



Review

Gynecological Health Concerns in Women with Schizophrenia and Related Disorders: A Narrative Review of Recent Studies

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Abstract: Sex and age are important factors influencing physical and mental health in schizophrenia. Our goal was to review the recent literature for associations between gynecological conditions and psychotic illness and to propose integrated strategies for their management in order to improve overall health outcomes in women. We addressed the following questions: What are the prevalence and risk factors of gynecological disorders in women with schizophrenia or delusional disorder (DD)? What are the rates of uptake of gynecological cancer screening and mortality in this population? What role does menopause play? We found an increased incidence of breast cancer in women with schizophrenia. Other gynecological comorbidities were less frequent, but the field has been understudied. Low rates of breast and cervical cancer screening characterize women with schizophrenia. Menopause, because of endocrine changes, aging effects, and resultant comorbidity is associated with high rates of aggressive breast cancer in this population. Uterine and ovarian cancers have been less investigated. Psychosocial determinants of health play an important role in cancer survival. The findings lead to the recommendation that primary care, psychiatry, gynecology, oncology, and endocrinology collaborate in early case finding, in research into etiological links, and in improvement of prevention and treatment.

Keywords: gynecology; oncology; schizophrenia; delusional disorder



Citation: González-Rodríguez, A.; Seeman, M.V.; Guàrdia, A.; Natividad, M.; Marín, M.; Labad, J.; Monreal, J.A. Gynecological Health Concerns in Women with Schizophrenia and Related Disorders: A Narrative Review of Recent Studies. *Women* **2022**, *2*, 1–14. <https://doi.org/10.3390/women2010001>

Academic Editor: Richard Kreider

Received: 5 December 2021

Accepted: 27 December 2021

Published: 04 January 2022

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1. Introduction

Over the last several decades, a significant amount of research has dealt with the study of gender and sex differences in the biological and behavioral expression of disease. Sex and gender have been found to impact the clinical manifestation of many diseases, as well as their epidemiology (prevalence and incidence) and pathophysiology [1].

Cardiology has been in the forefront of investigating and uncovering substantial biological and sociocultural differences between the sexes with respect to clinical manifestations and outcomes of hypertension, acute coronary syndrome, and heart failure, as well as other cardiac disease [2]. The World Health Organization now underscores the fact that “gender is a structural determinant of health” and that, globally, women receive less health care than men while bearing more family responsibilities, with the result that health outcomes are poorer in women than in men. An important example is ischemic heart disease. Women seek help later than men; once help is received, the correct diagnosis takes longer to arrive at, and treatment is too often suboptimal [2].

With respect to mental disorders, gender and sex differences have been described in the susceptibility to specific disorders, in their clinical expression, comorbidity, and

treatment response [3]. Unfortunately, although sex/gender differences are being reported, their importance has not sufficiently influenced the conduct of clinical treatment trials. Neither recruitment nor the analysis of findings has sufficiently taken sex/gender into account. The vast majority of early clinical trials chiefly recruit male participants, a fact that has led to treatment guidelines based, for the most part, on male response [3].

Although results differ and uncertainties remain, in schizophrenia and in first-episode psychoses, studying gender differences has been helpful in illustrating the heterogeneity of psychotic illness [4]. Most studies strongly support the findings that men experience an earlier age of psychosis onset and suffer more frequently than women from severe negative symptoms [4]. Comorbid substance use disorders (nicotine, cannabis, alcohol, cocaine) have been repeatedly demonstrated to be more prevalent in men than in women, and clinical outcomes to be superior in women, at least over the course of the reproductive years.

When the reproductive years come to an end, the seeming advantage for women wanes. Thus far, however, the effect of menopause on drug efficacy and on side-effects remains understudied [5]. A recent narrative review of randomized controlled trials targeting peri- and postmenopausal women with schizophrenia concludes that a decline in estrogen levels at menopause is associated with worsening psychosis outcomes [6]. More recently, Szeliga et al. reported that menopause exerts a negative effect on all women, and, in women with schizophrenia, schizoaffective disorder, and bipolar disorder, it negatively impacts the course of disease [7].

Prior to menopause, women with schizophrenia show a more robust antipsychotic response than they do post menopause. Raloxifene, a selective estrogen receptor modulator, combined with antipsychotics has been recommended as a potential adjunctive therapy to improve psychotic and cognitive symptoms in postmenopausal women with schizophrenia and related disorders [5]. Of additional importance is the observation that medical comorbidities increase in women at the time of menopause, more so than they do in male age peers. It is possible that prevention of comorbidities at this age could reduce mortality rates in psychotic illness in both men and women. Physical comorbidities and mental symptoms reinforce each other. For instance, Barker [8], comparing the incidence of mental health symptoms in women before and after hysterectomy, found that psychiatric referrals, especially for depression, significantly increased after surgery.

Besides the effect of menopause and comorbidities on gynecologic disease, personality traits may also have an impact. A community survey conducted by Gath and collaborators [521] and targeting women aged 35–59 found that neuroticism, as well as psychiatric morbidity, were strongly associated with dysmenorrhea, premenstrual tension, excessive menstruation, and hot flushes [9]. This association could be mediated via a number of routes including the use of psychiatric medications [10].

Both age and the advent of menopause have been shown to affect the somatic and psychological health of women with schizophrenia [5,6,11], which suggests the possibility that gynecological health, influenced by hormonal fluxes, impacts and, in turn, is impacted by, psychiatric health.

The aim of this narrative review is, thus, to search the recent literature for studies of association between gynecological health and psychotic illness (schizophrenia and delusional disorder) and to propose integrative management strategies that will improve health outcomes in women.

When starting the review, our questions were: (1) What is the epidemiology of gynecological disorders in women with schizophrenia and delusional disorder? (2) In this population, what are the risk factors for gynecological disorders? (3) What is the relative prevalence of malignant versus nonmalignant gynecological disease in schizophrenia and delusional disorders? (4) In these two related conditions, what are the rates of cancer screening and the mortality rates of gynecological tumors (breast, cervix, uterus)? (5) With respect to all these questions, what is the role of menopause? Depending on the answers to these questions, we wanted to be able to propose recommendations for an improved model of care that addressed both mental and gynecological health in women with psychotic illness.

2. Methods

We carried out a narrative (nonsystematic) review based on electronic searches in the PubMed database for English, German, French, and Spanish language papers published between 2015 and October 2021. Initial search terms were: (gynecology OR gynecological OR menopause OR postmenopausal) AND (schizophrenia OR psychosis OR delusional disorder), aiming for papers that referred to gynecological health concerns and their timing in the context of schizophrenia and delusional disorder (DD).

The screening and selection processes were performed by AGR and AG. Reference lists from included studies were scanned to identify potential papers relevant to our aim. Google Scholar was also searched with identical search terms in order to add relevant papers from disciplines outside of medicine. Papers were included if they were systematic reviews or meta-analyses, randomized controlled trials, or population-based or nationwide cohort studies. Studies referring to gynecologic concerns during pregnancy and the immediate postpartum period were not considered in the present review. Figure 1 shows the methodological procedure we undertook and the number of papers found through this selection process. After screening all potentially relevant full-text documents, a total of 46 records were identified as citable.

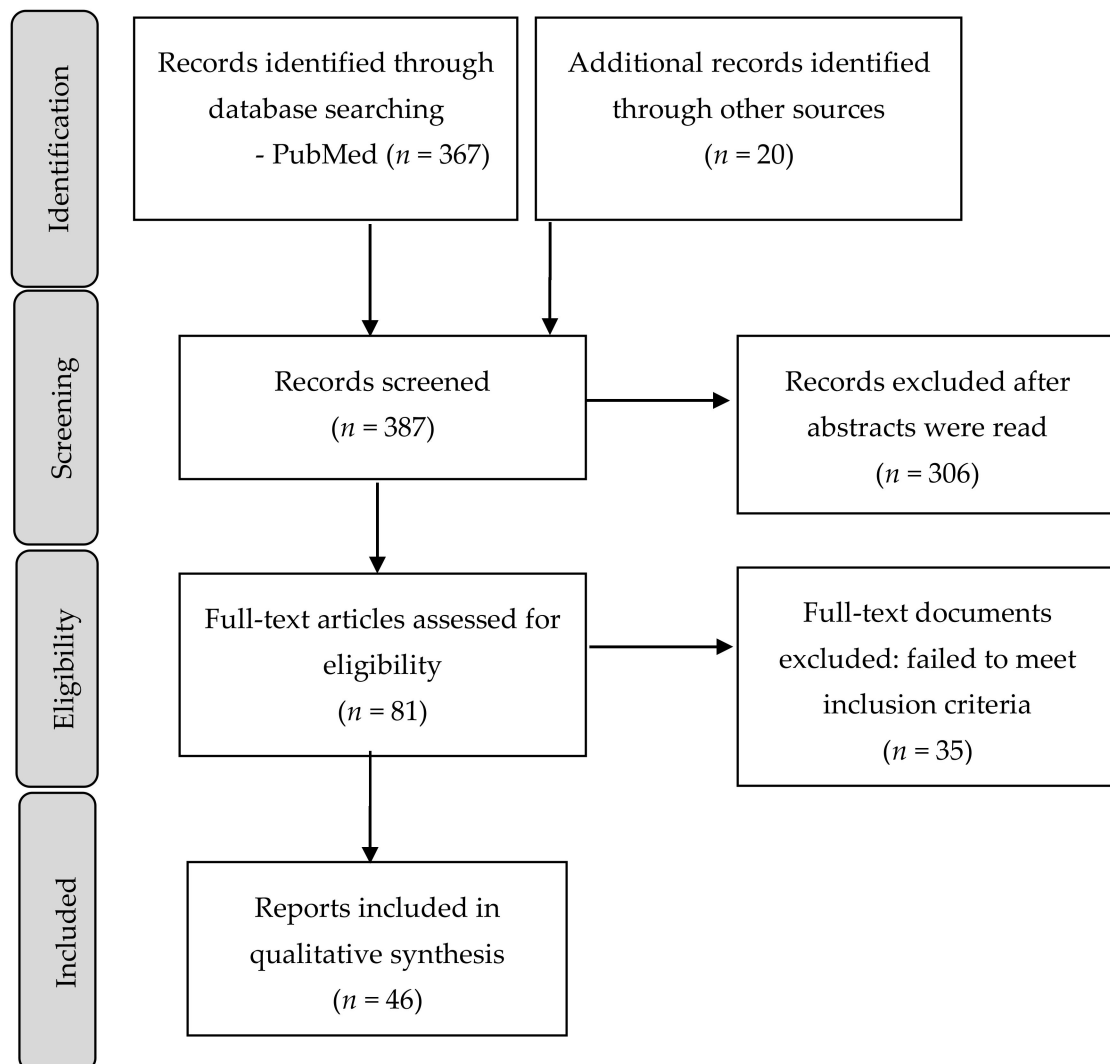


Figure 1. Flowchart for search leading to study inclusion.

3. Results

3.1. Prevalence of Gynecological Disorders in Women with Schizophrenia and Delusional Disorder

Medical comorbidity (MC) has been defined as the co-occurrence of more than one contemporaneous disease in the same person. That definition includes diseases that may share a common cause [12]. The investigation of MC is important because suffering more than one disease decreases health-related quality of life, increases the number and duration of hospitalizations, and shortens life expectancy.

Mariano and collaborators carried out a single-center, double-arm retrospective cohort study of 965 patients admitted to a psychiatry department in Italy between January 2017 and December 2020 [12]. Two psychiatric diagnoses of interest (schizophrenia and bipolar disorder) and MCs were identified according to the International Classification of Diseases, 9th Edition (ICD-9). Pregnant women and patients with psychiatric disease other than schizophrenia and bipolar disorder (BD) were excluded from the study. A total of 51% of the sample were women, and 53% of the women with a diagnosis of schizophrenia suffered MCs. The women with schizophrenia showed a frequency of gynecological diseases (including cancers) of approximately 5.2%, with an additional and similar frequency of urological and genital diseases (5.2%). After applying binary logistic regression models, women with BD had an odds ratio of 16.57 of having gynecological disease compared to those with schizophrenia. The conclusion of the overall study was that individuals with mental disorders (men and women) have more risk factors for cancer than those found in the general population. These factors are excessive smoking, excess weight, a sedentary lifestyle, overuse of substances, and excess exposure to infection. Of the various gynecologic conditions in women, endometriosis and polycystic ovary syndrome (PCOS) were more frequent in BD than in schizophrenia. Prevalence rates for gynecological diseases in women were not specified in detail.

With respect to cancer, Petterson and collaborators [13] carried out a population-based study using 1990–2013 data from three nationwide Swedish registries. Total incidence of lung, esophagus, pancreas, stomach, colon, prostate, and breast cancer were calculated by age and sex. Incidence rates in schizophrenia were compared to those found in the general population. Breast cancer was the only malignancy found to show significantly higher incidence in schizophrenia than in the general population.

Another recent study conducted by Taipale and colleagues investigated the association between breast cancer and schizophrenia by using a Finnish nationwide hospital register in a case-control design to determine whether antipsychotics that raised prolactin levels contribute to breast cancer risk in women with schizophrenia [14]. Women with schizophrenia and comorbid breast cancer served as cases, and women with schizophrenia without cancer were the controls. From a total sample of 30,785 women suffering from schizophrenia, 1069 had received a breast cancer diagnosis. Those with fewer than one to four years of exposure to prolactin-raising drugs did not show an increased risk of breast cancer. However, exposure for 5 or more years was significantly associated with increased incidence. The risk of developing lobular adenocarcinoma with long-term use of prolactin-raising antipsychotics was found to be higher than the risk of developing ductal adenocarcinoma, suggesting that high prolactin over prolonged periods may contribute to risk for specific types of breast cancers. The issue of breast cancer rates in women with schizophrenia treated with antipsychotic drugs has become a controversial topic because, apart from their therapeutic drugs, women with schizophrenia carry other risks for breast cancer, namely high rates of nulliparity, low rates of breast feeding and physical activity, high rates of obesity, alcohol use, smoking, and diabetes mellitus, as well as high levels of stress (which also raise prolactin levels) [15]. However, in the Taipale et al. study [14], long-term exposure to prolactin-sparing antipsychotics was *not* associated with an increased risk, suggesting that high levels of prolactin over long periods (the result of many years' exposure to prolactin-inducing drugs) do raise the risk for breast cancer, especially lobular breast cancer.

Recent results of meta-analyses also show significantly higher incidence of breast cancer in women with schizophrenia than in nonschizophrenia controls [16] and in women with schizophrenia compared to women in the general population [17].

In summary, while there is no evidence of other gynecologic problems being more commonly found in schizophrenia women than in other women, breast cancer stands out as the exception.

3.2. Risk Factors for Gynecological Disorders in Women with Schizophrenia and Delusional Disorder

Although the incidence of gynecologic disorders other than breast cancer has not been found to be excessively high in women with psychosis, these women do show many risk factors that make them vulnerable. Detecting risk is crucial in order to plan and institute prevention strategies.

Lu and collaborators have enumerated the risks for breast cancer (BC) in this population [18]:

1. Symptom and stigma-related stress;
2. Long term use of prolactin-raising and weight-inducing antipsychotics;
3. Nulliparity;
4. Relative lack of breastfeeding;
5. High rates of smoking;
6. Alcohol use;
7. Sedentary lifestyle.

The direction of effects can, theoretically, be reversed. Lu et al. found an increase in depression, anxiety, and posttraumatic stress disorder following breast cancer [19]. This effect is presumably mediated via raised stress levels and may well apply to psychotic disorders.

It is also possible that a third factor, perhaps a genetic predisposition common to both diseases, accounts for the association between schizophrenia and breast cancer (BC).

Through an elegant set of epidemiological and genetic comparisons, Lu et al. examined all these factors [18]. They used a Swedish health register of 94,626 (mean age of diagnosis = 63.6) women with invasive BC and age-matched each with 30 women who were cancer-free. By cross-linkage, they were able to obtain first-ever dates of the diagnosis of schizophrenia for cases (before and after BC) and controls. Schizophrenia was associated with a 49% increased risk of subsequent invasive BC over controls. The increase remained robust after accounting for parity, previous psychiatric disorders, substance abuse, and obesity.

The investigators next checked for a first diagnosis of schizophrenia following BC and found a 31% increase compared to controls. They concluded that they had shown a bidirectional influence.

They then looked for a genetic overlap between BC and schizophrenia, first by using linkage disequilibrium (LD) score regression. They estimated the genetic correlation between the two to be 0.14, which means that approximately 1/7 of the genetic contribution to these two phenotypes is shared. Looking next at polygenic risk scores, these were significantly associated with each other. The team then proceeded to search for a distinct signal shared by the two diseases. Fourteen loci were individually examined to assess co-localization of the signals, and a common locus was found at 19p13, positively associated with both BC and schizophrenia. This locus is also associated with total cholesterol (TC), triglycerides (TG), and low-density lipoprotein (LDL), but associations with lipid levels go in the opposite direction in the two conditions, potentially reflecting the action of antipsychotic medications on lipids. This shared locus (19p13) is also associated with two more hormone-related cancers—ovarian and prostate.

Lu et al. have opened an exciting avenue of exploration into the potential connection between schizophrenia and BC [18]. More than the signal at 19p13, they conclude that an enriched common pathway that regulates the biosynthesis of peptide hormones such as corticotropin may throw light on the relation, if any, between BC and schizophrenia.

A recent study investigated genetic correlations, causalities, and pathways between cancer-related exposures and ovarian and breast cancer [20]. The investigators identified 31 risk factors for breast and ovarian cancer. Body mass index, schizophrenia, and age at menopause were all significantly associated with BC (both its estrogen receptor positive form and its estrogen receptor negative form) but not with ovarian cancer. Shi and colleagues [21] had also estimated the potential effect of schizophrenia on BC risk in women based on a two-sample Mendelian randomization design that investigated the association between single nucleotide polymorphisms (SNPs) significantly associated with schizophrenia risk and BC risk. Genetically predicted risk for schizophrenia was associated with a modest increase in BC risk. Other reports support this association, a finding based on very large genome-wide association studies of schizophrenia and breast cancer [22].

Results from two cohort studies and three case-control studies were analyzed in a recent meta-analysis [23], which found four studies demonstrating a dose-response association between cigarette smoking and the presence of cervical cancer. Women with schizophrenia are known to have high rates of nicotine consumption [24], as well as obesity and metabolic syndrome, when compared to the general population, and all these factors are positively associated with gynecological cancers. With regard to nicotine dependence, several underlying mechanisms have been postulated to account for the association between schizophrenia and smoking. Results from the Chen et al. [24] study pointed to a shared genetic liability. Noncoding RNAs and RNA binding protein genes, protein modification genes, and energy production genes, which play a crucial role in cognitive performance and neuronal plasticity, were associated with both conditions.

Grassi and collaborators compared patients with severe mental illness with primary care attendees, controlling for gender and age [25]. Cancer risk factors, lifestyles leading to cancer, personal perceptions, family history of cancer, and knowledge about cancer risks were investigated. Patients with severe mental illness, mainly schizophrenia spectrum disorders, differed from primary care patients in terms of frequency of occult stool blood screening tests. They also showed a higher prevalence of current and past smoking frequency, lower awareness of physical symptoms, and lesser engagement in physical exercise. The investigators concluded that patients with severe mental illness engaged in risk behaviors that could lead to cancer.

With regard to ovarian cancers (OC), recent studies have tried to identify potential risk factors for developing epithelial OC. Because there is documented evidence of perturbed choline metabolism in both OC and schizophrenia, Adams and collaborators carried out a Mendelian randomization study to evaluate whether schizophrenia increased the risk for developing OC [26]. The conclusion was that schizophrenia conferred a weakly increased risk for epithelial OC but that there was no evidence for the reverse. OC did not raise the risk of schizophrenia.

Risk factors for other nonmalignant gynecological conditions have also been studied. With a genetic hypothesis in mind, several research groups have investigated the genetic association between polycystic ovary syndrome (PCOS) and schizophrenia. Jin and colleagues explored linkage between PCOS and psychiatric disorders (including schizophrenia) using data from genome wide-association studies in European populations and employing a two-sample Mendelian randomization method [27]. PCOS was genetically associated with obsessive-compulsive disorder but not with major depression, anxiety disorders, bipolar disorder, or schizophrenia. The conclusion was that PCOS was not genetically linked to schizophrenia, which is consistent with recent findings from Jiang and collaborators who also conducted a genome-wide genetic correlation analysis using bidirectional Mendelian randomization [28].

These findings are in contrast with nationwide population-based cohort studies. For instance, Chen et al. carried out one such study in Taiwan, which included 7146 PCOS patients and 28,580 controls [29]. Patients diagnosed with PCOS had an increased risk of incident schizophrenia compared to non-PCOS controls after adjusting for several variables such as age, treatment strategies, and comorbidities. PCOS patients showed an increased

risk of schizophrenia. A previous study hypothesized that the increase in androgens that accompanies PCOS may be implicated in the etiology of mental disorders [30]. Swedish national registers were utilized to compare women with PCOS, their full-siblings, and matched controls from the general population as well as their siblings. The finding was that women with PCOS were at increased risk for schizophrenia. In addition, the high risk found in their siblings suggested shared genetic factors between PCOS and psychiatric disorders. A recent systematic review of this issue concluded that the many difficulties in accurately assessing this connection makes findings difficult to interpret [31].

To summarize thus far, women with schizophrenia are at an increased risk for breast cancer. Excess risk factors for cervical cancers such as smoking and dietary habits have been found in women with schizophrenia. It is possible but controversial as to whether ovarian cancer risk or PCOS risk is linked to schizophrenia. Table 1 summarizes the main findings on the associations and risks of gynecological cancers in schizophrenia and DD.

Table 1. Associations and risks—gynecological cancers and schizophrenia and delusional disorders.

Gynecological Cancer	Findings	Reference
Breast cancer	Higher incidence compared to the general population.	[13,16,17]
	Exposure for 5 or more years to prolactin-raising drugs associated with increased incidence.	[14]
	Other risk factors contribute to the risks: obesity, alcohol use, smoking, diabetes mellitus, stress.	[15]
Cervical cancer	Smoking is associated with schizophrenia and risk for cervical cancer.	[24,25]
Ovarian cancer	Schizophrenia associated with weakly increased risk for epithelial ovarian cancer.	[26]
Overall gynecological cancers	Genetic and lifestyle factors associated with increased risk: weight gain, metabolic syndrome.	[23,24]

3.3. Prevalence of Malignant versus Non-Malignant Gynecological Disease in Schizophrenia and Delusional Disorders

Nonmalignant gynecological diseases have not been frequently investigated in the context of comorbidity with psychotic illness. Endometriosis, however, appears to be more common among women with mental illness than among controls [32]. The Gao et al. research group linked several Swedish national registers for psychiatric disorders and endometriosis and conducted sibling comparison analyses in a subsample of 173,650 families [32]. After adjusting for birth characteristics and education, women suffering from endometriosis showed an increased risk of a later diagnosis of depressive and anxiety disorders, including psychotic affective disorders, but not of schizophrenia.

The relevance of healthcare services and demographics in different countries has been highlighted in a recent study of endometriosis. Robert and collaborators [33] carried out a cross-sectional study based on the Nationwide Inpatient Sample (NIS, 2012–2014) comprised of a total of 63,160 women diagnosed with primary endometriosis. The aim of the study was to explore sociodemographic differences and clinical outcomes in patients with and without psychiatric comorbidities. Nearly 19% of inpatients with endometriosis had psychiatric comorbidities, anxiety and depression being the most common (45%, 31.3% respectively). Psychotic disorders (12.3%) came third. Endometriosis with psychiatric comorbidities, including psychosis, was most prevalent in young white females coming from middle income families. A recent meta-analysis [34], using systematic methodology and mixed-methods models, qualitatively and quantitatively analyzed data on the prevalence of mental health sequelae in endometriosis. Anxiety and depressive symptoms were the most common mental health outcomes. Psychosis was not mentioned.

Essentially, both malignant and nonmalignant gynecologic diseases occur among women with psychotic disorders. There may be shared risk factors, but both lifestyle and treatment factors may be responsible for raising the comorbidity risk.

3.4. Cancer Screening and Mortality in Schizophrenia and Delusional Disorder

Given an acknowledged high incidence of breast cancers among women with psychosis, cancer screening becomes critical.

Solmi and collaborators carried out a systematic review and meta-analysis, which included studies focusing on cancer screening rates in individuals diagnosed with mental illness compared to rates in the general population [35]. With a total sample of 4,717,839 individuals, nearly 70% women, screening was found to be significantly less frequent in people with a mental disorder than it was in the general population. This is in line with another recent review [36]. With these screening rates in mind, Murphy and collaborators in the U.S. tried to identify factors associated with cancer screening in severe mental illness by specifically analyzing screening rates for cervical, breast, colorectal, and prostate cancer [37]. The authors found that Black patients were more likely to receive screening for cervical cancer, breast cancer, and colorectal cancer than Whites. This association could well have resulted from the study's recruitment strategy. Significantly, those with severe mental illnesses plus comorbid substance use had the lowest rates of cancer screening.

A recent systematic review and meta-analysis specifically explored rates of breast cancer screening in women with schizophrenia [38]. The results of this study, which sampled 25,447 women with schizophrenia, showed that these women were substantially less likely to receive mammography screening than were women in the general population.

Woodhead et al. found that patients with severe mental illness—including women with schizophrenia and related disorders—received less breast and cervical cancer screening compared to individuals without severe mental illness [39]. An assessment of severe schizophrenia was associated with the lowest breast and cervical cancer screening in this sample. An important finding was that the frequency of primary care visits increased cancer screening.

Focusing on cervical cancer, Harder et al. conducted a nationwide register study in Denmark, taking note of demographic characteristics, reproductive histories, and mental and physical health of participants and nonparticipants of cervical screening programs [40]. Nonparticipants had lower incomes; higher likelihood of smoking during pregnancy; and a history of obesity, schizophrenia, and substance use disorders. These findings are consistent with a recent study by Hertzum-Larsen and collaborators [41] who carried out a nationwide register-based cohort study of cervical cancer screening in 610,907 female immigrants to Denmark. Predictors of low participation included low income, single status, and a previous history of schizophrenia or related disorders.

It has been reported that, with the exception of cervical cancers where mental disorders worsen prognosis, in general, mental disorders do not directly impact outcomes of gynecological cancers [42]. This would inevitably depend on rates and regularity of cancer screening in these populations, which differs in different regions of the world depending on access to and comprehensiveness of mental health care. This connection of geography to cancer outcome is very much supported by Ouk and collaborators [43].

In a Japanese population with schizophrenia, Inagaki et al. [44] investigated cancer screening rates as recorded in hospital files. The investigators found extremely low cancer screening rates in people with schizophrenia: 21% breast cancer and 14.1% for cervical cancer. Fujiwara et al. [45] found similar results for schizophrenia when they investigated cancer screening for colorectal, gastric, lung, breast, and cervical cancer. Screening rates were especially low in those with severe symptoms and functional disability.

Motivated by an early U.S. study by Lindhamer and colleagues [46] that found poor use of gynecological services in older women with schizophrenia, González-Rodríguez and colleagues [47] in Spain evaluated gynecological variables and psychopathology and gynecological service use in 25 women outpatients with delusional disorder (DD). Demographic,

clinical variables, gynecological characteristics, and attendance rates at gynecological services were recorded. The Hamilton Rating Scale for Depression was used for depression, and the Positive and Negative Syndrome Scale, for psychotic features. The results revealed that 48% of the women, whose mean age of onset of DD was 48, had not received gynecological attention in the prior 2–3 years. Table 2 summarizes recent research on screening of gynecological cancers in women with schizophrenia and DD.

Table 2. Cancer screening in women with schizophrenia and DD.

Cancer Type	Findings	References
Overall Cancer Screening	Cancer screening rates are lower in patients with severe mental illness compared to the general population	[35]
	Primary care use and long duration of Medicaid enrolment were associated with higher cancer screening rates	[37]
	Comorbid substance use disorders were associated with lower rates of cancer screening	[37]
Gynecological cancers	Women with schizophrenia were less likely to receive breast and cervical cancer screening	[39]
	The frequency of primary care visits influences cancer screening	[40]
Breast cancer	Women with schizophrenia and delusional disorders were less likely to receive mammography	[38,39]
Cervical cancer	Low income, smoking, obesity, schizophrenia, and substance use disorders were associated with low participation in cancer screening	[41]

With regard to mortality rates of specific cancers in schizophrenia, a recent systematic review and meta-analysis conducted by Ni and colleagues explored data on breast, colon, lung, and prostate cancer [48]. In a total sample of more than one million participants with schizophrenia, mortality risk of breast and lung cancer was higher in patients with schizophrenia compared to that of the general population. For colon cancer, increased risks were also high in women with schizophrenia. Recent work by Lawrence et al. confirmed an elevated mortality from breast cancer in women with severe mental illness [49]. Racial and ethnic characteristics may play a part in this association mediated by adherence rates to guideline treatment.

Dalton and collaborators explored the breast cancer-specific mortality in early-stage breast cancer patients with and without schizophrenia using the Danish national register [50]. A total of 56,152 women were identified as having early-stage breast cancer. Nearly 500 women were also diagnosed with schizophrenia and related disorders. Survival rates of women with schizophrenia were significantly worse than those free of schizophrenia. Women with schizophrenia were also found to be less likely than others to adequately follow guideline treatments. Moreover, focusing on elderly patients with breast cancer, Iglay and colleagues [51] found, in a retrospective cohort study using Medicare data from 19,208 women aged 68 or more, that patients with severe mental illness were more likely to be diagnosed with advanced breast cancer and aggressive tumors compared to patients without severe mental illness. Konishi and collaborators [52] explored short-term outcomes after breast cancer surgery in 3660 women with schizophrenia and 350,860 women without any psychiatric disorder. Patients with schizophrenia showed higher morbidity during hospitalization and more postoperative bleeding, surgical-site infections, and sepsis compared to those without mental illnesses. Here, the issue seems to have been the quality

of surgical care rather than either the aggressivity of the tumor or the patients' ability to follow guidelines.

When focusing on end-of-life populations, the most recent study on terminal breast cancer in women with schizophrenia asked whether the quality of palliative treatment differed in women with severe mental illness and those without mental illness [53]. The analysis included 1742 women with severe mental illness, of whom 380 were diagnosed with schizophrenia. Survival time was shorter in women with schizophrenia compared to the other groups.

There are probably many reasons why women with psychosis show a worse prognosis than other women once breast cancer has been diagnosed. Haskins and collaborators [54] analyzed a nationally representative cancer cohort to examine the role of preexisting mental illness on endocrine therapy adherence in women with breast cancer. The schizophrenia patients had a lower probability of starting endocrine therapy compared to the other groups. This could be attributed to patient apathy or to the influence of substance abuse but perhaps also to the indifference of their social support system, which includes their care providers. Irwin and collaborators [55] tried to identify modifiable predictors of disruptions in breast cancer care for individuals with schizophrenia and related disorders. Inadequate psychiatric treatment was one of the most important factors they hypothesized, which was confirmed by their results. Access to adequate treatment for those with severe mental illness (defined by number of previous psychiatric hospitalizations) was concluded to be a crucial factor in discontinuation of treatment.

3.5. Menopause in Women with Schizophrenia and Delusional Disorder and How It Affects Gynecologic Health

As breast cancer is a hormone-dependent disease, estrogen, progesterone, and prolactin are probably relevant to breast carcinogenesis [14]. At the time of menopause, risk for many cancers seems to increase in women, perhaps because of endocrine changes. Not only estrogen, but also progesterone and insulin-like growth factor 1, which all play important roles in neuroprotection, rapidly decrease after menopause [56]. A recent paper by Cheng et al. [56] discusses the several molecular signals that are profoundly affected by menopause and that exert influence on brain pathways potentially involved in psychotic illness.

Another recent study, previously mentioned, investigated the association between preexisting mental illness and mortality in insured women diagnosed with breast cancer [49]. Data were based on the New York State Cancer Registry and participants were 10,444 women with breast cancer. Women with severe mental illness showed higher mortality rates compared to those free of mental illness. In a secondary analysis, the investigators estimated menopause status by stratifying the sample into two groups by age: premenopausal (age < 50), postmenopausal (age > 50) [49]. Mortality rates were higher in women with preexisting severe mental illness who were postmenopausal and who used nicotine, suggesting a potential aggravating role for both menopause and cigarette smoking.

In summary, menopause, because of endocrine changes and because of the effect of increasing age and resultant comorbidity, is associated with higher rates of breast cancer and with more aggressive tumors [51].

4. Discussion

Addressing our initial questions, in terms of epidemiology, we found that recent studies support an increased incidence of breast cancer in women with schizophrenia [13,16,17]. Breast cancer rates in DD have not been studied, but prolactin-inducing antipsychotics, which are reported to raise overall breast cancer risk, are also used in this disorder, albeit for a shorter cumulative time period. Other gynecological comorbidities appear relatively frequent in psychotic conditions [12], but there is no evidence that their rate in these conditions is higher than it is in the general population. Our second question addressed cancer screening and cancer mortality in this population. All studies agree that the rates of breast and cervix screening for cancer are disproportionately low, and the high mortality rate from

breast cancer in these women is at least partially attributable to the lack of timely screening [38,39,41]. With respect to menopause, there is evidence that its advent is positively correlated with an increase in the incidence of breast cancer in women with psychotic illness and that it is associated with relatively aggressive tumors [51].

The findings of this review lead to a strong recommendation that psychiatrists and gynecologists work together, particularly with respect to breast cancer prevention and treatment in women with psychotic illness. Pettersson et al. have recommended the development of sex/disease specific prevention programs [13]. Gynecology–psychiatry partnerships would be ideal for improving health outcomes of women with psychosis.

The role of antipsychotics in increasing the risk of breast cancer in women with psychosis (via hyperprolactinemia or via weight gain) remains somewhat controversial [14] and may depend on the specifics of the antipsychotics used. In nationwide register-based data (2006–2013) that recorded all-cause mortality among Swedish patients with schizophrenia aged 16–64 [57], the lowest mortality was seen in patients on second generation depots, particularly monthly paliperidone injections. Depots were associated with an approximately 30% lower risk of death compared to that seen in patients taking oral antipsychotics. While breast cancer rates may be increased by antipsychotics, in general, adherence to antipsychotic regimens, as assured by depot medication, reduces overall mortality.

While rates may not be disproportional, cervical and ovarian cancers and nonmalignant gynecologic disease (PCOS and endometriosis) are potential problems in this population because of shared risk factors. The fact that women with psychosis lag behind other women with respect to engagement in both primary health care and cancer screening is a major mortality risk [36] that lends itself to prevention. Specific difficult-to-improve patient factors, such as cognitive problems, social isolation, apathy, and substance abuse, partially explain low screening rates, but provider factors, such as failure to educate, failure to remind, failure to encourage, and failure to link patients with necessary services, can all be reversed.

Importantly, this population of women lacks the social capital to successfully navigate the health system. Symptoms of psychosis such as amotivation interfere with adherence to treatment recommendations, but critical appointments are also missed because of nonexistent social support. In addition, because of an accumulation of prior risk factors, the tumors of women with psychosis appear to be more aggressive than those of other women [51]. Surgical care for these women may also not be optimal, perhaps because they are seen as poor candidates for life-saving procedures. End-of-life care of this population also suffers, and for similar reasons. This urgently calls for close collaboration between primary care, psychiatry, gynecology, and oncology.

In line with this idea, Irwin and collaborators [58] developed the Bridge intervention for patients with severe mental illness, a program that includes identification of severe mental illness, person-centered care, and a collaborative approach between psychiatry with oncology. Bridge is a feasible and well-accepted care model for patients with psychosis and comorbid cancer.

Because women with psychotic illness have specific health needs that differ according to stage of life, menopause and postmenopause constituting vulnerable stages [59], the gynecology/psychiatry/oncology partnership could also benefit from collaboration with endocrinology.

5. Conclusions

Recent studies point to an increased incidence of breast cancer in women with schizophrenia. Other gynecological comorbidities in women with psychotic illness are not more frequent than they are in the general population, but they carry a significant burden because their early detection and successful treatment are impaired in this population of women. Cancer screening in women with psychosis lags far behind the rate in other women. Treatment adherence also lags, and treatment adequacy is frequently suboptimal. Mortality rates from breast cancer, for instance, in women with psychosis far outstrip rates

in the general population. This review discusses several hypotheses to explain incidence rates, screening rates, and mortality rates.

We recommend implementation and evaluation of gynecology/psychiatry collaborations that support early detection and optimal treatment of gynecological conditions in women with schizophrenia and related conditions. Partnerships between gynecology and psychiatry would be well-positioned to explore any links that exist, genetic or psychosocial. We recommend that primary care and endocrinology participate in these collaborations because family physicians are critical in the goal of early detection and because hormonal influence is important in many gynecological and psychotic conditions.

This narrative review of the literature finds many links between gynecological and psychiatric disorders. Close collaboration among the relevant medical specialties will facilitate research and improve patient outcomes.

Author Contributions: A.G.-R., M.V.S., and A.G. were involved in the electronic search and selection of papers. A.G.-R., M.V.S., and A.G. wrote the first draft of the manuscript. M.N., M.M., and J.L. revised the paper, and J.A.M. revised the paper and supervised the review. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: The data presented in this review are available on request from the corresponding author.

Conflicts of Interest: A.G.-R. and A.G. have received registrations for congresses or travel funds from Janssen, Lundbeck–Otsuka, and Angelini. J.L. has received honoraria for lectures or advisory board membership from Janssen, Otsuka, Lundbeck, and Angelini. J.A.-M. has received consultancy and/or lecture honoraria from Sanofi, Pfizer, Servier, Janssen, and Lundbeck–Otsuka.

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