

Current Status and Problems of Breast Cancer Treatment with Schizophrenia

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Current Status and Problems of Breast Cancer Treatment with Schizophrenia

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Abstract

Patients with schizophrenia are often diagnosed with breast cancer in advanced stages. In addition, patients with schizophrenia with reduced ADL are less likely to receive chemotherapy or standard treatment. It is highly recommended that patients with schizophrenia undergo breast cancer screening so that they can be diagnosed early and treated adequately.

Background: Schizophrenia is a devastating mental disease that affects approximately 1% of the world's population. Breast cancer is the second most common type of cancer in the world that causes death in women. It is often unclear whether patients with schizophrenia receive recommended cancer treatment that met the guideline. This study characterized breast cancer treatment disruptions in schizophrenia patients and sought to identify and resolve correctable predictors of those disruptions. **Materials and methods:** A retrospective cohort study was conducted on 55 primary breast cancer patients diagnosed with schizophrenia and treated for breast cancer. We evaluated the characteristics of the breast cancer patients with schizophrenia compared to those of 610 breast cancer patients without schizophrenia. **Results:** Compared to the control group, the schizophrenia group had significantly advanced T and N factors and disease stage. Significantly fewer patients in the schizophrenia group than in the control group received chemotherapy ($P < .0001$) or recommended cancer treatment ($P = .0004$). Within the schizophrenia group, the patients in need of ADL support were significantly less likely to receive recommended cancer treatment. **Conclusion:** Patients with schizophrenia are often diagnosed with breast cancer in advanced stages. In addition, patients with schizophrenia with reduced ADL are less likely to receive chemotherapy or recommended cancer treatment. It is highly recommended that patients with schizophrenia undergo breast cancer screening so that they can be diagnosed early and treated adequately.

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Keywords: Breast cancer, Schizophrenia, Breast cancer screening, Guideline treatment, Chemotherapy

Introduction

Schizophrenia is a devastating mental disease that affects approximately 1% of the world's population.¹ The average age of death for schizophrenia patients is 57.3–65.5 years, which is 16.3–18.7 years earlier than that of the general population.^{2, 3, 4} Patients with schizophrenia can die prematurely due to accidents, suicide, or other illnesses.⁵

In recent years, various reports have linked schizophrenia and cancer.^{6,7} Some studies have found that patients with schizophrenia have a higher risk of cancer than the general population,⁸ while others have found that they have a lower risk of cancer^{9,10,11,12} or that there is no difference.¹³ Patients with schizophrenia, however, have a high risk of breast cancer.¹⁴

Breast cancer is the second most common type of cancer in the world, accounting for approximately 10.9% of cancer-related deaths in women.¹⁵ However, mortality due to breast cancer is steadily declining as a result of early detection by screening and advances in treatment.¹⁶ In fact, the 5-year survival rate for breast cancer has improved from 63% in the 1960s to approximately 90% today.¹⁶ Early diagnosis of breast cancer can improve prognosis. Postoperative endocrine therapy for hormone receptor-positive breast cancer has also been shown to reduce the risk of recurrence and death,^{17,18} and compared to surgery alone, chemotherapy after breast cancer surgery has been shown to improve both recurrence and survival rates.^{19,20}

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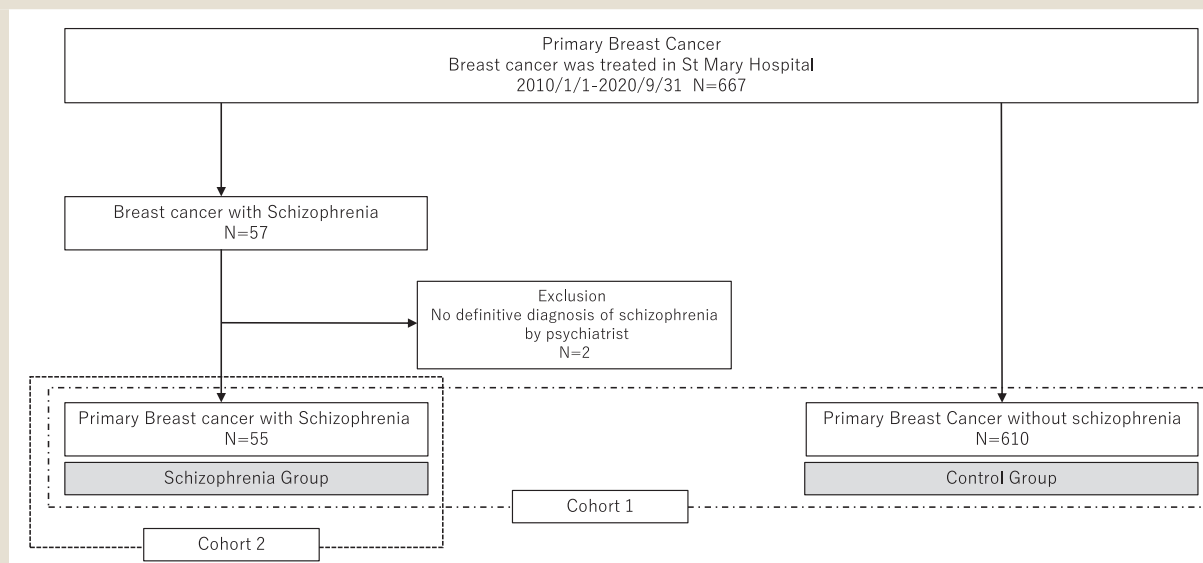
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Figure 1 Study flowchart of primary breast cancer.

However, these statistics do not apply to subjects with schizophrenia. People with schizophrenia have a lower rate of breast cancer screening.²¹ Additionally, patients with schizophrenia may not receive adequate recommended cancer treatment for breast cancer.^{22,23}

In reality, it is often unclear whether patients with schizophrenia receive recommended cancer treatment because past reports have not been focused on schizophrenia, made comparisons with the control group, or provided a solution. In this study, we sought to document the treatment of breast cancer in patients with schizophrenia.

Methods

Patients and Data Collection

We conducted a retrospective cohort study of 667 patients with primary breast cancer diagnosed between January 2010 and September 2020 and treated at St. Mary's Hospital. There were 57 patients with schizophrenia and breast cancer. 2 patients were excluded because their schizophrenia diagnosis was not confirmed by a psychiatrist; therefore, 55 patients comprised the schizophrenia group, and 610 breast cancer patients without schizophrenia were used as a control group. We compared the breast cancer characteristics between the two groups (Figure 1-Cohort 1).

The diagnosis of schizophrenia was made by a psychiatrist according to the diagnostic criteria of the International Classification of Diseases of the World Health Organization, 10th revision (ICD-10).²⁴ All the patients with schizophrenia were diagnosed before being diagnosed with breast cancer. The patients were identified through electronic medical records (Figure 1-Cohort 2).

We examined the details of the schizophrenia patients through these records.

Breast cancer was characterized by sex, age, tumour size, TNM classification, stage, estrogen receptor (ER) and human epidermal growth factor receptor type 2 (HER2) status, nuclear clade, surgical procedure, radiation therapy, hormone therapy, anti-HER2 therapy, chemotherapy, and recommended cancer treatment. The 7th edition of the TNM classification was used to determine staging.²⁵ The recommended cancer treatment was a combination of surgery, radiation therapy, hormone therapy, anti-HER2 therapy and chemotherapy that met the National Comprehensive Cancer Network Guidelines²⁶ and Japan Breast Cancer Society Clinical Practice Guidelines.²⁷ Adjuvant therapy and treatments by subtype were selected for each patient based on the characteristics of each case. We investigated whether postoperative hormone therapy was continued for more than 1 year.

Schizophrenia was characterized by age of onset, marital status, housing, body mass index (BMI), activities of daily living (ADL) assessed based on the Barthel index at admission, long-term hospitalization history (1 year or more), frequent hospitalization history (3 times or more), medical comorbidity measured by the Charlson comorbidity index (CCI),²⁸ the number and amount of psychotic drugs and the chlorpromazine conversion value.²⁹

We analysed the factors associated with the limited use of certain breast cancer treatments in the schizophrenia group. As factors of schizophrenia, schizophrenia onset under 20 years of age, marital status, housing, ADL, chlorpromazine conversion value, radiation therapy, hormone therapy, and chemotherapy were subjected to univariate analysis, while univariate and multivariate analyses were performed for recommended cancer treatment.

In addition, we examined the chief complaints of breast cancer in the schizophrenia group. The chief complaints were divided into screening and symptoms. The stage at the time of diagnosis and the

Table 1 Clinical Characteristics of the Schizophrenia Group

Patients characteristics (n = 55)		n (%)
Onset of Schizophrenia, ys	median (SD)	30.4 ± 13.9
	<20	16 (29.0)
	≥20	38 (69.1)
	Unknown	1 (1.8)
Marital status	Single or Divorced or Separated	40 (72.7)
	Married	15 (27.2)
Housing	Alone/With family/Supported housing	24 (43.6)
	Hospital	31 (56.4)
BMI	<25	41 (74.5)
	≥25	14 (25.5)
Long-term hospitalization or frequent hospitalization	Yes	38 (69.1)
	No	13 (23.6)
	Unknown	4 (7.2)
ADL	Complete Independence (Barthel Index =100)	31 (56.3)
	Partial assistance or All assistance (Barthel Index <100)	24 (43.6)
Charlson Comorbidity Index	0	38 (69.1)
	≥1	17 (30.9)
Chlorpromazine conversion value	≤600	25 (45.5)
	>600	29 (52.7)
	Unknown	1 (1.8)

period from detection to treatment were graphed, and the relationship was analysed.

This study was approved by the St. Mary's Hospital Institutional Review Board²⁰⁻⁰⁵⁰⁴ and patients provided written informed consent.

Statistical Analysis

A social science statistical package (JMP version 14.0, SAS, https://www.jmp.com/ja_jp/home.html) was used for the statistical analyses. The clinical factors between the groups were evaluated by analysis of variance for continuous variables, the chi-square test, Fisher's exact test, and the Wilcoxon rank-sum test for categorical variables, and the Cochran-Armitage test for trend analysis. *P*-values less than .05 were considered statistically significant.

Results

Table 1 shows the clinical features of the schizophrenia group. More than 70% of the patients with schizophrenia were unmarried or divorced. The average age at which schizophrenia was diagnosed was 30.4 years. More than half of the patients had a long or frequent history of psychiatric hospitalization. 56 percent of the patients had fully independent ADL (Table 1).

We compared the schizophrenia group with the control group (Table 2). Compared to the control group, the schizophrenia group had significantly advanced T and N factors and staging. There were no differences in pathological factors such as ER, HER2, and nuclear grade. For the treatment of breast cancer, 63.2% of the patients in the control group had a mastectomy, while 84.2% of the schizophrenia group had a mastectomy (*P* = .0024). Hormone therapy and anti-HER2 therapy were not significantly different

between the groups. Only 56% of the patients in the schizophrenia group received radiation therapy, which was less than the 75% of patients in the control group (*P* = .078). However, only 40% of the patients in the schizophrenia group received chemotherapy (*P* < .0001), and 61.8% received recommended cancer treatment (*P* = .0004); these values were significantly lower than those in the control group.

Table 3 shows the treatment details for each stage of the breast cancer patients with schizophrenia. All the patients with schizophrenia who needed surgery underwent surgery. Radiation therapy was available to only approximately half of the patients with schizophrenia. On the other hand, hormone therapy and anti-HER2 treatment were performed at a high rate. The patients with stage II disease did not receive adjuvant chemotherapy. In the meantime, it was performed in approximately half of the patients with stage III-IV disease. The rate at which recommended cancer treatment was available was high in patients with stage 0-I disease and low in patients with advanced stage II-IV disease (Table 3).

We analysed the factors associated with the limited use of certain treatments, namely, radiation therapy, chemotherapy and recommended cancer treatment, in schizophrenia patients (Table 4). Patients diagnosed with schizophrenia under the age of 20 did not receive significant radiation therapy on univariate analysis (*P* = .04). Univariate analysis also showed that chemotherapy was rarely used to treat patients admitted to psychiatric hospitals (*P* = .019) or those in need of ADL assistance (*P* = .028). Neither univariate nor multivariate analysis indicated that recommended cancer treatment was significantly performed in patients in need of assistance with ADL (*P* = .049, *P* = .044).

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Table 2 Breast Cancer Characteristics

Patients characteristics	Schizophrenia Group (<i>n</i> = 55) (%)	Control Group (<i>n</i> = 610) (%)	<i>P</i> value
Gender (Female)	100	99.3	1.000
Age of breast cancer diagnosis (y), mean (SD)	60.3 ± 10.4	60.9 ± 13.4	0.96
Tumor size (mm), mean (SD)	34.3 ± 23.9	22.3 ± 18.9	< 0.0001
T (0 / 1 / 2 / 3 / 4)	7.2 / 27.2 / 38.1 / 12.7 / 14.5	13.2 / 48.0 / 28.3 / 2.2 / 8.0	< 0.0001 ^b
N (0 / 1 / 2 / 3)	47.2 / 30.9 / 14.5 / 7.2	76.0 / 19.6 / 0.9 / 3.2	< 0.0001 ^b
M (0 / 1)	87.2 / 12.7	95.5 / 4.4	0.007
Cancer Stage (0 / I / II / III / IV)	7.2 / 18.1 / 38.1 / 23.6 / 12.7	12.9 / 43.9 / 31.9 / 6.7 / 4.4	< 0.0001 ^b
Estrogen receptor (Positive / Negative)	70.9 / 25.4	79.0 / 19.8	0.28
HER2 (Positive / Negative)	5.4 / 89.0	13.6 / 77.3	0.093
Nuclear Grade (1 / 2 / 3)	36.3 / 32.7 / 12.7	41.8 / 24.7 / 15.9	0.83
Surgery execution rate ^a	100 (51/51)	99.6 (595/597)	0.67
Total mastectomy rate in breast surgery	84.3 (43/51)	63.2 (376/595)	0.002
Radiation therapy execution rate ^a	56.2 (9/16)	75.9 (205/270)	0.078
Hormone therapy execution rate ^a	84.2 (32/38)	90.6 (397/438)	0.20
Anti-HER2 therapy execution rate ^a	50.0 (1/2)	81.5 (66/81)	0.35
Chemotherapy execution rate ^a	40.0 (8/20)	88.7 (189/213)	< 0.0001
Recommended cancer treatment execution rate ^a	61.8 (34/55)	79.1 (483/610)	0.0004

The % data is truncated to the second decimal place.

^a execution rate is Execution / Adaptation

^b *P* value for trend

Table 3 Stage-Based Treatment of the Schizophrenia Group

	Stage0 <i>n</i> = 4	StageI <i>n</i> = 10	StageII <i>n</i> = 21	StageIII <i>n</i> = 13	StageIV <i>n</i> = 7	Total <i>n</i> = 55
Surgery						
Execution / Adaptation (%)	4 / 4 (100)	10 / 10 (100)	21 / 21 (100)	13 / 13 (100)	3 / 3 (100)	51 / 51 (100)
Total mastectomy (%)	4 (100)	4 (40.0)	19 (90.5)	13 (100)	3 (100)	43 / 51 (84.3)
Breast conserving surgery (%)	0 (0)	6 (50.0)	2 (9.5)	0 (0)	0 (0)	8 / 51 (15.7)
Radiation therapy						
Execution / Adaptation (%)	-	3 / 6 (50)	2 / 3 (66.6)	3 / 6 (50)	1 / 1 (100)	9 / 16 (56.2)
Hormone therapy						
Execution / Adaptation (%)	-	9 / 10 (90.0)	13 / 16 (81.3)	6 / 8 (75.0)	4 / 4 (100)	32 / 38 (84.2)
Anti-HER2 therapy						
Execution / Adaptation (%)	-	-	0 / 1 (0)	-	1 / 1 (100)	1 / 2 (50)
Chemotherapy						
Execution / Adaptation (%)	-	-	0 / 4 (0)	6 / 11 (54.5)	2 / 5 (40)	8 / 20 (40.0)
Recommended cancer treatment						
Execution/Adaptation (%)	4 / 4 (100)	7 / 10 (70.0)	12 / 21 (57.1)	7 / 13 (53.8)	4 / 7 (57.1)	34 / 55 (61.8)
Recurrence						
Yes (%)	0 (0)	0 (0)	2 / 20 (10.0)	4 / 13 (30.8)	-	6 / 48 (12.5)
Observation period, mean, day	1202	1274	1619	870	932	1261

We investigated the chief complaints of breast cancer in the schizophrenia group, the stage at diagnosis, and the period until treatment (Figure 2). Patients diagnosed after a breast cancer screening were diagnosed earlier ($P = .013$) and tended to be treated sooner ($P = .068$) than symptomatic patients.

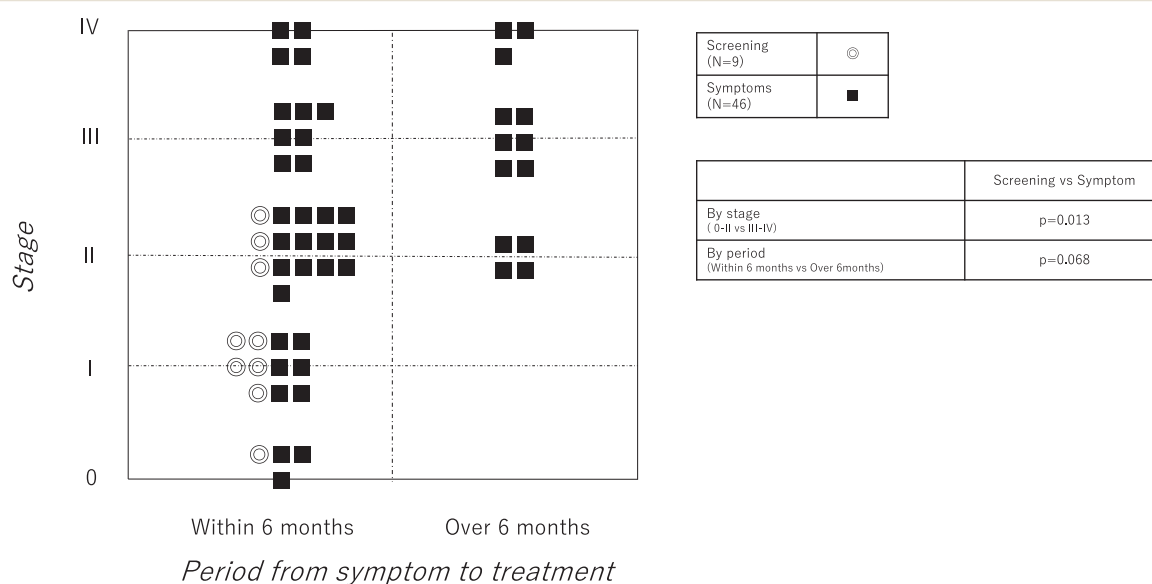
Discussion

This study indicated that only 56% of breast cancer patients with schizophrenia were characterized by independent ADL. The disease stage in these patients was more advanced than that in the controls. Regarding breast cancer treatment, the proportion of breast

Table 4 Predictors of Confusion in Breast Cancer Treatment in the Schizophrenia Group

	Radiation therapy (<i>n</i> = 16)			Hormone therapy (<i>n</i> = 38)			Chemotherapy (<i>n</i> = 20)			Recommended cancer treatment (<i>n</i> = 55)			
	Execution (<i>n</i> = 9) %(<i>n</i>)	Non- execution (<i>n</i> = 7) %(<i>n</i>)	Univariate Analysis <i>P</i> value	Execution (<i>n</i> = 32) %(<i>n</i>)	Non- execution (<i>n</i> = 6) %(<i>n</i>)	Univariate Analysis <i>P</i> value	Execution (<i>n</i> = 8) %(<i>n</i>)	Non- execution (<i>n</i> = 12) %(<i>n</i>)	Univariate Analysis <i>P</i> value	Execution (<i>n</i> = 34) %(<i>n</i>)	Non- execution (<i>N</i> = 21) %(<i>n</i>)	Univariate Analysis <i>P</i> value	Multivariate Analysis <i>P</i> value
Age at diagnosis of schizophrenia (>20 or ≤20)	22.2 (2/9)	85.7 (6/7)	.04	64.5 (20/32)	83.3 (5/6)	.64	62.5 (5/8)	83.3 (10/12)	.347	63.6 (21/34)	80.9 (17/21)	.370	.328
Marital status (married or not)	22.2 (2/9)	14.2 (1/7)	.000	21.8 (7/32)	33.3 (2/6)	.61	12.5 (1/5)	41.6 (5/12)	.324	23.5 (8/34)	33.3 (7/21)	.362	.156
Housing (not in Hospital or in Hospital)	66.7 (6/9)	57.1 (4/7)	.000	43.7 (14/32)	33.3 (2/6)	.00	87.5 (7/8)	25.0 (3/12)	.019	50.0 (17/34)	33.3 (7/21)	.594	.733
ADL (independence or assistance required)	88.8 (8/9)	42.6 (3/7)	.105	53.1 (17/32)	33.3 (2/6)	.65	87.5 (7/8)	33.3 (4/12)	.028	67.6 (23/34)	38.1 (8/21)	.049	.044
Chlorpromazine conversion value (≤600 or ≥600mg)	44.4 (4/9)	71.4 (5/7)	.357	46.8 (15/32)	16.7 (1/6)	.20	62.5 (5/8)	58.3 (7/12)	.000	45.4 (15/34)	52.3 (11/21)	.780	.977

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Figure 2 Correlation between stage and treatment initiation period by chief complaint of breast cancer in schizophrenia group.

cancer patients with schizophrenia that received radiation therapy, chemotherapy, or recommended cancer treatment was low.

The factor associated with the limited use of radiation therapy in these patients was an age at diagnosis of schizophrenia of 20 years or younger. The factors associated with the limited use of chemotherapy in these patients were that they were hospitalized in a psychiatric ward at the time of breast cancer treatment and that they had independent ADL. One of the factors associated with the limited use of recommended cancer treatment was the independence of ADL.

In addition, patients with schizophrenia who were diagnosed with breast cancer by screening were diagnosed earlier and started treatment earlier than symptomatic patients.

Breast cancer diagnosis was found to be delayed in patients with schizophrenia; therefore, the average tumour diameter in the patients with schizophrenia was 34 mm, which was significantly larger than the 22 mm in the control group. This finding is similar to those in other reports.^{30,31} Approximately 12.7% (7/55) of the patients with schizophrenia had distant metastases, which was much higher than the 4.4% (27/610) of the control group. A 6% rate of distant metastases has been reported among all US women with breast cancer.³² In addition to our results, Sharma et al reported that 19% of breast cancer schizophrenia patients showed distant metastases.³³ In all, 16.3% of the schizophrenia patients in the current study were diagnosed with breast cancer after a screening; therefore, these patients were diagnosed at an early stage of disease and were treated at an early stage. This number is similar to those reported in other studies and lower than the general public's screening rate. Unscreened patients are diagnosed with more advanced stages of breast cancer.^{34,35,36} Mastectomy tended to be the surgical treatment choice in the current study, which does not require radiation therapy or hospital visits. These results are similar to those of

Dalton et al., who reported that more patients with schizophrenia undergo mastectomy than breast-conserving surgery.^{21,31,37} On the other hand, there were cases in which the cosmetic appearance of the breast was very important and the breast was preserved.

Radiation therapy was available to approximately half of the patients in this study. According to the report of Abdullah K et al.,²³ only approximately half of patients with schizophrenia received postoperative radiation therapy. There are many cases in which treatment is refused after surgery.²³ In this study, the factor associated with the limited use of radiation therapy in these patients was an age at diagnosis of schizophrenia of 20 years or younger. Johanna et al. describe that a lower age at onset may result in poorer baseline functioning, especially regarding work and social adjustment, which may have some effect on the inability to receive radiation therapy.³⁸

Hormone therapy was initiated by 84% of the patients in the current study, which is on par with the rate of initiation among general breast cancer patients. Cole B et al. reported that hormone therapy could be introduced in 80% of breast cancer patients with mental illness. However, 25.7% of patients failed to continue hormone therapy for 5 years.³⁹ In this study, we considered the introduction of hormone therapy, but could not evaluate it until it continued for 5 years. Therefore, it is important to note that schizophrenic patients may not be able to receive hormone therapy for 5 years.

The patients with stage II breast cancer did not receive adjuvant chemotherapy. Approximately half of the patients with stage III and stage IV breast cancer received chemotherapy. In the patients with stage II breast cancer with a low risk of recurrence, postoperative adjuvant chemotherapy to prevent recurrence may be in low demand. Shinden et al.³⁴ similarly concluded that patients with

schizophrenia often do not receive adjuvant therapy. Only approximately half of the patients with stage III or stage IV metastases, with a high risk of recurrence, received chemotherapy. Postoperative adjuvant chemotherapy for breast cancer generally consists of infusion chemotherapy with anthracyclines and taxanes.^{26,27} However, for triple-negative breast cancer, oral chemotherapy may also be expected to have some effect as postoperative chemotherapy.⁴⁰ In addition, there was a result that oral chemotherapy had the same effect as taxanes for metastatic breast cancer.⁴¹ In the future, evidence of the efficacy of oral chemotherapy will be needed for breast cancer patients who have difficulty with infusion chemotherapy.

The completion rate for recommended cancer treatment was 61.8%, which was lower than that of general breast cancer patients. This may be the result of poor ADL in patients with long-term schizophrenia and the inability to receive radiation therapy or chemotherapy.

Patients with schizophrenia, even if they become aware of lumps, may not have sufficient knowledge, may not be able to tell the people around them due to fear of treatment, may be delayed in seeing a medical expert, or may be delayed in going to a medical institution. In addition, treatment may be delayed due to continued refusal to receive treatment.^{35,36} On the other hand, in the current study, neither the diagnosis nor treatment were delayed in patients with schizophrenia who had been screened for breast cancer.

Generally, in cancer treatment, the treatment becomes complicated as the cancer progresses.²⁸ The same is true for breast cancer, where resection and hormone therapy are important for early-stage breast cancer, but for advanced-stage breast cancer, chemotherapy becomes more important and requires multidisciplinary treatment.²⁸ Prognosis has been shown to improve after receiving postoperative adjuvant treatment for breast cancer (hormone therapy, chemotherapy).^{17,18,19,20}

However, in this study, the patients with schizophrenia were often diagnosed with advanced-stage breast cancer and did not receive adequate recommended cancer treatment due to the high proportion of ADL assistance required. Therefore, the prognosis for breast cancer patients with schizophrenia is expected to be poor. Can breast cancer be prevented in patients with schizophrenia? Byrne et al. reported no genetically significant association between schizophrenia and breast cancer.⁴² Patients with schizophrenia have many risk factors for breast cancer, including an uncontrolled diet, lack of exercise, obesity, hyperprolactinemia due to antipsychotics, and strong exposure to female hormones due to unmarried pregnancy and lack of lactation.⁷ We believe that it is not easy to eliminate these risks in patients with schizophrenia and that breast cancer cannot be completely prevented. Therefore, we think that breast cancer should be detected in patients with schizophrenia as soon as possible. We emphasize that breast cancer screening is important for patients with schizophrenia.

We are aware of the limits of this research. This study was a retrospective cohort study at a single institution. In addition, the observation period was short, and the prognosis of schizophrenia patients could not be analysed. In the future, we would like to understand the course of schizophrenia patients and analyse their prognosis in joint research with other institutions.

Conclusion

Patients with schizophrenia are often diagnosed with breast cancer in advanced stages. In addition, the rate of radiation therapy and chemotherapy in these patients is low, and recommended cancer treatment for breast cancer is not adequate. These findings may be the result of limited ADL due to long-term schizophrenia and hospitalization in a psychiatric department. It is highly recommended that patients with schizophrenia undergo breast cancer screening so that they can be diagnosed early and treated adequately.

Clinical Practice Point

Breast cancer patients with schizophrenia have been found to be less likely to undergo breast cancer screening. Therefore, we also know that many of them are often found as advanced breast cancer. And there are a few reports that they are not receiving postoperative radiation therapy, chemotherapy and recommended cancer treatment for breast cancer because of the mental dysfunction of schizophrenia.

However, there is no report that analyzes in detail what kind of patients with schizophrenia were not treated. We analyzed why schizophrenic patients did not receive radiation therapy, hormone therapy, chemotherapy, or recommended cancer treatment.

As the result, it was confirmed for the first time that the cause of lack of chemotherapy or recommended cancer treatment was a decrease in ADL.

From the analysis of the complaint, breast cancer screening is the best way to detect breast cancer early.

This discovery will encourage schizophrenic patients to undergo breast cancer screening in the future.

Author Contributions

Study conception and design: Kazuhisa Kaneshiro, Masahiko Taniguchi, Makoto Kubo

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Drafting of manuscript: Kazuhisa Kaneshiro, Naohiro Yoshida, Mai Yamada, Masaya Kai

Critical revision: Kazuhisa Kaneshiro, Masahiko Taniguchi, Makoto Kubo, Masafumi Nakamura

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Disclosure

Kazuhisa Kaneshiro, Masahiko Taniguchi, Makoto Kubo, Mai Yamada, Yoshihiko Sadakari, Masaya Kai, Chiyo Tsutsumi, Tatsuo Tsukamoto, Naohiro Yoshida, Masaya Tanaka, Toshiro Ogata, Masafumi Nakamura have no conflicts of interest or financial ties to disclose.

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