,35] with longer follow-up in the same population. Another study was excluded because the participants already had cancer at baseline, with a focus on cancer fatality rather than mortality from cancer.[36]

The following data were extracted from each included article: title, author, publication year, location, study design, number of participants, methods used for the assessment of schizophrenia and cancer death, statistical methods used for the analysis, risk estimates and 95% confidence intervals after adjustment for covariates, and any covariates that were adjusted or matched for in the multivariate model. When the original studies reported the results separately in men and women we considered them independent populations and extracted the risk estimates separately.

Statistical analysis

Risk estimates and 95% confidence intervals reported in individual studies were pooled in a meta-analysis using the DerSimonian–Laird random-effects model, which incorporates between-study heterogeneity in addition to sampling variation.[37] The majority of studies on cancer mortality in patients with schizophrenia used SMRs compared with the general population as their risk estimates. The relative risk (RR) of cancer mortality in comparing patients with schizophrenia with the general population, as reported in one study,[19] was assumed to approximate SMRs. Several studies reported hazard ratios (HRs) using a Cox proportional hazards model to compare individuals with schizophrenia with those who did not have schizophrenia.[13,23,25,26] Therefore, we separately summarised the results as pooled SMRs and pooled HRs in the meta-analysis given the difference in comparator populations. In one study,[26] the 95% confidence intervals were not directly reported, and therefore we calculated these on the basis of reported risk estimates and *P*-values following the method of Altman & Bland.[38]

Heterogeneity across studies was assessed by both the χ^2-based Cochran's *Q* statistic and the I^2 metric.[39] To explore the potential sources of heterogeneity, we conducted meta-regression analyses with the following factors: geographical location, sample size ($\geqslant$3000 *v.* $<$3000), follow-up duration ($\geqslant$10 *v.* $<$10 years) or adjustment for covariates (age and gender only *v.* age, gender and other factors). Additionally, we conducted stratified analyses by gender because of the observed gender disparity in several earlier studies.

The possibility of publication bias was visually inspected by funnel plot and statistically assessed using the Egger regression asymmetry test.[40] Sensitivity analyses were performed by omitting one study at a time and calculating a pooled estimate for the remainder of the studies to determine whether the results were markedly affected by a single study. We also used the fixed-effect model for all above analyses as another set of sensitivity analyses. All statistical analyses were performed using Stata software (version 14.0). A $P<0.05$ was considered statistically significant.

Results

Characteristics of the included studies

Through a systematic search in literature databases and reference lists of relevant articles, we identified 356 potentially relevant articles. After implementing the screening process, we finally included 19 studies[9,10,13–27,35,41] that fulfilled our eligibility criteria in the meta-analysis (Fig. 1). Two[10,35] of the included studies updated the data of their earlier reports[33,34] in the same population; thus, the earlier studies[33,34] were not included in our list. Of the 19 included studies 11 were conducted in Europe, 4 in Australia, 3 in North America, and 1 in East Asia (Table 1). The majority of the included studies had a retrospective cohort study design with population-based record linkage data. In those studies, schizophrenia was usually defined according to clinical diagnosis in medical records, register, or administrative data and cancer death was ascertained from national or regional registries of vital statistics. The number of patients with schizophrenia in the included studies ranged from 370 to 1 138 853, with most studies having over 1000 patients. The follow-up period varied from 6 to 37 years, and the majority of the included studies had a follow-up duration of 10 years or longer.

Association between schizophrenia and cancer mortality

Among the 19 included studies, 15 studies[9,10,14–22,24,27,35,41] reported SMRs comparing patients with schizophrenia with the general population. An inverse, null or positive association between schizophrenia and cancer mortality was observed in those studies, with the reported SMRs ranging from 0.81 to 2.02 (Fig. 2). In the random-effects meta-analysis, the pooled SMR of cancer mortality in patients with schizophrenia compared with the

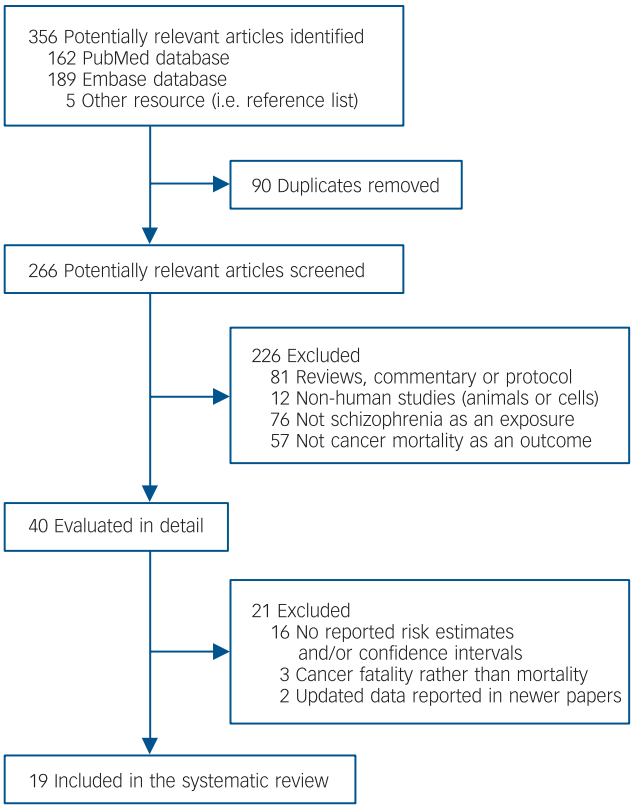

Fig. 1 Flow diagram for literature search and study selection.

Table 1 Characteristics of the studies included in the meta-analysis

Authors, year	Location	Study design	Participants with schizophrenia, *n*	Assessment of schizophrenia	Assessment of cancer death	Follow-up, years	Risk estimate (95% CI)	Adjusted covariates
Mortensen & Juel (1990)[14]	Denmark	Retrospective cohort study, 1957–1986	6178	Hospital records based on the Kraepelinian concept	Danish Register of Causes of Death	29	SMR: 0.85 (0.76–0.94) in men and 1.17 (1.06–1.28) in women	Age (reported separately by gender)
Mortensen & Juel (1993)[41]	Denmark	Retrospective cohort study, 1970–1987	9156	Danish Psychiatric Case Register	Danish Register of Causes of Death	17	SMR: 0.81 (0.54–1.19) in men and 1.01 (0.75–1.33) in women	Age (reported separately by gender)
Saku *et al* (1995)[15]	Japan	Retrospective cohort study, 1948–1985	4980	Medical records, according to DSM-III-R 1987	Japanese family registration system (*Koseki*) and death certificate	37	SMR: 0.84 (0.54–1.25) in men and 1.37 (0.80–2.19) in women	Age (reported separately by gender)
Lawrence *et al* (2000)[16]	Australia	Retrospective cohort study, 1982–1995	N/A	Western Australian Health Services Research Linked Database	Western Australian Cancer Register and Death Register	13	SMR: 0.90 (0.71–1.80) in men and 1.19 (1.05–1.40) in women	Age (reported separately by gender)
Heila *et al* (2005)[19]	Finland	Retrospective cohort study, 1980–1996	58 761	Finnish National Hospital Discharge Register	Finnish National Causes of Death Register	16	RR: 1.50 (1.41–1.58) in men and 1.48 (1.40–1.57) in women[a]	Age and calendar year (reported separately by gender)
Laursen *et al* (2007)[17]	Denmark	Retrospective cohort study, 1973–2000	17 660	Danish Psychiatric Central Register	Danish Register of Causes of Death	27	SMR: 1.24 (1.08–1.43) in men and 1.32 (1.18–1.48) in women	Age and calendar period (reported separately by gender)
Tran *et al* (2009)[20]	France	Prospective cohort study, 1993–2003	3470	Questionnaire and/or hospital records	National death certificate	11	SMR: 1.5 (1.2–1.9)	Age and gender
Brown *et al* (2010)[10]	UK	Prospective cohort study, 1981–2006	370	Hospital records	UK Office of National Statistics database	25	SMR: 1.93 (1.18–2.98) in men and 1.02 (0.49–1.88) in women	Age (reported separately by gender)
Daumit *et al* (2010)[21]	USA	Retrospective cohort study, 1992–2001	N/A	Medicaid database	National Death Index	9	SMR: 1.4 (1.3–1.5)	Age, gender and ethnicity
Talaslahti *et al* (2012)[22]	Finland	Retrospective cohort study, 1999–2008	9461	Finnish Hospital Discharge Register	National Causes of Death Register of Statistics Finland	9	SMR: 1.9 (1.7–2.1) in men and 2.0 (1.8–2.1) in women	Age (reported separately by gender)
Castagnini *et al* (2013)[18]	Denmark	Retrospective cohort study, 1995–2008	4576	Danish Psychiatric Register	Danish Register of Causes of Death	13	SMR: 1.5 (1.0–2.3)	Age and gender
Crump *et al* (2013)[13]	Sweden	Retrospective cohort study, 2001–2009	8277	Swedish Outpatient Registry and Swedish Hospital Registry	Swedish Death Registry	9	HR: 1.39 (1.11–1.74) in men and 1.68 (1.36–2.07) in women	Age, marital status, education, employment status, income and substance use disorder (reported separately by gender)
Guan *et al* (2013)[23]	The Netherlands	Retrospective cohort study, 1999–2009	4590	Psychiatric Case Register Middle Netherlands	Death Register of Statistics Netherlands	11	HR: 1.61 (1.26–2.06)	Age, gender, ethnicity and mean income of last-registered neighbourhood
Kisely *et al* (2013)[24]	Australia	Retrospective cohort study, 1988–2007	N/A	Hospital Morbidity Data System, and Mental Health Information System	Registrar General's Death Registration Data	19	SMR: 2.00 (1.51–2.64) in men and 1.68 (1.29–2.18) in women	Age and gender
Almeida *et al* (2014)[25]	Australia	Prospective cohort study, 1996–2010	444	Western Australian Data Linkage System	Western Australian Data Linkage System	14	HR: 2.0 (1.8–2.2)	Age (all participants were men)
Kredentser *et al* (2014)[26]	Canada	Retrospective cohort study, 1999–2008	9038	Population Health Research Data Repository	Population Health Research Data Repository	10	HR: 1.05 (0.93–1.18)[b]	Age and gender
Perini *et al* (2014)[35]	Italy	Retrospective cohort study, 1982–2006	695	South Verona Psychiatric Case Register	Mortality Registry of the Local Health District of Verona, and other Registries of Deaths	25	SMR: 0.83 (0.50–1.30)	Age and gender
Olfson *et al* (2015)[9]	USA	Retrospective cohort study, 2001–2007	1 138 853	National Medicaid Analytic eXtract (MAX) database	National Death Index	7	SMR: 1.7 (1.7–1.8) in men and 1.8 (1.8–1.8) in women	Age, ethnicity and geographic region (reported separately by gender)
Kisely *et al* (2016)[27]	Australia	Retrospective cohort study, 2002–2007	N/A	Queensland Hospital Admitted Patients' Data Collection or Queensland Client Event Services Application	Queensland Registrar General's Death Registration Data	6	SMR: 2.02 (1.61–2.53)	Age, gender, residence, socioeconomic status and length of mental health service in-patient stay

SMR, standardised mortality ratio; N/A, not applicable; RR, relative risk; HR, hazard ratio.
a. The risk estimates were pooled from the original values that were separately reported for cancer mortality after 0–5, 5–10 and >10 years after the first admission to hospital with schizophrenia.
b. The 95% confidence intervals were not directly reported in the original article, and therefore they were calculated from the *P*-value along with the risk estimate following the method by Altman & Bland.[38]

general population was 1.40 (95% CI 1.29–1.52; $P<0.001$). There was evidence of heterogeneity across studies ($I^2=95\%$, $P<0.001$). In meta-regression analyses, we observed no evidence that the heterogeneity was caused by a difference in the geographical location, sample size, follow-up duration or adjustment for covariates. In several[10,14–16,41] although not all[9,17,19,22,24] previous studies, a gender difference was noted; however, gender did not appear to be a significant source of heterogeneity in this meta-analysis. Stratified analyses by gender showed that the pooled SMR of cancer mortality was 1.32 (95% CI 1.11–1.57) in men, 1.42 (95% CI 1.24–1.63) in women, and 1.47 (95% CI 1.20–1.79) in studies with both men and women (online Fig. DS1). Further exploration using a cumulative meta-analysis showed evidence of cohort effects; the pooled estimates shifted from an inverse association to a positive association with overall time (online Fig. DS2). There was also evidence for publication bias, as indicated by the funnel plot (online Fig. DS3) and the Egger regression asymmetry test ($P<0.01$). Sensitivity analyses by omitting one study at a time did not substantially alter the pooled results, which ranged from 1.37 (95% CI 1.26–1.49) to 1.46 (95% CI 1.35–1.57). Additionally, similar results but with a stronger positive association were obtained when a fixed-effect model was used instead of a random-effects model.

The other four studies[13,23,25,26] reported HRs comparing patients with schizophrenia with those without schizophrenia. All of those studies with the exception of the one by Kredentser *et al*[26] reported a positive association between schizophrenia and cancer mortality (Fig. 2). The pooled HR of cancer mortality in individuals with schizophrenia compared with those without schizophrenia was 1.51 (95% CI 1.13–2.03, $P=0.006$). Similarly, there was evidence for heterogeneity across studies ($I^2=94\%$, $P<0.001$). Only the study by Crump *et al*[13] reported the HRs separately by gender, in which the HRs were 1.39 (95% CI 1.11–1.74) in men and 1.68 (95% CI 1.36–2.07) in women.

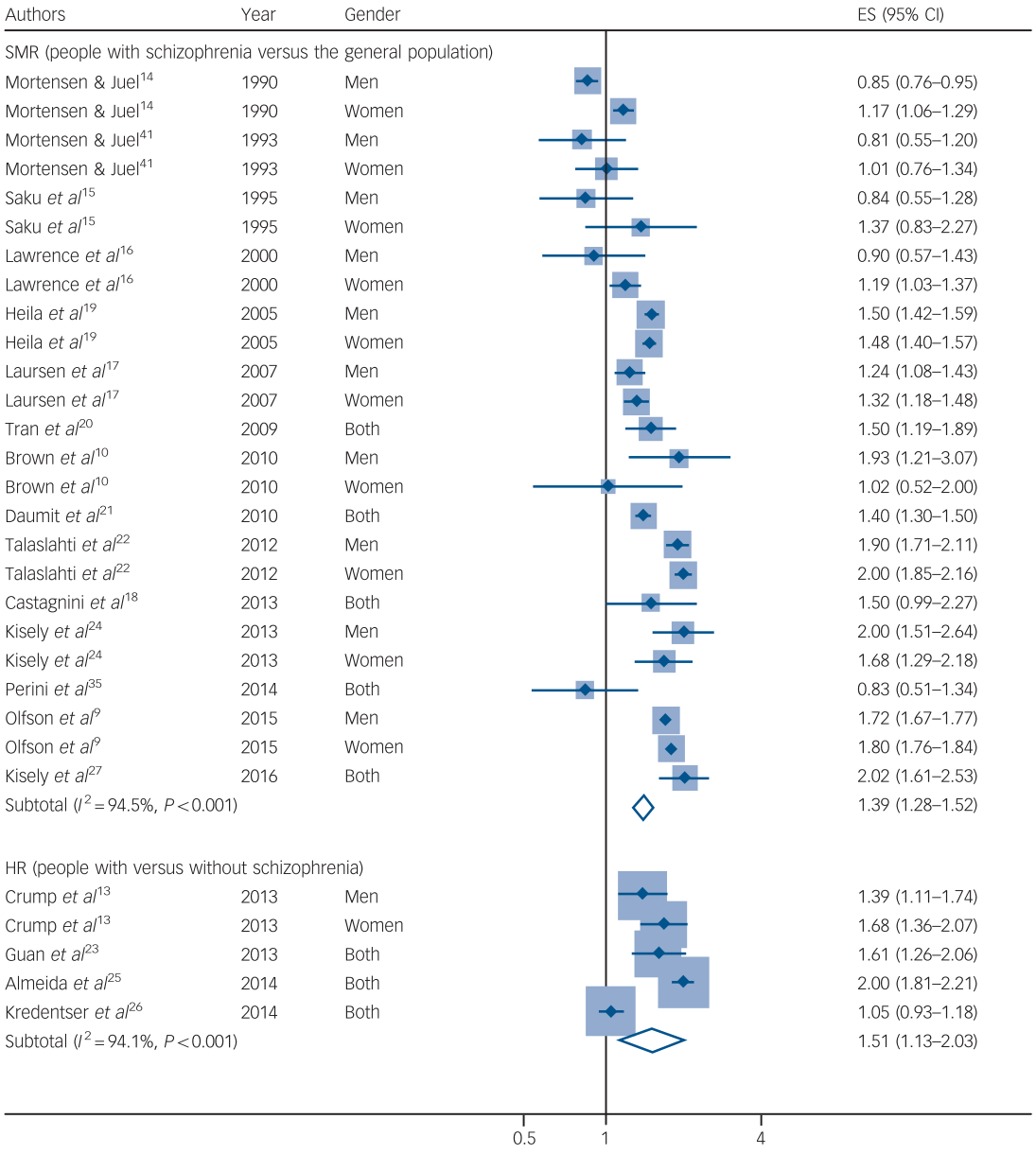

Fig. 2 Forest plot of the risk of cancer mortality in patients with schizophrenia compared with the general population (above) or people without schizophrenia (below).

ES, effect size; HR, hazard ratio; SMR, standardised mortality ratio.

We did not perform a meta-regression analysis for those studies because the limited number of included studies did not allow sufficient statistical robustness in meta regression. There was no evidence for significant publication bias ($P = 0.84$ in the Egger regression asymmetry test). Sensitivity analyses by omitting one study at a time did not substantially alter the pooled results, which ranged from 1.39 (95% CI 1.08–1.80) to 1.69 (95% CI 1.42–2.01). We also observed similar results when a fixed-effect model was used instead of a random-effects model.

Discussion

Main findings

In this study, we found that patients with schizophrenia had a higher risk of cancer mortality. Specifically, the risk of cancer mortality in patients with schizophrenia was 40% higher than the general population and 51% higher than individuals without schizophrenia.

The risk of cancer mortality in patients with schizophrenia has not been previously quantified using a meta-analysis. The present study, based on a systematic review of epidemiological studies, was conducted to provide an updated estimate for the risk of cancer mortality in patients with schizophrenia by pooling original data from individual studies.

Interpretation of our findings and comparison with other studies

In the current study, we observed heterogeneity in previous individual studies looking at the association between schizophrenia and cancer mortality, which was not convincingly explained by differences in gender, geographical location, sample size, follow-up duration or adjusting for covariates. We noted possible cohort effects showing a relatively consistent and positive association in recent publications; this was in contrast to inconsistent associations in earlier publications. However, this may be a result of publication bias, and such findings should be interpreted with caution.

Interestingly, there appeared to be a paradox in the associations between schizophrenia and cancer incidence versus cancer mortality.[28–31] Whereas our study showed a significantly increased risk of cancer mortality in patients with schizophrenia, a previous meta-analysis on the association of schizophrenia and cancer incidence showed no significant association in general, although there were variations in the risk of specific cancer sites.[30] Several factors have been suggested to explain the divergent associations between schizophrenia and cancer incidence and mortality. Cancer mortality is influenced by not only cancer incidence, but also the survival of those who develop cancer.[15] Several studies on cancer fatality in schizophrenia[36,42,43] have consistently indicated that the presence of schizophrenia increases cancer fatality in patients who had cancer (online Table DS1). Compromised accessibility to treatment facilities and lower quality of care may be the primary reasons for the increased cancer mortality observed in patients with schizophrenia, indicating an imperative need to increase access and popularise cancer screening and detection in this patient population.[42,44] Reduced cancer screening and delayed cancer diagnosis in those with schizophrenia, which results in a late staging of cancer and a higher prevalence of metastasis at the time of cancer diagnosis, may also contribute to worse cancer survival.[24,45,46] Patients with schizophrenia are also more likely to have physical health multimorbidity,[47] engage in more smoking, and are less likely to receive smoking cessation advice,[48] which can increase the risk of cancer mortality. Additionally, different types of antipsychotic drugs may also complicate the risk of cancer mortality in patients with schizophrenia.[49] In female patients with schizophrenia, prolactin and antipsychotic-induced hyperprolactinaemia have been hypothesised to play a role in the development and progression of breast cancer, but available evidence remains controversial and inconclusive.[50–52]

Strengths and limitations

The major strength of this study is the use of a systematic approach to identify and analyse available evidence. Additionally, the inclusion of data from a large number of identified studies ensures a robust pooled estimate with a high statistical power. There appears to be a high validity of death status and causes of death in the included studies. Information on death status and causes in all the included studies was ascertained from well-established general death registries (such as the National Death Index in the USA and Swedish Death Registry), specific registries of cause of death (for example Danish Register of Causes of Death and Finnish National Causes of Death Register) or directly from national or local death certificates. Death certificates and other official documents were referred to in order to establish the causes of death in all those death registries. Furthermore, there was evidence indicating that the causes of death on death certificates in patients with schizophrenia were probably more accurate than in the general population, because rates of post-mortem examination (54% *v.* 22%) and coroner's inquest (15% *v.* 6%) were higher than the national average.[10]

There are also several limitations. First, the use of SMRs in most previous studies may underestimate the true risk of cancer mortality in patients with schizophrenia, because in calculating SMRs, the comparator group is usually the general population, which is comprised of individuals with and without schizophrenia. As shown in previous methodological papers,[53,54] this bias was obvious when the risk was assessed in cohort studies of people with common diseases or exposures and/or when large SMRs were observed. However, because the prevalence of schizophrenia is low (~1%) in the general population and the observed SMRs for cancer mortality after a diagnosis of schizophrenia in most studies were modest, the underestimation of true risk by SMRs in the current scenario would be minor.[53,54] In this meta-analysis, such concerns were further reduced because we presented not only the pooled SMRs, but also the pooled HRs, which appeared to be stronger than the pooled SMRs. Second, the risk of cancer mortality by specific types/sites (i.e. lung cancer, breast cancer, etc.) was not summarised in this study because a possible selective reporting bias was observed for the risk of mortality from certain types of cancer in previous studies. In addition to the risk of overall cancer mortality, many studies simply chose to report significant findings for certain types of cancer. Some other studies may be unable to derive a risk estimate for certain types of cancer because the sample size was too small. Apparently, pooling the results from those studies will lead to a biased estimation. In the large study by Olfson *et al*,[9] increased mortality was consistently observed in all cancer subtypes (i.e. lung, colon, breast, liver, pancreas, haematological), with nearly identical SMRs in men and women. This indicates that variations in the risk of mortality from different types of cancer may not be substantial. Further investigation on this is warranted in future studies. Third, information on antipsychotic medication and smoking status was not available in most studies. Whether these factors moderate or mediate the association between schizophrenia and cancer mortality needs further investigation.

Implications

This study has important clinical implications. Because of the high social and economic burden associated with schizophrenia,[2] it is important to clearly understand schizophrenia-related clinical outcomes such as morbidity and mortality risk. Findings from our study emphasise the need for clinicians to be aware of the increased risk of cancer mortality in people with schizophrenia. It appears to be imperative to address health disparities and improve cancer survival among patients with schizophrenia through an integrated approach, which may involve an improvement in access and quality of care, early cancer screening and diagnosis, as well as smoking cessation services.

In conclusion, this systematic review and meta-analysis found a significantly increased risk of cancer mortality in patients with schizophrenia. Future cohort studies with a large sample size and long follow-up are warranted to confirm our findings and to elucidate the risk of mortality from specific types/sites of cancers.

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EXTRA CONTENT ONLINE

psychiatry in the movies

From lesion theory of mental illness to *Westworld* and back

Abdi Sanati

What is mental illness? This question has challenged psychiatrists for several decades and despite lengthy debates we still do not have a clear answer. Yet we continue to treat mental illnesses and are quite successful at it – there is evidence that our treatments are as effective as those in other medical disciplines. One of the main criticisms of the concept of mental illness is that as there are no observable lesions in the brain, there is no pathology.

This issue came to my mind recently when I was watching the movie *Westworld*. It was made in 1973 and starred Yul Brynner. The recent TV series has got much attention, yet the 1973 film was more original. It is the first time that the concept of computer virus is referred to in a film, in fact one of the first references to viruses in any medium. What amused me was the shock of the computer scientists and technicians who, seeing nothing wrong with the hardware, could not comprehend how things could have gone wrong. A philosophical doctrine that addresses that issue is called emergentism. It states that as systems become more complex, their behaviour cannot be predicted solely by determining the behaviour of their constituting elements. One cannot approach a computer the same way as a tape recorder. Given the fact that the brain is immensely more complex than any system known to us, the way things can go wrong in the brain could also be more complex than its constituting elements and its physical structure, and colleagues who manage functional disorders can vouch for that. Interestingly, I found that the late Frank Fish had stated the same in his comprehensive psychopathology textbook.

It seems to me that when discussing disorders of the mind, we mainly focus on the disorder parts. Yet we also need to focus on the mind – and for that, we may find an ally in philosophy of mind.

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