

Schizophrenia and Cancer: Low Incidence, High Mortality

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Abstract

There have been disagreements in the literature about the incidence of cancer among persons with a schizophrenia diagnosis. Risk factors are prevalent in this population, but overall incidence of cancer is reported as low. By contrast, mortality from cancer among those with schizophrenia is universally held to be high. The aim of this review is to collect recent publications on this paradox in an attempt to help resolve it. The literature on the subject is vast, so that the review focuses on articles published in the last few years and covers the latest writings on the cancer protection hypothesis, uptake of cancer screening, provider issues, delays and disruptions in treatment for cancer, quality of care and mortality rates, all in the context of schizophrenia. The conclusion of the review is that persons with schizophrenia receive substandard quality of cancer care due, in part, to their psychopathology, in part to bias and stigma of care providers and, in part, to the organization of health services that isolate psychiatric care from more general medical care.

Keywords: Severe mental illness; Psychopathology; Screening; Quality of cancer care

Introduction

Questions about the incidence of cancer in persons with serious mental illness have, over the years, received different answers. There is credible epidemiological evidence that schizophrenia and related disorders (or their treatment) protect against cancer, but there is other work showing a heightened risk due to lifestyle (high rates of cigarette smoking and substance abuse) and to treatment effects (weight gain and elevated prolactin levels).

There are, of course, many kinds of cancer, each susceptible perhaps to different triggers and there are many variations of psychotic illness, each perhaps exerting its own impact on lifestyle and cancer risk. Moreover, there are major difficulties in the ascertainment of cancer in the context of psychosis

because of poor health monitoring, unclear subjective complaints, uncertain family histories, diagnostic overshadowing, and low rates of routine cancer screening.

Current thinking is that, despite differences attributable to age, gender, severity of psychosis, smoking habits, body mass index, substance abuse, diet, physical activity, medication, and co-morbidity, the incidence of cancers of all types in schizophrenia is essentially equivalent to that of the general population, but cancer mortality is significantly higher. Importantly, the cancer mortality gap between schizophrenia patients and age peers appears to be increasing with time [1], making this a critical area of study.

A preliminary scan of the literature suggests that the principal explanation for the high cancer mortality in chronic psychotic illness is the comparatively poor quality of medical care this population receives, a consequence of the lack of 'parity of esteem' with respect to physical and mental illness [2]. In other words, for many reasons, the medical care received by persons with severe mental illness is thought to be inferior to that received by others, and this appears to be true in all countries where this question has been addressed.

Methods

This narrative review explores the incidence/mortality paradox in schizophrenia based on recent publications. The review is divided into the following subsections: the schizophrenia cancer protection hypothesis, uptake of cancer screening in schizophrenia, provider issues, delays and disruptions in treatment for cancer, quality of care, mortality rates and discussion/conclusions.

Review Findings

Schizophrenia cancer protection hypothesis

There is epidemiological evidence that, while some cancers such as breast cancer are more prevalent within the schizophrenia population than elsewhere, most other cancers are less prevalent, a seeming paradox in light of heightened risk factors and also in light of the high cancer mortality in this population [3]. The overall lower incidence of cancer in

schizophrenia may only be true for men, probably because of the high rates of breast cancer in schizophrenia women. A 2017 study of over two million Israeli men and women aged 25-74, among whom 32,748 had received a diagnosis of schizophrenia, showed that all types of cancer were significantly lower in men with schizophrenia than men without schizophrenia but that the prevalence of cancer in women with schizophrenia was, to a slight degree, higher than in other women [4].

The relative protection also depends on age. A study from Taiwan showed that cancer risks in schizophrenia patients were significantly lower than in the general population only for cancers that develop in older age -e.g. stomach, pancreas, and prostate cancer. In contrast, cancer risks were higher than in the general population for cancers with a younger age of onset e.g. nasopharynx and uterus [5]. Because of an overall increase in mortality rate in schizophrenia attributable to cardiovascular disease and suicide [6] the former is probably hastened by antipsychotic treatment whereas the latter is reduced by treatment [7], persons with schizophrenia die 10 to 25 years earlier than their peers and, thus, before the appearance of late onset cancers [8].

A 2017 meta-analysis of 16 cohort studies detected a small but significant decrease in overall risk of general cancer incidence among all patients with schizophrenia, with a significantly decreased incidence rate of colorectal cancer and prostate cancer in men but a paradoxically increased rate of lung cancer in women [9].

Importantly, the general reduction in cancer risk has been demonstrated not only in schizophrenia patients but in their siblings and parents as well [10,11], suggesting the involvement of genetic protective factors, thought to be genes mediating oxidative stress, DNA damage and DNA repair [12,13]. The simplified genetic protection hypothesis can be summed up in the following way: a common set of genes and biological processes are deregulated in opposite directions in schizophrenia and cancer [14]. Protection theories of this sort are popular because they provide an explanation as to why schizophrenia has persisted over the course of evolution in the face of low levels of fitness [15].

Reduced incidence of cancer in schizophrenia has also been explained in non-genetic ways. Because of a sedentary and essentially indoor lifestyle, individuals with schizophrenia are relatively protected from environmental cancer-inducing exposures such as pollutants, X-Rays, and excessive sunshine [15]. In line with this thinking, schizophrenia expert, Torrey [16], has hypothesized that the reduced rate of age-standardized prostate cancer in men with schizophrenia could be due to a decreased opportunity for heterosexual intercourse.

Undiagnosed cancer in this population is yet another explanation since many patients with schizophrenia avoid medical services [17]. Furthermore, it has been proposed that the antipsychotic drugs used to treat schizophrenia may have cancer-preventive properties [18,19].

Cancer screening

Comparative uptake of cancer screening could explain increased mortality in the face of a relatively low incidence rate. Screening is less frequent than expected in the schizophrenia population, which results in later diagnosis and more advanced cancer stage at the time of diagnosis [20-22]. The more severe the mental illness, the lower the screening rate. More specifically, cancer screening has been shown to be significantly reduced in schizophrenia in the US and Canada for cancer of the cervix [23-25], and for breast cancer [26,27].

The main barriers to cancer screening in this population have been identified as: apathy, lack of accurate knowledge about the purpose of screening and poor access to screening, practical issues of transportation and lack of reminders, patients' cognitive challenges, and patients' negative experiences with screening [28-33]. Poor communication and collaboration between service user and health provider has often been pointed to as the root cause of low screening rates [34,35].

Provider issues

An important provider issue that may help to explain late diagnosis is 'diagnostic overshadowing' whereby the symptoms of one illness conceal or overshadow the symptoms of another. When patients with schizophrenia present with physical complaints, care providers may, for instance, attribute the complaints to delusional thinking [36,37] and dismiss them. It has been shown that physicians spend relatively little time with their severely mentally ill patients [38]. This may be because they disapprove of their patients' unhealthy choices (smoking, substance abuse, overeating). Physicians may also dislike the fact that severely mentally ill patients are often late for appointments, forgetful, disruptive or uncooperative, noisy, disheveled, badly groomed, uninsured, and mistrustful [34,39].

During examination, people with schizophrenia are less likely than healthy controls to spontaneously report physical symptoms because of reticence and suspiciousness or because of cognitive impairment, or lack of social communication skills, or because of reduced pain sensitivity attributable to antipsychotic medication [40,41]. In addition, primary care physicians may underestimate the decisional competence of patients with schizophrenia or their ability to adhere to treatment protocols or to maintain healthy behaviors [42]. They may, therefore, offer them few choices. It is a fact that patients with a severe mental illness report significant problems communicating with their doctors [43].

Provider issues interact with patient and system-level factors (the separation of physical health and mental health facilities) to increase the risk of substandard care provision to people with serious mental illness.

Delays and disruptions of treatment

Although poor cancer outcomes in this population have been attributed to the many risk factors, the prevalence of comorbidity, the lack of preventive measures and the low rates

of screening and the diagnostic delays, a recent Finnish study found that factors following diagnosis rather than preceding it are to blame for the bulk of poor outcomes [44]. Further results of this study were that the mortality gap between patients with psychosis and cancer patients without SMI appeared to be increasing over time due to post-diagnosis factors. This can be explained in a number of ways. The negative symptoms of schizophrenia (apathy, isolation, cognitive difficulty) make it difficult for patients to understand and cooperate with cancer treatment [45]. The cognitive difficulty and also the lack of social support contribute to poor adherence to cancer treatment [46]. Patients with severe mental illness in general show poor self-management skills; they may also harbor delusions. For instance, they may so strongly believe that God will cure them that they prematurely stop treatment [47].

Disruptions of treatment are commonplace in this population. At one academic health centre, half the patients with schizophrenia who had breast cancer suffered at least one breast cancer care disruption in stage-appropriate treatment. What was striking in this study was that disruptions robustly predicted cancer recurrence at 5 years. The main risks for disruptions were the following: not having a psychiatrist, not taking antipsychotics, and a psychiatric hospitalization occurring after the diagnosis of cancer [48].

A United States retrospective cohort study of 16,636 older women (68 years and over) with stage I-IIIa breast cancer found that those with any mental illness diagnosis experienced an increased risk for chemotherapy delay of ≥ 90 days post-surgery. Those with severe mental illness were at especially high risk for treatment delay [49]. Farasatpour et al. [50] report that women with schizophrenia often deny their breast cancer symptoms, which means that the cancer reaches an advanced stage by the time of diagnosis. After diagnosis, many of the women continue to deny the reality of cancer and often refuse therapy. While these investigators found distant metastases in 21% of schizophrenia women at the time of diagnosis, another 25% of women developed metastases after diagnosis because of treatment delays or refusals.

For any cancer, patients with schizophrenia have been found less likely than the general population to ever receive chemotherapy or radiotherapy or, for that matter, to access palliative care [34].

When social workers who work closely with severely mentally ill patients were asked for potential reasons why cancer care is often delayed in this population, their view was that their patients' cancer-related concerns were habitually discredited. They attributed this to the compartmentalization of mental and physical health care [51].

Quality of care

Not only are there disruptions and delays and gaps in treatment, but the quality of care offered to patients with psychosis is often below par. Mateen et al. [52], in a retrospective study, found that patients with pre-existing schizophrenia who developed lung cancer were prescribed less

aggressive therapy than others at the same stage of cancer. After thorough investigation, these investigators determined that the reason was not bias or mental illness stigma. State of the art treatment was withheld because of concurrent pulmonary disease or infection, or because patients refused, or because their psychotic symptoms rendered certain treatments impractical, or because some of the patients were disoriented and, thus, unable to co-operate with treatment. A nursing study found that patient factors (psychopathology, cognitive and communication difficulties), health system factors (fragmentation of care, unequal access to care) and provider bias all undermined quality care for seriously mentally ill patients [53]. Druss, who is a leader in this field, has attributed both low levels of primary care utilization and the provision of poor quality of medical care to psychiatric patients to barriers erected by patients, providers, and health systems [54].

Mortality

A 2017 meta-analysis of 19 studies of cancer mortality in schizophrenia [55] concluded that patients with schizophrenia were at a significantly increased risk of cancer mortality compared to the general population. Iglay et al. [56] found the mortality rate from breast cancer in women with severe mental illness was 20% higher than that of women without mental illness after adjusting for age, income, race, ethnicity, geographic location, and marital status. They found that cancer in these women was already advanced at the time of diagnosis and that their tumors grew aggressively after diagnosis. They also found increased tobacco use and more comorbidities among these women, which could help to account for an overall two-fold increase in all-cause mortality risk.

An earlier study from France [57] had found a four-fold higher mortality rate in schizophrenia, with cancer being the second most common cause of death (after cardiovascular disease). For all cancers, the mortality risk was slightly higher in men with schizophrenia but almost twice as high in women, breast cancer showing a 2.8 higher risk of mortality over the general population of women. Men with schizophrenia were more likely than average to die from lung cancer, probably attributable to smoking. In a large Veteran Affairs study specific to lung cancer outcomes, and controlled for age, gender, smoking status, marital status, service connection, homelessness status, and presence of a substance use disorder, the hazard ratio of all-cause mortality for those with schizophrenia and lung cancer was 1.33 [58].

Kisely et al. found a 2.27 hazard ratio for psychiatric patients' mortality rates and attributed it to potential inequity in accessing specialist services [59]. Other explanations for the higher mortality from cancer among psychiatric patients (despite equal or lower incidence) are: low rates of routine cancer screening, the increased length of time it takes to be diagnosed after presenting with symptoms, the more advanced cancer stage at diagnosis and the reduced likelihood (compared to those without mental illness) of surgical intervention. Interestingly, for men diagnosed with prostate

cancer through prostate-specific antigen screening who then underwent treatment with external beam radiation, a concurrent psychiatric diagnosis had no effect on outcome, which suggests that the removal of screening and treatment barriers reduces the survival disparities of psychiatric patients, at least in the case of prostate cancer [60].

There are noteworthy gender differences in cancer mortality in this population. In women, 8% of lost life years are attributable to cancer whereas, in men, cancer does not appreciably affect the duration of life [61].

Although late diagnosis probably plays a part in the increased mortality from cancer [62], the relatively poor survival of people with severe mental illness is most likely accounted for by disparities occurring after cancer diagnosis rather than by a delay in diagnosis [63].

Discussion and Conclusion

This review has highlighted medical disparities in the treatment of persons with serious mental illnesses. Treatment differences have been documented in all regions of the world where this phenomenon has been studied [64]. A diagnosis of schizophrenia reduces life expectancy for many reasons. There are firstly the health constraints imposed by financial deprivation. The social withdrawal that is part of schizophrenia further reduces opportunities for active participation in physical activities, resulting in an essentially sedentary life. Apathy, lethargy and cognitive problems, all commonly seen in schizophrenia, serve as obstacles to healthy eating habits. Many persons with schizophrenia are socially isolated and estranged from family and friends, which means that they are under-exposed to public health messaging. Antipsychotic medication, the standard treatment for schizophrenia, increases the risk of obesity and further reduces physical activity. Perhaps to counter the side effects of medication, people with schizophrenia tend to smoke more than others and use alcohol more than others. As noted earlier, antipsychotic drugs also lead to hyperprolactinemia, although a recent study and a recent review paper exonerate prolactin [65,66] from responsibility in the high rate of breast cancer in women with schizophrenia [67]. The low uptake of cancer screening can be attributed to social isolation, constricted social networks and apathy, all characteristic of schizophrenia, even psychiatric disease less severe than schizophrenia has been shown capable of negatively impacting cancer patients [68]. On the provider side, clinicians spend relatively little time with severely mentally ill persons. Moreover, they tend to dismiss many of the complaints of people with psychosis as being fanciful or delusional. Most importantly, there is documented evidence of substandard cancer care, which inevitably leads to poor outcomes.

This review ends on the recommendation that systematic physical health monitoring be mandatory for people with serious mental illness. Patients with schizophrenia and related illness need to be informed about health risks and guided/encouraged in their diet, activity, smoking/alcohol, and health screening choices. Physicians need to pay special attention to

this group of patients, and medical and psychiatric treatment services need to be better integrated. Only then will the high mortality rates from cancer in this population be reversed.

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