



Cancer and schizophrenia

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Purpose of review

On the basis of articles published in 2018, 2019 and 2020, the first aim of this review is to present estimates of incidence rates and excess mortality of overall cancer and organ-specific cancers for patients with schizophrenia compared with the general population.

The second aim is to explore if underdiagnosis and undertreatment can explain – at least partly – the increased mortality of cancer in patients with schizophrenia compared with the general population.

Recent findings

Patients diagnosed with schizophrenia have an approximately 50% increased risk of death by cancer compared to age and sex-matched people in the general population. Studies have confirmed an increased mortality from breast, lung and colon cancer in patients with schizophrenia.

Analyses of incidence of cancer revealed contradicting results, with some studies showing no increase in incidence and others a modestly increased incidence in overall cancer. Studies of incidence of specific types of cancers showed modestly increased risk of pancreas, oesophagus, breast cancer and contradicting results regarding lung cancer.

In studies identified that compared to the general population, patients with schizophrenia were at an increased risk of not being diagnosed or treated for cancer before death of cancer. In addition, patients with schizophrenia had lower chances of getting optimal treatment for colon cancer after diagnosis.

Summary

This review indicates that patients with schizophrenia are at increased risk of dying of cancer and of several specific types of cancer. This increased mortality can be reduced if the price of tobacco is increased, if smoking cessation programmes are offered systematically, screening programs better implemented in this highly vulnerable group, and if procedures to facilitate access to early diagnosis and effective treatment are implemented.

Keywords

cancer, morbidity, mortality, schizophrenia

INTRODUCTION

Schizophrenia is one of the most costly and debilitating disorders in terms of personal suffering for those affected, for the relatives and society [1]. It is associated with an increased risk of comorbid somatic illness and a reduced life expectancy [2,3,4^{**},5^{***}].

In order to highlight the incidence and mortality of cancer in schizophrenia, a literature search in PubMed with the mesh terms #schizophrenia# and #cancer# was conducted for 2018, 2019 and 2020. On the basis of review of titles and abstracts, relevant longitudinal articles were chosen by MN and confirmed and supplied by OP-R and TML.

Schizophrenia and death of cancer

Schizophrenia is associated with an increased risk of dying from cancer. In a recent Danish register-based

study including 6.6 million individuals aged 10 years and above, the risk of death of cancer in patients with schizophrenia ($N = 47\,554$) was compared with the risk in those without schizophrenia, adjusted for age, sex and calendar year. An increased mortality risk was identified with a mortality rate ratio of 1.53 (1.43–1.65) for men and 1.54 (1.43–1.65) for

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KEY POINTS

- Schizophrenia was associated with increased incidence and mortality by cancer.
- Studies confirmed an increased mortality from breast, lung and colon cancer.
- Patients with schizophrenia-initiated treatment for cancer at a more advanced stage and were less likely to receive effective treatment after diagnosis.
- Universal interventions to prevent start of smoking and smoking cessation programmes are recommended.
- Shared care programmes to improve diagnosis and treatment of cancer in patients with schizophrenia should be implemented.

women [6]. Updated analyses of the Danish population ($N=7.4$ million individuals, no age restrictions) were presented in a landmark article from Plana-Ripoll *et al.* [5^{**}] in which mortality rate ratios of 1.41 (1.34–1.48) for men and 1.36 (1.31–1.42) for women were found for 103 848 individuals with schizophrenia spectrum disorders (ICD-10 codes F20-F29).

As different mechanisms play a role in cancer in different organs, there is a good rationale for investigating mortality due to cancer in specific organs.

Conflicting results are present in the literature. Yung *et al.* [7] examined four cause-specific cancer mortality rates in schizophrenia compared with the general population in a large cohort in Hong Kong. They found a similar mortality in all subgroups, except lung cancer wherein the mortality was only 0.77 (0.67–0.89) in persons with schizophrenia. Overall cancer mortality in persons with schizophrenia was 0.97 (0.91–1.03). However, in a meta-analysis based on seven studies consisting of 1 162 971 participants with schizophrenia compared with the general population, the pooled results showed increases in mortality risk of breast cancer [relative risk (RR) = 1.97, 95% confidence interval (95% CI) 1.38–2.83], lung cancer (RR = 1.93, 95% CI 1.46–2.54) and colon cancer (RR = 1.69, 95% CI 1.60–1.80) [8^{*}]. Inconsistency between findings in different studies could reflect true differences in diagnosis and treatment of comorbid cancer in schizophrenia in different samples, but differences in sampling and registration practice should be considered. In the article by Yung *et al.* [7] for example, 19.9% of deaths among patients with schizophrenia were coded as ‘unknown’, while this percentage was only 1% in the general population. Therefore, some deaths due to cancer could have been misclassified among those with schizophrenia.

In order to investigate possibilities for prevention, more studies of organ-specific cancer should be carried out, as preventive measures most likely differ between different types of cancer.

Population attributable fraction

A Danish register-based study calculated population attributable fraction (PAF) due to overall cancer in both the group of persons with schizophrenia and in the general population without a diagnosis of schizophrenia [9]. Both groups showed higher mortality rates in those with cancer compared with those without cancer, but the mortality rate ratio for those with cancer was lower within the group of individuals with schizophrenia (RR = 1.36, 95% CI 1.25–1.49) than in the general population (RR = 2.02, 95% CI 2.00–2.04). Consequently, the PAF for overall cancer – which measures the theoretical proportion of deaths that might be prevented if cancer was not present, given that other diseases and causes of death remain stable – was only 4.96% (3.73–6.17%) in schizophrenia, in contrast to 17.26% (17.12–17.40%) in the general population. Although those with schizophrenia also experienced excess mortality due to cancer, this finding suggests that diagnosed cancer plays a smaller role in mortality in persons with schizophrenia compared with the general population, simply because those with schizophrenia are already at higher risk of mortality, even if they do not suffer from cancer.

Years lost to cancer

Among people in the general population not being diagnosed with any mental illness in secondary health services, cancer is responsible for loss of life expectancy of 5.25 and 4.38 years for men and women, respectively [10]. In patients with schizophrenia spectrum disorders, the number of excess years lost to cancer compared to the general population of same sex and age is -0.04 (-0.18 to 0.09) years for women and -0.99 (-1.17 to -0.82) years for men [5^{**}]. Consequently, women with schizophrenia lose a similar amount of life due to cancer as women in the general population; however, in men, cancer reduces life expectancy by an additional year in the general population compared to those with schizophrenia. The reason for this seemingly paradoxical finding is that cancer often occurs in older age groups, and therefore might be the cause of death for patients who have survived to an older age than the average age for people with schizophrenia.

Schizophrenia and incidence of cancer

Regarding incidence of cancer, studies have identified different, partly contradicting results.

In a meta-analysis based on 16 cohort studies including a total of 480 356 participants with schizophrenia and 41 999 cases of cancer, pooled results showed a decreased overall risk of cancer incidence among patients with schizophrenia (RR = 0.90, 95% CI 0.81–0.99) [11]. However, in a recent study, based on Danish data including 5.9 million individuals, Momen *et al.* identified a slightly increased risk of being diagnosed with cancer for the first time after diagnosis of schizophrenia [hazard ratio 1.05 (1.03–1.08)] [4[■]]. A similar analysis of Swedish register-based data concluded that people with schizophrenia did not have a higher overall incidence of cancer than people in the general population [12[■]]. The Swedish study also analysed organ specific cancer and identified a higher risk for cancer in lung [incidence risk ratio (IRR) 1.42 (1.28–1.58)], oesophagus [IRR 1.25 (1.07–1.46)] and pancreas [IRR 1.10 (1.01–1.21)]. A higher risk of breast cancer [IRR 1.19 (1.12–1.26)] and a lower risk of prostate cancer [IRR 0.66 (0.55–0.79)] were found.

A 50-year follow-up study on the famous northern Finland birth cohort from 1966 found adjusted hazard ratios of 1.33 (1.01–1.74) for men and women with schizophrenia for overall cancer compared with the nonpsychotic control population, which is slightly higher than the Danish register-based estimates [13]. Due to the smaller sample size, confidence limits were considerably broader, and the estimate was nonsignificant after adjustment for multiple comparisons.

Two meta-analyses of the association between schizophrenia and breast cancer were published in 2018 and 2019. In 2018, in a meta-analysis of 12 cohorts including 125 760 women, Zhuo *et al.* [14] showed that schizophrenia was associated with a standardized incidence ratio of 1.31 (CI, 1.14–1.50). In the meta-analysis from 2019, 15 studies were identified. The analyses showed that patients with schizophrenia had a slightly higher incidence of breast cancer [IRR 1.18 (1.05–1.32)] than the general population [15[■]]. Similarly, in a meta-analysis based on 12 studies with a total of 496 265 patients, the incidence of lung cancer in patients with schizophrenia was compared with the general population. There was no significant increase in incidence rate ratio. Thus, in spite of evidence of tobacco smoking being more prevalent in most schizophrenia populations, the study could not identify an association between schizophrenia diagnosis and lung cancer incidence. As mortality by lung cancer is increased, the finding of no increase in lung cancer incidence indicates that most likely lung cancer was underdiagnosed [16].

The discrepancy between incidence of cancer and mortality of cancer could reflect that patients with schizophrenia are diagnosed with cancer in a more advanced stage, that they are less likely to receive effective treatment or that they are not diagnosed at all before death. In a recent Danish study, this discrepancy between incidence rate and mortality rate was analysed in 4924 patients with schizophrenia aged 70 years or above. It was found that the probability of having been diagnosed prior to dying from cancer was markedly reduced [odds ratio 0.38 (0.27, 0.55)] in schizophrenia cases compared with controls [17[■]]. This finding indicates that a substantial proportion of patients with schizophrenia who die from cancer have not been diagnosed or received any kind of hospital-based treatment before death. This finding also indicates that incidence rates of cancer based on hospital diagnosis for individuals with schizophrenia are likely to underestimate the true incidence of cancer. However, it should be considered if methodological issues could explain why cancer is not diagnosed before death of cancer.

A study from Denmark [18] also examined the discrepancy between incidence rates and high mortality rates in persons with schizophrenia and bipolar disorder, and found no evidence that the excess mortality was explained by more advanced stages of cancer.

One possibility is that cancer diagnosed during psychiatric inpatient stay was not formally entered into the register as a diagnosis, but if the cancer diagnosis was followed by any kind of treatment in somatic department, this type of lack of registration would not occur. Another possibility is that some types of cancer could be diagnosed and treated solely in primary healthcare settings, but this would only be the case for some rather benign types of skin cancer, and it is not probable that patients with schizophrenia would be more likely to be treated solely in primary care settings than people in the general population.

A Canadian cohort study of patients who were diagnosed with colorectal cancer showed that those with severe psychiatric illness (schizophrenia and related disorders, bipolar disorders and major depressive disorders) had significantly lower survival rates after diagnosis of colorectal cancer than patients with no history of mental illness. The patients with severe psychiatric disorders were also significantly less likely to receive guideline recommended treatment such as potentially curative surgical resection and adjuvant radiation or chemotherapy [19[■]]. A similar pattern was identified in a Danish study of 56 152 women with early-stage breast cancer. In this study, it was shown that

women with schizophrenia and related disorders were more likely not to be allocated to guideline treatment (hazard ratio 1.50, CI 1.15–1.94) [20].

This finding is parallel to the finding of reduced chances of being treated with, for example, invasive cardiac procedures after admission with acute myocardial infarction for patients with schizophrenia compared with the general population [21].

Patient's or doctor's delay

There are good reasons to explore the seemingly paradoxical difference between on the one hand the consistent finding of significantly increased mortality rates of cancer in patients with schizophrenia compared with the general population and on the other hand a weak and in some studies absent link between schizophrenia and incidence of cancer. In most populations, morbidity and mortality in cancer are expected to be associated, but in schizophrenia, this association is not so strong. There are several possible explanations. Patients with schizophrenia are more likely to develop cancer due to overlapping genetic factors and due to unhealthy lifestyle. When this expected result is not reflected in several studies, theoretically, it could be due to publication bias. However, it is unlikely that results showing no association are published more often than those showing an association. Another potential explanation, which is more likely, is that patients with schizophrenia might have reduced recognition of physical warning signs, lower level of help seeking behaviour, difficulties in breaking through barriers in healthcare services and reduced access to healthcare due to insufficient or absent insurance. The latter is not relevant for Scandinavian countries where there is tax-financed free access to healthcare. All this can be seen as patient's delay. This term is not meant as a derogatory term, but to point out that patients with schizophrenia may have more difficulties in identifying signs of illness and in ensuring proper assessment and treatment. The finding that a proportion of patients are not diagnosed with cancer before death of cancer indicates that some patients do not seek or do not have access to healthcare. The delay can also be caused by factors in the healthcare system. This could be primary healthcare doctors or psychiatrists misinterpreting discrete symptoms of cancer as signs of mental illness. It could also be lack of systematic procedures for examination of physical health indicators in patients with schizophrenia. There could also be a perception that the patient would not be likely to comply with complicated diagnostic procedures. All this could be reflected

in the finding that patients with schizophrenia receive less optimal treatment and screening than patients without schizophrenia, diagnosed with the same type of cancer. This problem was identified in the systematic review and meta-analysis by Hwong *et al.* [22], wherein they examined mammography screening for women with schizophrenia and other psychotic disorders. Overall, the women with schizophrenia only had an OR=0.50 (95% CI 0.38–0.64) for attending the screening compared with women without schizophrenia. Solmi *et al.* [23] found the same pattern for screening for cancers in schizophrenia and other nonaffective psychoses, with ORs being 0.52 (0.43–0.62) in breast cancer and 0.75 (0.60–0.93) for cervical cancer. Persons with schizophrenia were also less likely to undergo cervical cancer screening [24], and had low participation rates in lung cancer screening [25].

Causal factors related to cancer in schizophrenia

Several genetic studies have analysed whether there is an occurrence of common genetic factors in schizophrenia and cancer.

In analyses of large genome-wide association studies of schizophrenia and breast cancer, Byrne *et al.* [26[¶]] found evidence for significant but small shared genetic risk factors. They concluded that the association between schizophrenia and breast cancer is partly due to schizophrenia causally increasing risk for breast cancer [26[¶]]. In recent analyses, on the basis of a Swedish population-based cohort, Lu *et al.* [27[¶]] found a genetic correlation associated with risks of breast cancer and schizophrenia, likely to be caused by the genetic overlap between the two phenotypes and thus a shared biological mechanism [27[¶]].

With regard to environmental factors, smoking is the single most important causal factor for several types of cancer, and smoking is far more common in patients with schizophrenia than in the general population [28]. There is good evidence for the effectiveness of smoking cessation programmes consisting of behavioural support and pharmacological aids for smoking cessation for patients with severe mental disorders [29[¶]]. Yet, in a study by Irwin *et al.* [30], it was shown that among older persons with schizophrenia only one in three current smokers reported that their primary care provider or psychiatrist assisted them in obtaining medications for tobacco cessation.

Prevention of smoking in schizophrenia is likely to be influenced and maybe prevented by high prices for tobacco [31–33].

CONCLUSION

In order to prevent incidence of cancer more preventive interventions should be in place, and the single most relevant target will be smoking. Efforts to prevent start of smoking and to stop smoking should be promoted. Low rates of screening for cancers in persons with schizophrenia seem to be a particular problem that needs to be prioritized. The underdiagnosis and undertreatment of cancer in patients with schizophrenia should be targeted by systematic shared care programmes involving general practice and the secondary health sector in order to ensure assessment and diagnosis of cancer, and to ensure optimal treatment for patients with schizophrenia.

Analyses of incidence and mortality of organ-specific cancer should be carried out, and patterns of treatment, screening programmes and survival after diagnosis should be investigated. Different programmes aiming to ensure diagnosis and optimal treatment after diagnosis should be evaluated in randomized clinical trials.

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Conflicts of interest

There are no conflicts of interest.

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