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Mini Review

Exploring the Interplay of Schizophrenia and Breast Cancer: Unravelling Social, Biological, and Pharmacological Links

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Abstract

Introduction: Rates of mortality due to breast cancer among Schizophrenic patients are as high as 15% higher than the control population. This linkage between the two conditions is a serious concern for both psychiatrists and oncologists. In this study, we attempt to explore the various reasons for enhanced morbidities in either condition and thereby educate ourselves regarding how to mitigate them.

Methods: The authors conducted a comprehensive scientific review of recent data available for both diseases and analyzed it to find any connections and aggravating factors.

Results: The lack of awareness and knowledge of schizophrenic patients was not the only factor contributing to the increased risk of breast cancer. The use of antipsychotic drugs, especially second-generation antipsychotics, plays a major role in the occurrence of breast cancer. Antipsychotic-mediated increased serum prolactin levels in schizophrenic patients often leads to an increase in breast cancer. Conclusive evidence of genetic defects that link the two conditions has been identified. Mendelian randomization estimated that nearly 170 non-pleiotropic genes linked to schizophrenia can be responsible for the risk of breast cancer in female schizophrenic patients. Hormones also play an important role in this association, and hence females are more affected than males.

Conclusion: The present review throws light on the reasons behind the increasing occurrence of breast cancer and mortality in schizophrenic female patients suffering from the same. This study can also help in controlling the causes that can lead to cancer in schizophrenic patients and provide guidelines necessary for regulating the line of treatment in such a way that it can help in reducing the risk of breast cancer in schizophrenic patients.

Keywords: Cancer, Genetic Linkage, Etiopathology, Antipsychotic Drugs, Hormones

Introduction

Schizophrenia is one of the most dreadful mental disorders and the is leading cause of disability. It has always been a point of concern for society, psychiatrists, and now even oncologists. The role of genetics in schizophrenia has been studied extensively and is well established. Interestingly, there has been genetic overlap noted between schizophrenia and many other diseases, including cardiovascular and neurological systems.[1,2] Due to the wide variety of inheritance patterns that schizophrenia possesses, it is more likely to share common genetic mutations with other diseases as well.[3] Likewise, the link between schizophrenia and cancer may also be drawn from this genetic linkage. There are some schools of thought that people suffering from schizophrenic usually have a lower chance of having cancer but a higher chance of mortality when they get cancer. Research and studies are trying to establish a connection between these two major conditions. Since then, a proportionate relationship has been established between the two diseases. The causes and reasons could also be discovered through thorough research and literature studies. It has thus been observed that people suffering from schizophrenia have an increased risk of breast cancer. The aim of this present study is to explore the various reasons for enhanced morbidities of either condition due to the other and thereby educate ourselves regarding approaches to mitigate them. Hence, this comprehensive scientific review of recent data for both diseases and analysis to find and deal with the connections and

aggravating factors between the two diseases.

Lifestyle Risk Factors

Unhealthy lifestyles, including smoking, alcohol disorders, obesity, and reduced physical activities, in people suffering from schizophrenia, may contribute to the increasing risk of developing breast cancer.4 Consumption of alcohol, especially in patients with schizophrenia, is a proven risk factor for breast cancer. It has been reported that uncontrolled consumption of alcohol and genotype-predisposing schizophrenia are associated with ER-positive and ER-negative breast cancers.5-7 Researchers have found enough data to conclude that risk factors for cancer like pollution, smoking, and alcohol consumption result in higher risks of developing schizophrenia.[8] Environmental risk factors often trigger cellular pathways that transmit epigenetic modifications from one generation to the next.[9]

However, the main reasons behind the association between schizophrenia and breast cancer cannot be explained only by an unhealthy lifestyle. The more important factors are discussed herein in this article.

Genetic Risk Factors

One of the most widely established and accepted hypotheses for the association of these two diseases is shared genetic mutations. The risk of developing breast cancer with the comorbidity of schizophrenia is distinct from other types of cancer. It has been observed that the risk of developing cancers like colorectal cancer, prostate cancer, and malignant melanoma decreases in people suffering from schizophrenia after the age of fifty years.[5] On the other hand, there is an increased risk of developing breast cancer in people suffering from schizophrenia at all ages. This hints at the role of shared genetic mutations. Almost fifteen percent of all cases of breast cancer are genetically linked to mutations in schizophrenia.[10,11] Genetic interlinking between schizophrenia and a few other cancers, like ovarian cancer, has also been noticed in a few recent studies.[12] Recent genome-wide association studies done on a large scale were able to identify multiple genetic variants of schizophrenia and breast cancer, which allowed for the prediction of a genetic correlation between the two diseases with more statistical accuracy.[13-16] Shi *et al*. have used Mendelian randomization to successfully establish schizophrenia as a statistically significant risk factor for developing breast cancer by assessing one hundred seventy non-pleiotropic genes linked with schizophrenia. These genes were linked to females suffering from schizophrenia, and thus an association could be established.[7] Mary-Claire King reported mutations of BRCA1, one of the commonest mutations in breast cancer, in the form of deletion and duplication that were powerful enough to disrupt the brain during its developmental phase, resulting in various mental diseases, including schizophrenia.[17]

However, some reports claimed that, more than the underlying genetics, antipsychotic drugs prescribed for schizophrenia play a major role in the development of breast cancer, an argument that is evidenced by unaffected first-degree relatives of people with schizophrenia.[18]

Pharmacological Risk Factors

Reports have shown that with the use of antipsychotic drugs for schizophrenia, breast cancer has seen an increase of almost 16%.[19] It has been seen from a population-based cohort study that the risk of developing breast cancer in female patients increases with the use of antipsychotic drugs, especially with the use of second-generation anti-psychotics such as paliperidone, risperidone, and amisulpride. Patients receiving a combination of first- and second-generation antipsychotics and those on higher doses show a higher risk of developing breast cancer.[20-22] A population-based cohort study done by Chou et al. on Taiwanese schizophrenia female patients shows how breast cancer increases in female patients with the occurrence of schizophrenia (Figure 1), and Figure 2 shows how breast cancer occurrence depends upon the usage of first- and second-generation antipsychotic drugs, especially a class of secondary antipsychotic drugs. Chou et al. also statistically showed that breast cancer increases in female schizophrenia patients with age.

It is known that surges in prolactin levels are common amongst people receiving antipsychotics due to their dopamine receptor antagonism property upon receptors located in the tubero-infundibular pathway. Breast cancer being hormone-dependent, such as prolactin surges, in females receiving antipsychotics for schizophrenia has been well established as a risk factor for the former.[20,23] Altered levels of sex hormones courtesy of receiving antipsychotics have a definite role in schizophrenia, which is also confirmed

by its differential effect on male and female patients. Levels of circulating sex hormones like estrogen and androgen are statistically associated with premenopausal breast cancer.[24,25]

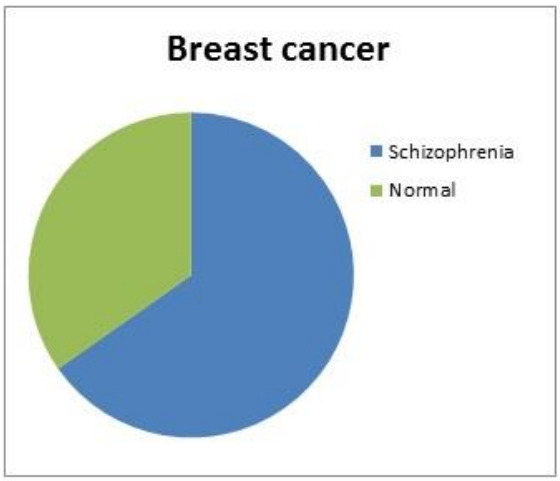

Figure 1. Breast Cancer Prevalence in Normal Female and Female Schizophrenia Patients.

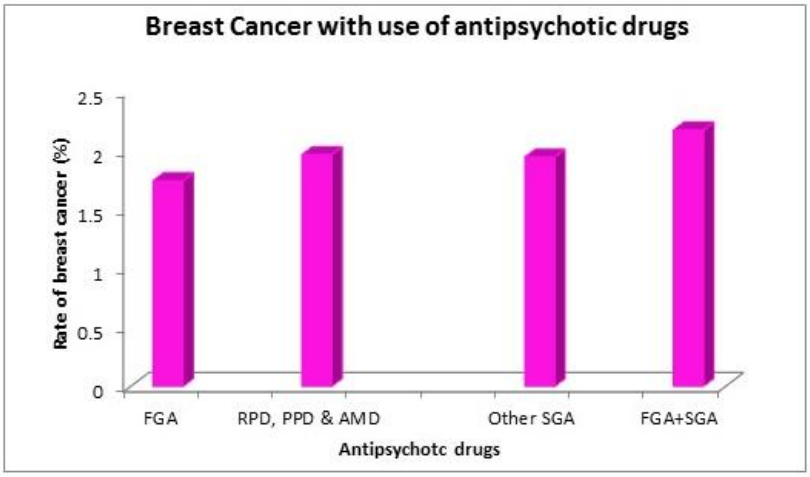

Figure 2. Occurrence of Breast Cancer in Female Schizophrenia Patients using FGA (First- generation antipsychotic drugs), SGA (Second- generation antipsychotic drugs, RPD (Risperidone), PPD (Paliperidone), AMD (Amisulpride).

Exploring further on the hormonal correlation of these two diseases, it was found that schizophrenia and breast cancer have established common genetic loci of 19p13, which plays a crucial role in the pathway of biosynthesis of peptide hormones like corticotrophin that has a role in regulating hormone release and feedback.[26,27] Reproductive hormones, including progesterone, estrogen, and prolactin, have a vital role in the cause of breast cancer since this is a disease that can also be caused by hormonal disturbance.[28] Antipsychotic drugs, especially a class of second-generation drugs, work by blocking the dopamine-2 receptor, which in turn causes an increase in prolactin levels, which has a direct impact on breast cancer.[29]

It has been observed that patients with schizophrenia have more distantly metastasized breast cancer. Prolactin levels increase in distant metastasis breast cancer, resulting in increased cases of schizophrenia.[30,31] A Finnish population-based cohort study showed that the use of schizophrenic drugs that increase the prolactin level increases the risk of developing lobular adenocarcinoma many fold more than treatment with other drugs for schizophrenia.[32] Psychiatric medications like antipsychotics often destroy the natural killer (NK) cells, which directly have an effect on the development of antitumor

immunity and thereby increase the chances of developing any cancer, something that a psychiatrist is wary of.[33] This also draws attention to the immunological basis of the shared etiologies of these two diseases.

Immunological and Inflammatory Risk Factors

In recent cancer research, the role of immunotherapeutics has been established. It has been seen that increased expression of PD-1, a protein in T cells in cancer patients, can be inhibited by PD-L1, the ligand for PD-1, which also helps immune T cells to work and develop antitumor immunity.[34] Strikingly, an increase in PD-1 levels has been commonly detected in people with schizophrenia, thereby further establishing a shared etiology.[35]

It has been reported that there is an overexpression of the cytokines of the Interleukin-1 receptor family, mainly Interleukin-33 (IL-33) and Soluble suppression of tumorigenicity 2 (sST2), in breast cancer patients.[36,37] At the same time, it has also been found that IL-33 and sST2 are responsible for a higher impact of positive symptoms and negative symptoms of schizophrenia, respectively.[38,39]

Risk Due to a Lack of Awareness

Morbidity in people suffering from schizophrenia having breast cancer is higher than in general patients due to the fact that the patients are less aware and alert about the onset and severity of the disease. Often, they do not receive proper cancer screening.[40,41] Schizophrenia is associated with varying effects on cognition, which may make it difficult to detect pain or a growing lump, which leads to a late diagnosis and often ends up in advanced stages. This often leads to a delay in diagnosis as compared to the general population suffering from breast cancer.[13,42] Females suffering from schizophrenia are almost half as likely to get mammographic screening done as compared to the general female population, and no solutions have been drawn out to address this disparity.[43]

Lack of insight regarding the graveness of the disease and often a reluctance to accept palliative care contribute to the higher morbidity of breast cancers. These all delay access to life-saving chemotherapy, adding to the risk of mortality.[44,45]

Mitigating the Risk

Since antipsychotics show an increased risk of developing breast cancer in a dose-dependent manner with long-term use, a measured approach to the use of antipsychotic drugs can help inhibit the progression of breast cancer in people suffering from schizophrenia.[21] Many of the antipsychotic drugs used in the treatment of schizophrenia, especially Risperidone, not only result in hyperprolactinemia in the serum but also activate the signal transducer and activator of transcription 5 (STAT5), which inhibits apoptosis and induces cell death.[46,47] Joo et al. reported that the use of olanzapine has shown the highest risk of breast cancer, especially when observed for a long period of at least six years in a dose-dependent manner.[20] Use of drugs like safer drugs instead, in patients with established risk factors for developing breast cancer, like sertindole and penfluridol, would be a game changer. These drugs have double the benefits of reducing the growth of primary triple-negative breast cancer and also possessing anti-proliferative effects on breast cancer cell lines.[48-50] They also reduce the risk of metastasis through the inhibition of integrin signaling.[51]

Few reports have claimed that there is still some doubt regarding the incidences of increasing breast cancer in people suffering from schizophrenia; however, almost all studies and reports believe that mortality in schizophrenic patients has increased in recent times, especially after the introduction of second-generation antipsychotic drugs.[52,53] Tran et al.'s cohort study to come to the final conclusion that there has been an increase in mortality in patients with schizophrenia by 2-3 times, mainly due to an increase in breast cancer mortality in females and lung cancer risk in males, respectively.[54] Catts et al. and Gulbinat et al. have found that this trend of increasing breast cancer is more common in Asian schizophrenic female patients.[52,55]

A way to tackle the problem of people with schizophrenia developing breast cancer is to increase screening for breast and cervical cancer should be taken.[56] If screening is done at the proper time, then cancer mortality in patients with schizophrenia could be reduced to a great extent and the survival rate would be improved.[57] Screening at the proper time can be improved by improving factors such as awareness, communication, and attitudes at the levels of service, service provider, and practitioner.[58] People with psychiatric disabilities should be made aware of the importance of cancer screening through educational

interventions or by training mental health professionals to conduct proper cancer screening programs as part of their role.[59-61]

The outcomes of treatments for physical illness in patients with mental illness are not only understudied but also under-attended, especially in the case of schizophrenia, where problems like caregiver burden, abandonment, and social stigma exist.[62]

Discussion

It is interesting to note that breast cancer increases with schizophrenia, which is not the case with most of the other cancers except ovarian cancer, where anti-NMDA receptor antibodies are produced, which are known causes of clinical psychosis, including schizophrenia. In spite of a few reports claiming no genetic association between schizophrenia and breast cancer, we would like to conclude that genetic overlapping, lifestyle, behavioral factors, therapies, and treatments all should be kept in strong vigilance so that a person suffering from schizophrenia does not end up developing breast cancer. The relationship between environmental risks and epigenetic modulation will no longer remain limited to cancer research alone but also to the cause of schizophrenia. Hence, environmentalists also have a huge role to play in maintaining an efficient health system. It has been observed that patients with schizophrenia have a life expectancy of 15-20 years less than the normal population.[63] The Advanced Medical System has recommended recent treatment guidelines that monitor cardiovascular and other metabolic disorders in schizophrenia patients, but screening for cancer is still not clearly recommended.[22,64] People suffering from schizophrenia need regular screening and review of the use of schizophrenic drugs that cause an increase in prolactin levels. The increase in morbidity among people suffering from schizophrenia due to breast cancer is alarming. A collaboration between the psychiatrist and oncologist to treat people suffering from schizophrenia can also save a patient in a bidirectional way. Thorough functional studies should be done to unveil the genetic signals that contribute to and interlink the pathogenesis of both diseases. Psychiatrists have to strictly suggest screening for female patients with schizophrenia who have a family history of breast cancer. Increasing the frequency of primary care contact can have a great impact on cancer screening, thus decreasing breast cancer incidents as well as breast cancer mortality in people suffering from schizophrenia.

Conflict of Interest

The authors declare no conflicts of interest.

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