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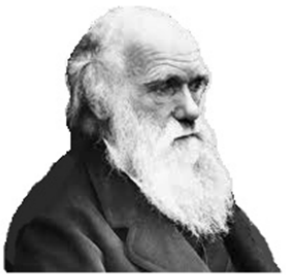

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A review on cancer treatment and the risk developing severe mental illness

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ABSTRACT

Cancer, the second primary cause of death for patients with serious mental illness (SMI) continues to be responsible for over 14 million new cases and approximately 8 million cases annually. Delays in diagnosis and unequal access to cancer care contribute to cancer mortality that is two to fourfold higher in people with SMI than in the general populace. Severe mental illness is an emotional, mental and behavioural disorder leading to a serious impairment and ultimately has major effect of life activities. Patients with the history of severe mental illness are at high risk of incurable cancer via a number of factors including overshadowing of diagnosis, low socioeconomic level and fragmented healthcare. Likewise, individual diagnosed and undergoing cancer therapy are prone to develop mental illness as an aftermath of chemotherapy. Averagely, patients with serious mental illness, for example bipolar disorder and schizophrenia, die 15-20 years earlier than the general populace, and thus widening the mortality gap. The primary causes of death for this population include cancer and cardiovascular disease, signifying that access to appropriate and timely precautionary services could help decrease untimely deaths. Also, severe mental illness can be effectively managed with increased access to mental-based treatment services to reduced related morbidity. Therefore, having a better understanding of subjects regarding early detection of cancer, mental health treatment/management and the association between these, could have a significant step in detecting possible causes of early mortality in patients with SMI.

***Keywords*:** Cancer, Severe mental illness, Global burden, mortality, chemotherapy, Neurologic complication, Neurotransmitters

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INTRODUCTION

The association between a severe mental illness (SMI) and worse cancer survival has received less attention than other physical diseases, although physical illness is the leading cause of death among people with mental health disorders (De Hert *et al*., 2011). Individuals with an SMI likely have a similar cancer burden, yet higher than expected case-fatality rates (Weinstein *et al*., 2016; Kisely *et al*., 2016). The majority of evidence supporting this conclusion is based on a comparison of mortality rates in individuals with a mental illness to a non-mental population, rather than in relating survival within cancer populaces or is hindered by low study-power and inappropriate regulation for intermediate variables on the causal pathway. Multiple cancer sites are sometimes grouped together in order to get an adequate sample size, despite the high probability that cancer related prognosis is likely not uniformly worse across cancer sites (Kisely *et al*., 2016; Sun *et al*., 2015 and Davies *et al*., 2019).

Studies also control for many variables that make up the constellation of factors contributing to vulnerability, such as socioeconomic status, which may underreport the magnitude of association (Kisely *et al*., 2013). Changes in cancer survival could be described by the non-receipt of guideline-coherent cancer treatment. Though understudied, there is indication of disparities in cancer care given to individuals with an SMI across the cancer continuum, from screening to palliative care, case reports, opinion pieces, review articles and case series form an important part of the literature on the basis of cancer care recommendations for individuals with an SMI (Weinstein *et al*., 2016, and Abdullah *et al*., 2015).

A small amount of research has been performed to understand if individuals with an SMI are more likely to receive suboptimal oncology care (Lin *et al*., 2016, and Safdieh *et al*., 2015) or investigated specific barriers to providing cancer care to individuals with a serious mental illness (Sinding *et al*., 2013). These studies consistently document the suboptimal cancer treatment of individuals with an SMI and cancer. Few have investigated treatment for a single cancer site within the context of clinical guidelines (Bergamo *et al*., 2014), which limits the interpretation and application of the study results to clinical practice. Clearer evidence around potential cancer care disparities for individuals with an SMI is needed to form the basis of clinical management and health policy reform (Safdieh *et al*., 2015). This review aims to investigate the association between an SMI and the risk of cancer development.

Cancer Incidence and Global Burden

Cancer is a common malady affecting approximately 30 percent of the population before the age of 75 in countries located in Northern Europe and likewise, globally, it is the second most common cause of death (Engholm *et al*., 2016; Badru *et al*., 2019). In economically developing countries, cancer burden is increasing due to population growth, aging as well as increase in the adoption of cancer-related lifestyle, for example physical inactivity, smoking and ‘‘westernized’’ diets (Ferlay *et al*., 2008; Kanmodi *et al*., 2019; Adesina, 2020; Hamzat, Kanmodi and Adesina, 2020).

Cancer is a major cause of mortality and morbidity globally, with about 14 million new cases and eight million deaths in 2012 (Ferlay *et al*., 2010). The large burden is estimated to increase, with an expected 22 million new cancer cases and 13 million cancer-related deaths occurring each year by 2030 (Ferlay *et al*., 2010). This increasing cancer magnitude is a result of the population age, growth while economic, societal and lifestyle changes associated to

increase in human development are possible to be additionally factor to an increase scale and modify cancer profile in the next decades.

Cancer which is a heterogeneous mix of diseases with different types of cancer more common in some populations than in others, sometimes substantially so (Badru *et al*., 2019); with very different causes, in which some are well understood while some are poorly understood, and differences in the temporal and regional distribution of risk factors will define the geographical and secular patterns of cancer (Tokarz and Blasiak, 2014). Thus, many barriers exist to the understanding of global patterns of cancer—the availability of information about disease incidence and mortality, an understanding of the underlying causes and how these can change, and knowledge of the demographics of populations in terms of size and age structure (Polk and Peek, 2010).

Global action is needed to stem the increasing burden of non-communicable diseases, especially in low income and middle-income countries (Adams *et al*., 2010; Adesina *et al*., 2021) which now bear 80% of the worldwide burden of such diseases (Badru, 2019). Cancer, confirmed leading cause of death in several high-income countries, is set to become the main cause of morbidity and mortality in the next few decades in all regions of the world, regardless of the level of resource (Jemal *et al*., 2011). The UN has forecast that the global population will reach 7 billion by 2012 and 8.3 billion by 2030. The effect of population ageing and growth will be the greatest in low-income and middle-income countries. These modifications translate to an expected global burden of 20.3 million new cancer cases by 2030 relative to an expected 12.7 million cases in 2008, and a projected 13.2 million cancer-associated deaths globally by 2030, up from 7.6 million in 2008 (Ferlay *et al*., 2010). Such a demographic change and the subsequent increase in cancer incidence and mortality rate are contingent on population predictions that assume decreases in population growth and human fertility due continuous economic and social development, (Myrskyla *et al*., 2009) and on incidence and mortality rates of all cancer types combined remaining unaltered over the next few decades.

The fixed trends in cancer risk in future decades appear the less robust of the two assumptions, particularly in view of the cancer-specific mortality and incidence trends observed over the past half century (Varan and Kebudi, 2011). Rather than demonstrating constant rates over time, various reports have reported lagged variations in lung and other tobacco-associated cancers in relation to the sex-specific and country-specific phases of the tobacco epidemic, even decreases in stomach cancer due to major prevention efforts, and an increasing frequency of prostate, colorectal and breast cancers, initially in affluent populations and within the last couple of decades, in historically less-affluent populations at lower cancer risk (Lacour *et al*., 2014). The changes can be attributed to a combination of adverse changes in various ill-defined dietary, reproductive, hormonal, metabolic and other behavioural factors capable of increasing the risk of these cancers.

Establishing the incidence of cancer in patients with severe mental illness requires large population based studies that link mental health databases to cancer registers to identify sufficient numbers of patients with new cancers. Several such studies are available and a review of physical illness in schizophrenia included 17 cancer studies from developed countries, published between 1966 and 2006 (Leucht *et al*., 2007).

Overview on Cancer Development

Cancer was illustrated for the first time by Hippocrates as ‘karkinos’. Galeno introduced the term neoplasia only in the II century; he defined it as the growth of a body area averse to

nature (Gutiérrez and Salsamendi, 2001). Carcinogenesis is a complex process described by the progression of different molecular changes that eventually transform and reprogram a cell to undergo unregulated cellular division (Loeb and Harris, 2008). During the last fifty years, research has uncovered innumerable critical molecular players and targeted pathways, and highlighted the underlying balance of aberrant activation of proto-oncogenes and inactivation of tumor suppressor genes. With each disruption, cells undergo changes fundamentally represented by tumor initiation, promotion and progression (Tokarz and Blasiak, 2014).

Tumor initiation is a swift and irreversible process starting from an exposure to a carcinogenic agent, followed by its transportation and distribution to neighbouring tissues leading to non-lethal mutations in cellular DNA. These "initiated cells" begin to accumulate additional irreversible genetic changes which persist with each new cycle of proliferation (Barcellos-Hoff *et al*., 2013). Functionally, initiated cells are more immune to inhibitory signals mediated by cell differentiation inducers and negative growth regulators (Quail and Joyce, 2013).

Tumor promotion involves the selective clonal expansion and proliferation of initiated cells allowing for additional mutations to accumulate. In contrast to initiation, tumor promotion is a relatively lengthy and reversible process in which actively proliferating pre-neoplastic cells begin to divide and propagate. Tumor progression, the final stage of neoplastic transformation, occurs after these mutations result in an invasive cellular phenotype with metastatic potential (Barcellos-Hoff *et al*., 2013). Advances in tumor development and progression understandings reveal that each step constitutes highly variable and intricate systems. For instance, epigenetic changes of tumor suppressor genes through DNA methylation in pre neoplastic tissues may result in accelerated carcinogenesis (Aoi *et al*., 2014).

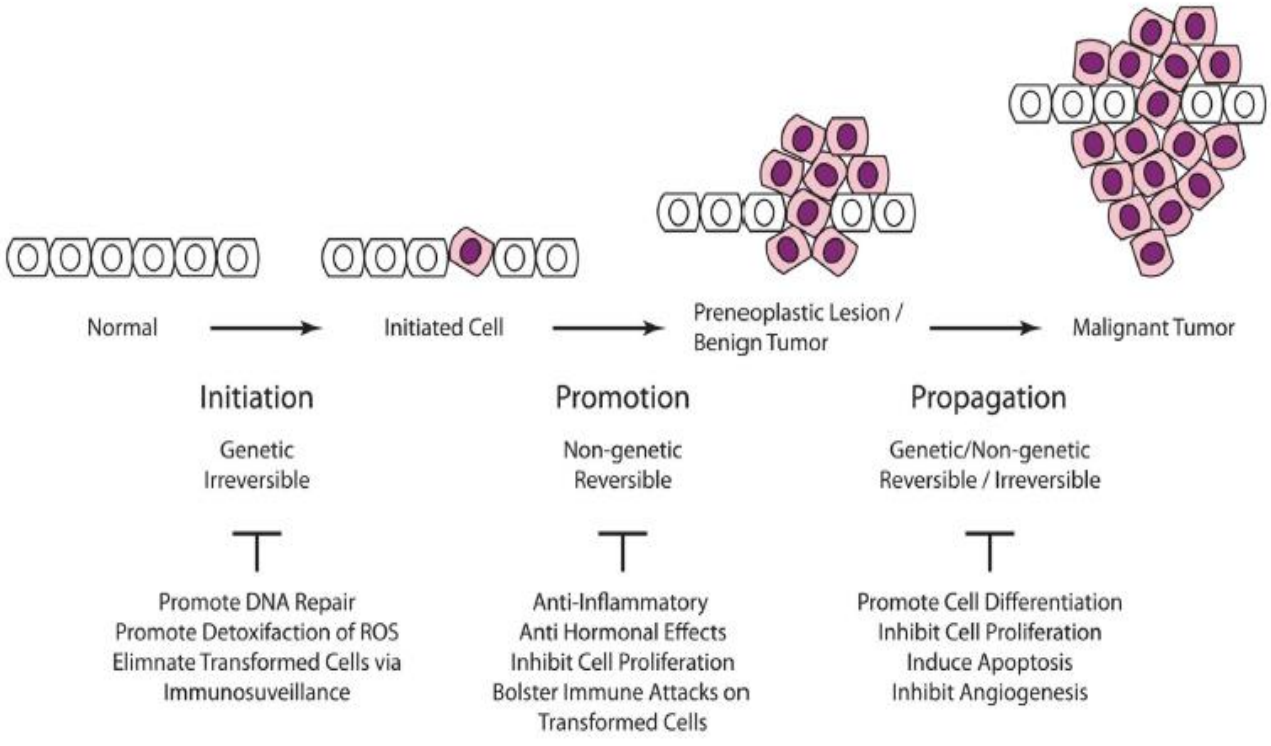

Figure 1. Mechanism of Cancer Development (Sapienza and Issa, 2016)

Neurologic Complications of Cancer Treatment

Radiation therapy (RT) and chemotherapy both can exert dose-dependent adverse effects on the central or peripheral nervous systems which often interact (Vigliani *et al*., 1997). RT can have both acute and delayed effects, and has been associated with necrosis and leukoencephalopathy, a pathology of white matter (WM), which are the presumed substrates for cognitive impairment. Most early reports were unable to separate the effects of chemotherapy from the known adverse effects of cranial RT. Posner (1995) described several relatively nonspecific clinical pictures of neurologic complications of chemotherapy, including acute encephalopathy, cerebrovascular stroke-like episodes, delayed development of a chronic encephalopathy with a subcortical type dementia (apathy, cognitive/memory loss, frontal features, sleep disorders, incontinence, gait disorders, and possible seizures), as well as cerebellar syndromes.

One common finding in clinical reports of neurologic complications of chemotherapy is toxic leukoencephalopathy (Filley, 1999). Cerebral WM is vulnerable to many neurotoxins, and with the wide availability of magnetic resonance imaging (MRI), there is increased recognition of WM changes. Leukoencephalopathy has been reported in patients with leukemia, lymphoma, and after immunosuppressive drugs. There may be multifocal areas of demyelination, surrounded by abnormal glia and other pathologic features such as inclusion bodies in glial cells.

Neurotoxic Mechanisms in Chemotherapy

Many chemotherapy agents are highly neurotoxic, with frequent adverse effects that depend on the specific agents, combinations, and dosages. The specific neurotoxic effects of most chemotherapy agents in isolation, and particularly in interactive combinations, have not been studied experimentally in detail in human trials or with animal models. Many investigators initially thought that antineoplastic agents had little ability to penetrate the blood–brain barrier (BBB) (Troy *et al*., 2000). However, more recent studies have indicated higher concentrations in cerebrospinal fluid (CSF) and brain tissue than previously expected. Although the specific pathophysiological mechanisms leading to cognitive and memory deficits are not well understood, 3 major non-exclusive mechanisms have been hypothesized, and these are:

(1) direct neurotoxic damage to the cerebral parenchyma, such as the neuronal axons, oligodendrocytes and microglia, producing altered or demyelination water content
(2) secondary inflammatory response, an immunologic mechanism, for example autoimmune vasculitis and allergic hypersensitivity, and
(3) microvascular injury resulting to blockade of small and medium-sized blood vessels, ischemia/ infarction, spontaneous thrombosis and parenchymal necrosis.

Altered neurotransmitter levels, particularly brain amines, and metabolites can constitute an additional mechanism related to neurotoxic effects (Madhyastha *et al*., 2002).
Indirect chemical toxicity and oxidative damage are other potential mechanisms (Barton and Loprinzi, 2002). Along these lines, based on MR spectroscopy data, Brown *et al*. (1995) suggest that chemotherapy-induced WM disease is predominantly a water space and perhaps extraneuronal process. There are clearly numerous and probably related pathophysiological mechanisms that could account for various aspects of the neural substrate of chemotherapy-induced cognitive impairments.

Glucocorticosteroids

Glucocorticosteroids are widely used in cancer therapy, including in patients with brain tumors, and in adjuvant therapy for other tumors, including lymphoma, in part as a result of immunosuppressive activity. Glucocorticosteroids appear to reduce capillary permeability of the BBB and to reduce cerebral blood flow (CBF). Cognitive and affective side effects are common. They act at the receptors in the hippocampus and are involved in memory deficits following chemotherapy and in major depression, Alzheimer's disease and Cushing's syndrome (Martigoni *et al*., 1992). There is evidence of reduced hippocampal volume in these conditions, and glucocorticoid-mediated excitotoxicity is one hypothesized mechanism. An intriguing study in normal young men suggests that corticosteroid effects on memory might be memory system-specific. Lupien *et al*. (1999) found that working memory was more sensitive than episodic memory or arousal/ vigilance to hydrocortisone infusion. There is also evidence of sex differences in glucocorticoid influences in the hippocampus, indicating a need for studies of both males and females.

Cytokines

Cytokines are non-antibody proteins that are released by activated immune cells after exposure to an antigen that can exert antiviral activity. CNS infections, inflammatory processes, and autoimmune and degenerative brain disorders have neuropsychologic consequences ranging in their nature and severity. Animal studies have suggested that cytokines can play an important role in man brain disorders, but the specific mechanisms are unclear. There is evidence that proinflammatory cytokines are involved in bloodborne and neural signaling in the brain and can influence neural activity (Maier and Watkins, 2003).

Available data on the effects of cytokines and other immunotherapy for cancer data document adverse effects on cognition and affect (Meyers, 1999) Interleukin-2, a cytokine used to boost immune response in cancer therapy, has been associated with leukoencephalopathy in at least one case report. Capuron *et al*. (2001) studied cognitive changes in patients with cancer treated with interleukin-2 and interferon-alpha. Patients treated with interleukin-2 showed impaired spatial working memory and decreased planning skills.

Those treated with interferon-alpha did not show deficits in accuracy but had longer response latencies on a reaction time test. Of direct relevance to neuropsychologic deficits, there is evidence that cytokines in the hippocampus can disrupt memory consolidation (Maier and Watkins, 2003). Consistent with reports in patients with cancer, a recent study in healthy human volunteers by Reichenberg *et al*. (2001) used low-dose endotoxemia to stimulate host defenses and found adverse effects on verbal and nonverbal memory and emotion that were interpreted as related to cytokine release.

In addition, these authors reported significant correlations between cytokine secretion and anxiety, depression, and decreased memory. In fact, there is a considerable recent evidence for elevated risk of depression in patients undergoing treatment with recombinant cytokines for cancer and viral infection (Capuron and Dantzer, 2003). Although the mechanism is uncertain, Capuron and Dantzer (2003) suggest that tryptophan depletion could represent an important mediator for the development of depression following cytokine therapy.

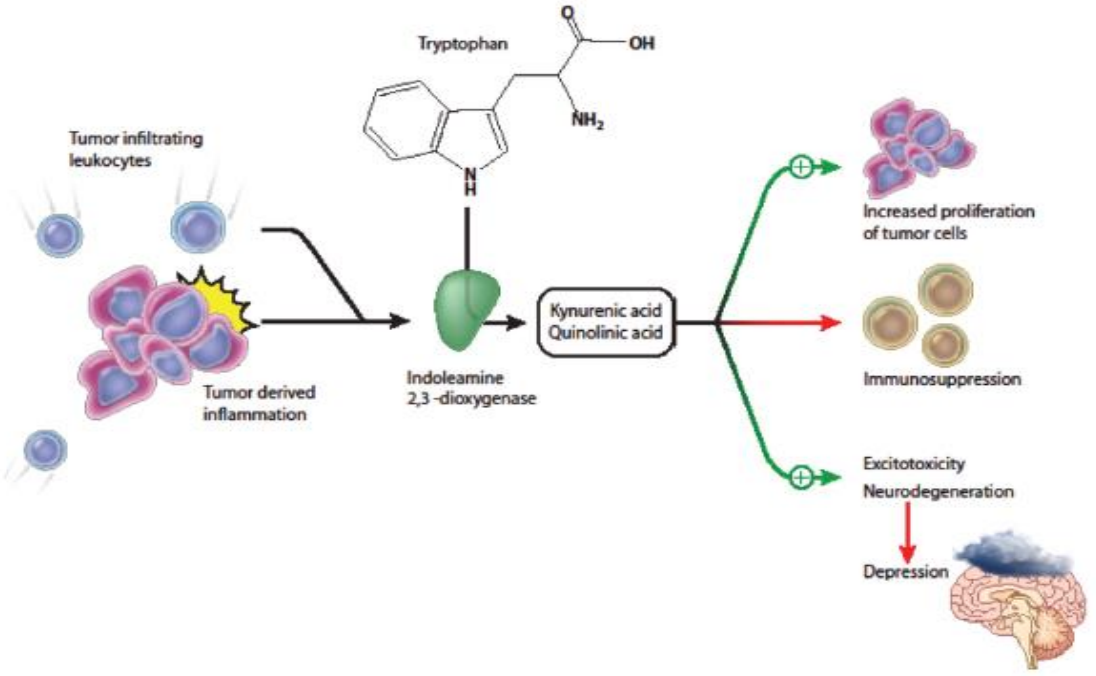

Figure 2. Tumour-related inflammation metabolites induces neural excitotoxicity and neurodegeneration (Mihaela *et al*., 2014)

Neurotransmitter Metabolism

In the brain, monoamine neurotransmitters have been shown to play significant roles in mood control. Of the several monoamines, for example norepinephrine, dopamine, serotonin (5 hydroxytryptamine, 5-HT) has possibly garnered the most consideration, specifically with broad selective serotonin reuptake inhibitors (SSRIs) that have emerged as anti-depressants. Tumor- initiated cytokines are capable of dysregulating serotonin synthesis through their ability to activate the enzyme indoleamine 2,3-dioxygenase (IDO). Widely distributed in the brain, kidneys, lungs, and immune cells, IDO has been found to be overly expressed in a variety of different cancers (Leonard, 2017, and Bortolato, 2017). IDO transforms tryptophan which is the primary amino acid precursor of serotonin into kynurenine (KYN). The consequences of IDO activation are twofold: (a) decreased levels of tryptophan, resulting in serotonin deprivation; and (b) activation of the KYN pathway, the process whereby KYN is converted into neurotoxic metabolites (Miller *et al*., 2009, and Bortolato, 2017).

In astrocytes, KYN is converted to kynurenic acid (KYNA) whereas it is preferentially converted into quinolinic acid (QUIN) in microglia (Bortolato, 2017). QUIN is an effective N-Methyl-D-aspartate (NMDA) receptor agonist, leading to excess release of glutamate, astrocyte apoptosis and oxidative stress, all of which result to neural excitotoxicity and neurodegeneration related to depression (Leonard, 2017; Currier and Nemeroff, 2014).

Overview of Severe Mental Illness

The term mental illness denotes all diagnosable mental disorders, characterized by persistent, abnormal changes in mood, behavior or thinking related with impaired functioning

and distress (Lawrence *et al*., 2013). Related to other diseases, mental illness is severe in some cases and can be mild in others. There are many different mental illnesses, including depression, schizophrenia, attention deficit hyperactivity disorder (ADHD), autism and obsessive-compulsive disorder. Each illness changes a person's feelings, thoughts and/or behaviours in distinct ways. Not all brain diseases are categorized as mental illnesses. Disorders such as epilepsy, Parkinson's disease, and multiple sclerosis are brain disorders, but they are considered neurological diseases rather than mental illnesses (Weinstein *et al*., 2016).

Mental illness is an important domestic and global public health problem because the condition it is associated with other chronic diseases, further increasing their morbidity and mortality. According to the World Health Organization (WHO), mental illness accounts for a number of disabilities in the developed countries than any group of illnesses, for example heart disease and cancer (Adesina, 2020). In adults, mental illness leads to significant occupational impairments, (Reeves *et al*., 2011) heightened morbidity, and premature mortality from concurrent chronic diseases. Mental illness may further increase the risk for adverse health outcomes associated with cardiovascular disease, diabetes, obesity, asthma, epilepsy, and cancer (El-Gabalawy *et al*., 2010) owing to lesser use of medical care and treatment adherence and concomitant abuse of tobacco and alcohol products (Levinson *et al*., 2008, Adesina *et al*., 2019).

Figure 3. Diagram showing Severe Mental Illness

Severe mental illness is defined by the National Institutes of Mental Health (NIMH) as "a mental, behavioral, or emotional disorder resulting in a serious impairment, which substantially interferes with or limits one or more major life activities (Olufadewa and Adesina, 2020). Severe mental illness affects approximately 4% of adults and approximately 21% of adolescents in the United States annually (Olufadewa *et al*., 2020). The prevalence of mental illness worldwide is thought to be around 25% in both developed and undeveloped countries

(Badru *et al*., 2019). Mental disorders are characterized by fundamental and characteristic distortions of thinking and perception, and an inappropriate or lack of emotional responsiveness. Clear consciousness and intellectual capacity are usually maintained, although certain cognitive deficits can develop over time.

Delusions and hallucinatory voices discussing the patient, disorganized speech, and negative symptoms (marked apathy, paucity of speech, and blunting or incongruity of emotional responses, usually resulting in social withdrawal and lowering of social performance) can occur (Adesina, 2020). Bipolar disorder is characterized by two or more episodes where the patient's mood and activity are substantially disturbed, on some occasions mood is elevated, energy and activity increased (mania or hypomania) and others mood is lowered and energy together with activity is decreased (depression). Repeated episodes of mania or hypomania only are classified as bipolar disorder (Badru *et al*., 2019).

Association Between Severe Mental Illness (SMI) And Cancer Prevalence

Cancer incidence has been reported to be largely the same in individuals with and without SMI, despite considerable life style differences between these two groups (Chang *et al*., 2014; Kisely *et al*., 2016; Laursen *et al*., 2014). In contrast, mortality rates from cancer in individuals with SMI are higher (Chang *et al*., 2014; Kisely *et al*., 2016).

People with severe mental illness (SMI), such as schizophrenia and bipolar affective disorder, have higher rates of morbidity and mortality (Liu *et al*., 2017). With that, the life-expectancy is 10–20 years lower than the general population (Lawrence *et al*., 2013; Liu *et al*., 2017), although incidence rates of some cancers, including prostate and colorectal cancer are similar between people with and without SMI (Kisely *et al*., 2008). Given the similar incidence rates, differences in risk factor prevalence (smoking, alcohol consumption, obesity) are less likely to be the cause of higher cancer mortality in those with SMI. One explanation might be that people with SMI present with more advanced cancer at diagnosis or receive less cancer-directed treatment, which could be due to either diagnostic delays, poorer access to cancer services or lower participation in cancer screening programmes (Kisely *et al*., 2013).

Prior studies have investigated particular types of cancer screening in people with SMI, but these were mostly conducted in specific populations and results may not be broadly generalizable (Howard *et al*., 2010). Furthermore, some studies used self-reported participation in screening, which may not be optimal in this population (Fujiwara *et al*., 2017; Howard *et al*., 2010, and Siantz *et al*., 2017), while others had no comparison group (Howard *et al.,* 2010; James *et al*., 2017).

The effect of cancer stage on mortality in people with SMI compared to those without SMI has, however, shown conflicting results. Four studies found decreased survival after cancer diagnosis in individuals with SMI compared to individuals without SMI, and no effect was found on survival difference when adjusting for cancer stage (Chang *et al*., 2014; Manderbacka *et al*., 2017). In contrast, Cunningham *et al*. found stage to be an important contributor to decreased survival in individuals with SMI compared to those without SMI (Cunningham *et al*., 2015). The reasons for these conflicting results may be age restrictions, small sample sizes, and different exposure groups and outcome measures. Hence, current knowledge is sparse on the impact of disease stage at the time of diagnosis on mortality in people with SMI.

As there is increase in cancer survival rates, the mental health of individual with cancer is increasingly noticeable. A cancer diagnosis is life-threatening with major effects psychologically. Individual's awareness of their cancer diagnosis could lead to psychological

stress (Bray *et al*., 2018). Additionally, fear of death, grief about losses, and worries about friends and family could also contribute to psychological distress (Jung *et al*., 2018).

Furthermore, chemotherapeutic or radiotherapeutic interventions can also affect patients' mental status. Such psychological distress can increase their susceptibility to mental health complications, affecting their health behavior patterns and turn into a diagnosable psychiatric disorders. Hence, treating mental health is a crucial clinical oncology issue (Kissane *et al*., 2004). Patients with cancer have higher rates of psychiatric disorders than the general population, including major depression, anxiety, adjustment disorders, delirium, and substance dependence disorders. Approximately 30% of patients with cancer suffer from psychiatric disorders (Mitchell *et al*., 2011). Particularly, depression is two to four times more common in patients with cancer than in the general population (Walker *et al*., 2014; Lutgendorf *et al*., 2015). In individuals with cancer, psychiatric distress needs to be treated swiftly, as delayed diagnosis or treatment may incur side effects, which could affect their health outcomes (Rodin, 2014). Untreated psychological distress is associated with desire for death, disability, reduced quality of life aggravated pain, diminished ability to plan end of life, and caregivers' diminished psychosocial functioning as well as prolonged hospitalization and reduced cancer treatment adherence. Since psychiatric disorders among cancer patients could be treatable, appropriate and timely methods for diagnosis and treatment are required to avoid adverse consequences (Lee *et al*., 2017, and Hwangbo *et al*., 2018).

Recommendation

Having highlighted the relationship between severe mental illness and cancer development, this review aims to make some recommendations. Application of existing cancer knowledge and treatment approach should be re-assessed when managing mentally-impaired patients. The mental health and stability of a cancer undergoing cancer treatment should be assessed overtime, and after a long period also, there should be mental awareness intervention programs. Consultation with patients, their families, oncologists, oncology nurses, social workers, as well as the key care providers in the mental healthcare system could help inform policymakers on the barriers to ensuring good outcomes for cancer patients with an SMI, or how processes of care can be developed or modified to ensure individuals with an SMI are equally likely to be offered and receive evidence-based cancer care (Adesina *et al*., 2020).

CONCLUSION

If the psychiatric disorder interferes with appropriate provision of cancer care, an emphasis on patient-centered care would dictate that the cancer care team identifies ways to provide adequate support throughout cancer treatment. Meanwhile, limited training, resources and experience could generate difficulties to providing patient-centered care for oncologists, psychiatrists and the cancer-care team.

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