Clinicopathological prognostic characteristics and long-term outcomes of patients with breast cancer and collagen disorder in comparison to those without collagen disorder

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Abstract. Collagen disorders are chronic autoimmune diseases with a complex clinical course; however, the risk of breast cancer in patients with collagen disorders remains unclear. The present study aimed to investigate long-term outcomes in women with breast cancer and collagen disorders. A total of 25 patients with breast cancer and collagen disorders who were treated between January 2004 and December 2011 were included. The clinicopathological factors, treatment, recurrence-free survival (RFS) and overall survival (OS) were reviewed. The mean age was 56.4±12.6 years, and 14, eight and three patients had cancer of clinical stages I, II and III, respectively. Regarding comorbid collagen disorders, 11 patients had rheumatoid arthritis, four had systemic lupus erythematosus, four had polymyositis/dermatomyositis, two had mixed connective tissue disease, two had Sjogren's syndrome, one had scleroderma and one had adult-onset Still's disease. The expression statuses of hormone receptors (HR) and human epidermal growth factor receptor 2 (HER2) were HR(+), HER2(+) and HR(-)HER2(-) in 20 (80.0%), four (16.0%) and four (16.0%) patients, respectively. A total of 22 (84.0%) patients received steroids or immunosuppressive drugs for collagen disorders. The collagen disorder group had a higher mean Ki-67 labeling index than the control group (41.1 vs. 20.8%; P=0.007). After median observation periods of 103 and 114 months, the RFS and OS rates were lower in the collagen group than in the control group (64.5 and 80.7% vs. 85.3 and 94.3%, respectively; P<0.01). Patients with breast cancer and collagen disorders had relatively high Ki-67 expression, and relatively low RFS and OS rates. Thorough follow-up is necessary for patients with breast cancer who also have collagen disorders and high Ki-67 values.

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Abbreviations: RFS, recurrence-free survival; OS, overall survival; HR, hormone receptors; HER2, human epidermal growth factor receptor 2; PM, polymyositis; DM, dermatomyositis; SLE, systemic lupus erythematosus; ER, estrogen receptor; PgR, progesterone receptor; LI, labeling index

Key words: breast cancer, collagen disorder, prognosis, Ki-67 LI, RFS, OS

Introduction

In recent years, with the aging population, the likelihood of breast cancer with various complications and other malignancies has increased. Notably, associations between chronic disease and cancer risk have been emphasized at various levels. For example, patients with systemic lupus erythematosus (SLE) have a higher susceptibility to cancer than the general population (1). Furthermore, treatment for breast cancer with collagen disorder is complicated due to the use of various concomitant drugs and its clinical course is thus interesting.

Collagen disorders are chronic autoimmune diseases with complex clinical courses. Moreover, breast cancer with comorbid collagen disorders involving steroids and immunosuppressants complicates treatment protocols. Although the use of immunosuppressants increases the risk of opportunistic infections, their influence on prognosis remains unclear (1).

As reported in previous studies, collagen disorders comorbid with breast cancer include polymyositis (PM) and dermatomyositis (DM) (2,3). Moreover, the risk of malignant disease was the highest at time of myositis diagnosis in both PM and DM; specifically, the former was associated with a raised risk of non-Hodgkin lymphoma, lung, and bladder cancers, while the latter was strongly associated with malignant disease, particularly ovarian, lung, pancreatic, stomach, and colorectal cancers, and non-Hodgkin lymphoma (3). Patients with SLE are at a high risk of developing hematopoietic malignancies, especially non-Hodgkin's lymphoma, but at a low risk of developing solid carcinomas, such as breast,

ovarian, endometrial, and prostate cancers (1,4). Previous studies have investigated the risk factors for malignancy in patients with DM and PM (5). However, studies on patients with breast cancer and collagen disorders had small sample sizes and did not elucidate the biological and treatment status of patients with breast cancer (6,7). Therefore, this study aimed to clarify the clinicopathological characteristics and long-term prognoses of patients with breast cancer and collagen disorders.

Materials and methods

Patients. Between January 2004 and December 2011, 25 patients with histologically diagnosed invasive cancer who underwent surgery for primary breast lesions and were concomitantly diagnosed with collagen disorders were included in the study. Patients with stage IV disease, those who had received systemic chemotherapy, and male patients were excluded from the study. Furthermore, a control group of patients with breast cancer but without collagen disorders (n=58) matched for approximately contemporaneous surgery, age, disease stage, and nodal status was included. On April 7, 2021, the Ethics Committee of Saitama Medical School General Medical Center approved this retrospective study (approval no. 2021-006). Given the retrospective nature of this study, the requirement for informed consent was waived.

Methods. We obtained the following clinicopathological factors from hospital medical records: estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor type 2 (HER2), and Ki-67 labeling index (LI) (using monoclonal mouse anti-human antigen clone MIB-1; Dako Denmark A/S). ER and PgR positivity was determined when ≥1% of the nuclei in the tumor were stained using immunohistochemical staining. HER2 positivity was defined as an immunohistochemistry (VENTANA I-VIEW, clone 6F11) score of 3+ or a positive result on fluorescence in situ hybridization.

Statistical analysis. The differences in the background factors between the groups were analyzed using the χ^2, Fisher's exact, or unpaired two-group t-test. The results are summarized in Table I. Regarding survival analyses, we performed intergroup comparisons for recurrence-free survival (RFS), measured from the time of surgery until the recurrence of breast cancer, and overall survival (OS), calculated from the date of surgery until the date of death or last patient contact. RFS and OS were assessed using the Kaplan-Meier and log-rank tests. A multivariate Cox regression model was used to analyze the RFS. We defined the model using the forced entry method, including age, invasive tumor size, nodal status, histological tumor grade, lymphovascular invasion, comorbidity with collagen disorder, and steroid use. The independent effect of each variable was described using hazard ratios with 95% confidence intervals (CIs). All P values were two-sided, and P<0.05 was considered to indicate a statistically significant difference. IBM SPSS Statistics for Windows version 27 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. The date of outcome evaluation was February 25, 2022. The median potential observation periods for recurrence-free endpoints and overall survival were 103 months and 114 months, respectively.

Table I. Patient characteristics.

Variable	Patients with collagen disorder (n=25)	Patients without collagen disorder (n=58)	P-value
Mean age, years (range)	56 (31-75)	55 (32-84)	N.S.
Stage, n (%)			N.S.
I	14 (56.0)	25 (43.1)	
IIA	5 (20.0)	21 (36.2)	
IIB	3 (12.0)	9 (15.5)	
III	3 (12.0)	3 (5.2)	
Tumor size, n (%)			N.S.
T1 (≤2 cm)	15 (60.0)	35 (60.3)	
T2-3 (>2 cm)	10 (40.0)	23 (39.7)	
Nodal status, n (%)			N.S.
Negative	13 (52.0)	36 (62.1)	
Positive	10 (40.0)	21 (36.2)	
Missing	2 (8.0)	1 (1.7)	
Lymphatic invasion, n (%)			0.015
0	17 (68.0)	47 (81.0)	
1	2 (8.0)	9 (15.5)	
2-3	5 (20.0)	2 (3.4)	
Missing	1 (4.0)	0 (0.0)	
Histological grade, n (%)			0.029
I	8 (32.0)	23 (39.7)	
II	10 (40.0)	30 (51.7)	
III	6 (24.0)	2 (3.4)	
Missing	1 (4.0)	3 (5.2)	
Estrogen receptor, n (%)			
Positive	20 (80.0)	44 (75.9)	N.S.
Negative	5 (20.0)	14 (24.1)	
Progesterone receptor, n (%)			N.S.
Positive	12 (48.0)	35 (60.3)	
Negative	13 (52.0)	23 (39.7)	
HER2, n (%)			N.S.
Positive	4 (16.0)	7 (12.1)	
Negative	20 (80.0)	51 (87.9)	
Missing	1 (4.0)	0 (0.0)	
Adjuvant chemotherapy, n (%)			N.S.
Yes	5 (20.0)	14 (24.1)	
No	20 (80.0)	44 (75.9)	

HER2, human epidermal growth factor receptor 2; N.S., not significant.

Table II. Comorbid collagen disorders and treatment.

Collagen disorder	No. of patients (%)	No. of patients with treatment[a]
Rheumatoid arthritis	11 (44.0)	10
Systemic lupus erythematosus	4 (16.0)	4
Polymyositis/Dermatomyositis	4 (16.0)	3
Mixed connective tissue disease	2 (8.0)	2
Sjögren's syndrome	2 (8.0)	1
Scleroderma	1 (4.0)	1
Adult-onset Still's disease	1 (4.0)	1

[a]Steroids and/or immunosuppressants.

Results

Background of patients. The mean age of the patients was 56.4 (±12.6) years. In addition, 14, 8, and 3 patients had disease of clinical stages I, II, and III, respectively. The status of lymph node metastasis was N0 and N1 in 15 and 10 patients, respectively (Table I). The comorbidities included rheumatoid arthritis (11 patients), systemic lupus erythematosus (four patients), PM/DM (four patients), mixed connective tissue disease (two patients), Sjögren's syndrome (four patients), scleroderma (one patient), and adult-onset Still's disease (one patient) (Table II). The status of hormone receptor (HR) and HER2 expression was as follows: HR(+), 20 (80.0%) patients; HER2(+), four (16.0%) patients; and HR(-)HER2(-), four (16.0%) patients. All but two patients in the collagen disorder group who were scheduled for chemotherapy owing to nodal positivity, histological grade 3 disease, or both received chemotherapy. Although there was no between-group difference in the clinicopathological factors (Table I), 22 (88.0%), 14 (56%), 12 (48%), and 3 (12%) patients in the collagen disorder group received medications, steroids, immunosuppressants, and biological agents (tumor necrosis factor-α inhibitor), respectively, for treatment (Table II).

Subtypes and Ki-67 values. Regarding breast cancer subtypes and growth factors, Table III shows the number of cases stratified according to biological factors and Ki-67 LI values. There was no between-group difference in subtype distribution. The collagen disorder group had a higher mean Ki-67 LI value than the control group (41.1% vs. 20.8%). Of the 20 patients with recurrent disease, 11 (55%) were in the collagen disorder group. Among the patients with recurrent disease in the collagen disorder group, eight (73%) had a Ki-67 LI value of ≥20% (Fig. 1).

Prognostic analyses. After a median observation period of 103 and 114 months, the RFS and OS rates in the collagen disorder group were 49.0% (Fig. 2) and 68.8% (Fig. 3), respectively, which were lower than those in the control group (RFS, 73.9%; OS, 92.9%). Among other clinicopathological factors evaluated in the RFS, tumor diameter of >2 cm and lymphatic invasion were significantly associated (Figs. S1 and S2), while node positivity and histological grade 2 or 3 were marginally but significantly associated with poor prognosis (Figs. S3 and S4). In the multivariate analysis, four patients with missing data (two patients each with and without collagen disease) were excluded, as shown in Table IV, in addition to tumor diameter of >2 cm (P=0.034; hazard ratio, 3.076; 95% CI, 1.091-8.674), comorbidity of collagen disorder was a significant risk factor for breast cancer recurrence (P=0.014; hazard ratio, 4.855; 95% CI, 1.369-17.223).

Table III. Subtypes and Ki-67 values in patients with breast cancer stratified according to collagen disorder comorbidity (n=83).

Variable	Patients with collagen disorder (n=25)	Patients without collagen disorder (n=58)	P-value
Subtypes			N.S.
Luminal, n (%)[a]	17 (68.0)	42 (72.4)	
Luminal·HER2+, n (%)	3 (12.0)	2 (3.4)	
HER2+, n (%)	1 (4.0)	5 (8.6)	
Triple negative, n (%)	4 (16.0)	9 (15.6)	
Ki-67 LI (%)			
Range	0.4-96.1	1.9-75.6[b]	
Mean	41.1	20.8	0.007
Median	36.9	16.9	

[a]One patient's HER2 status was unknown. [b]n=22 (not all cases, but data from August 2006 onwards). N.S., not significant; HER2, human epidermal growth factor receptor 2; LI, labeling index.

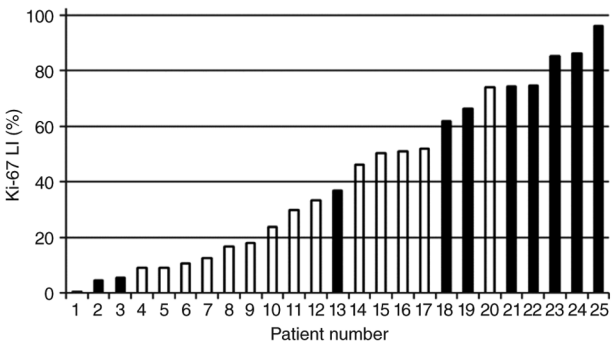

Figure 1. Relationship between the Ki-67 LI and breast cancer recurrence in patients with collagen disorder. The values are arranged in ascending order. The solid columns show patients with recurrent breast cancer. LI, labeling index

Discussion

Our findings demonstrated relatively low RFS and OS rates in patients with breast cancer and collagen disorder who frequently received steroids or other immunosuppressants for the treatment of collagen disorder.

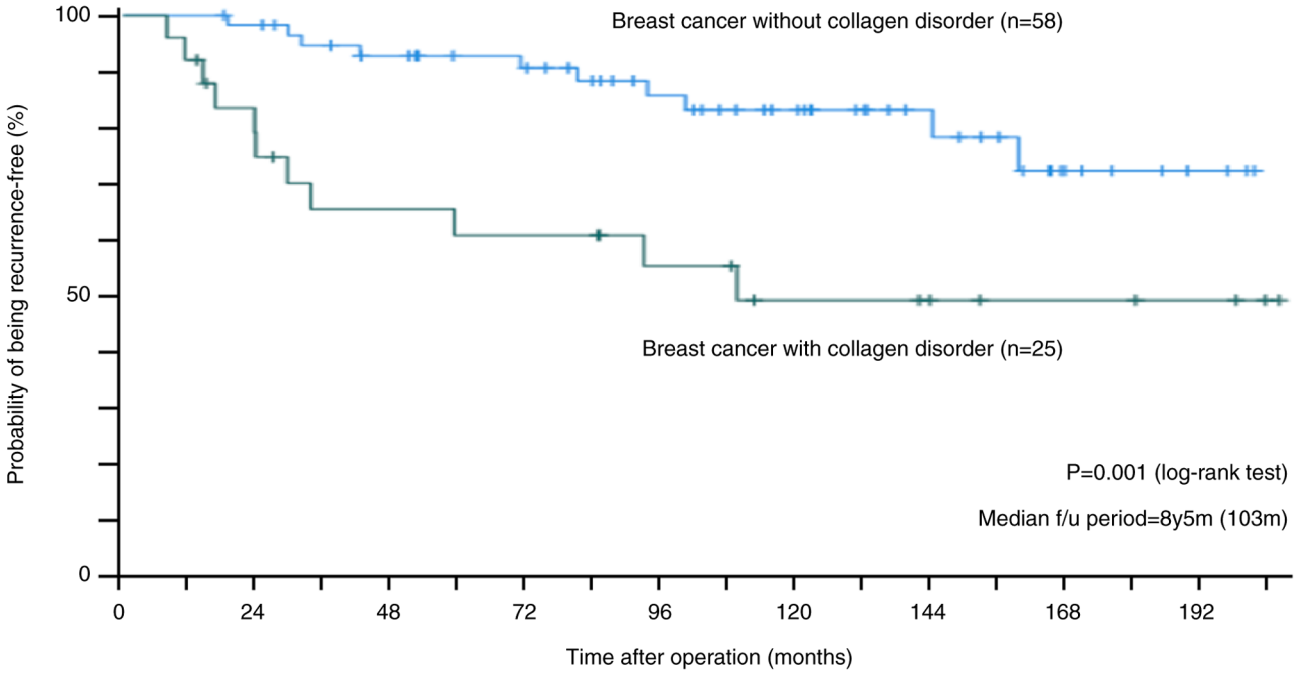

Figure 2. The recurrence-free survival of patients with breast cancer who have comorbid collagen disorder. Kaplan-Meier estimates of the probability of recurrence-free survival in patients with breast cancer with and without collagen disorders. P=0.001 (log-rank test; median f/u period, 103 months). f/u, follow-up.

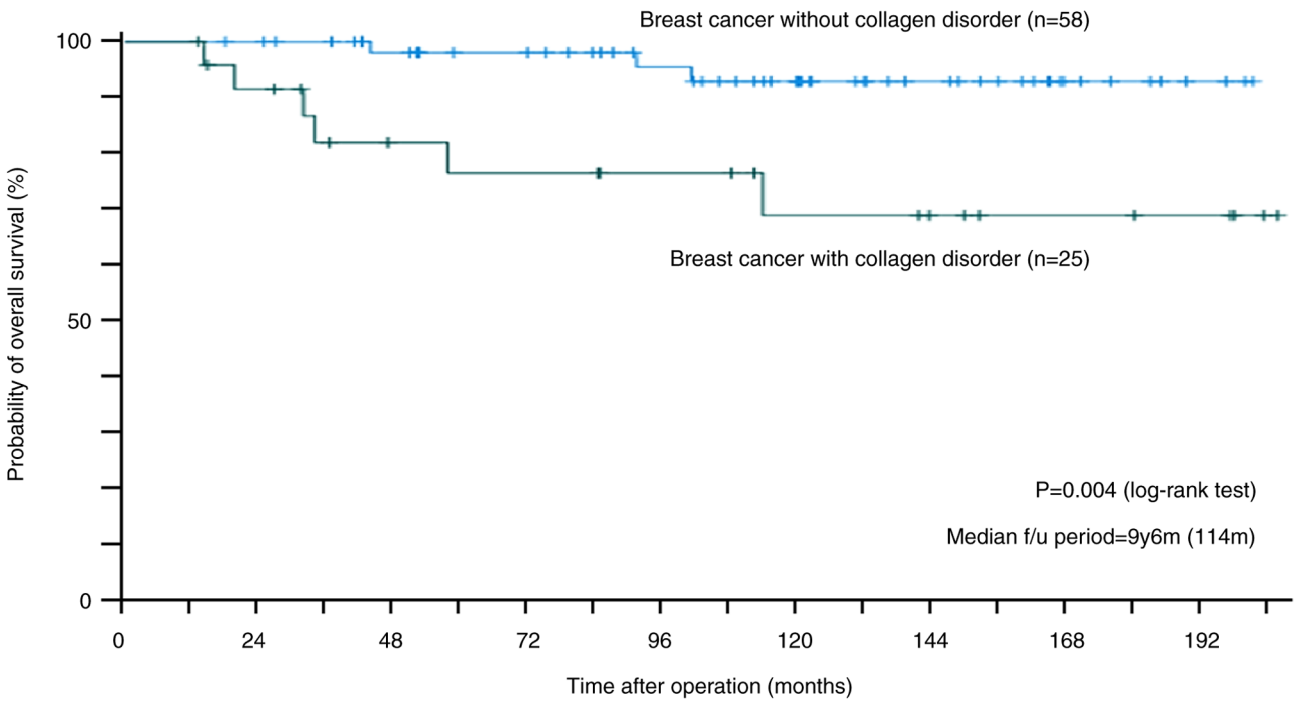

Figure 3. Overall survival of patients with breast cancer with collagen disorder. Kaplan-Meier estimates of the probability of overall survival in patients with breast cancer with and without collagen disorders. P=0.004 (log-rank test; median follow-up period, 114 months). f/u, follow-up.

The survival rate of patients with SLE, a typical collagen disorder, has dramatically improved from >40% in the 1950s to >90% since the 1980s (8,9). The main causes of death for these patients are disease activity, infections, and cardiovascular complications (10), although cancer is not one of the comorbidities. Furthermore, the 10-year survival rate among patients with PM or DM has been reported to be 62%, with the major causes of death being cardiac complications, pulmonary complications, infections, and cancer (11). Patients with rheumatoid arthritis, the most common collagen disorder in our study, had a lower mortality rate than the general population. Moreover, the major risk factor for mortality is accelerated cardiovascular disease, especially in patients with high disease activity and chronic inflammation (12). In our study, the

Table IV. Multivariate analysis of factors related to recurrence of breast cancer.

Parameter	P-value	Hazard ratio (95%CI)
Age (increase per year)	0.293	0.979 (0.941-1.019)
Tumor size (≤2 cm vs. >2 cm)	0.034	3.076 (1.091-8.674)
Lymph node metastasis (negative vs. positive)	0.854	0.889 (0.255-3.103)
Tumor grade (1 vs. 2-3)	0.054	3.107 (0.980-9.846)
Lymphovascular invasion (negative vs. positive)	0.090	3.160 (0.837-11.932)
Comorbidity with collagen disorder (no vs. yes)	0.014	4.855 (1.369-17.223)
Use of steroids (no vs. yes)	0.737	0.795 (0.209-3.030)

CI, confidence interval.

10-year survival rate was lower in the collagen disorder group than in the control group (68.8% vs. 92.9%). Furthermore, in our study, the cause of death was the progression of breast cancer rather than the progression or complications of collagen disorders.

Steroids and immunosuppressants can adversely affect the immune system of patients with collagen disorders. Moreover, patients with collagen disorders may receive insufficient or moderate treatment for breast cancer, given their systemic fragility. Cairat *et al* (13) reported that systemic glucocorticoid use is associated with an increased risk of in situ breast cancer and a decreased risk of invasive breast cancer and progression to stage 3/4. Although glucocorticoid-induced immunosuppression can theoretically increase the risk of cancer (14,15), the relationship between systemic glucocorticoid use and cancer may differ according to tumor type and stage (16). In our study, 76% of the patients in the collagen disorder group received steroid medications or other immunosuppressants, suggesting that immunological fragility leads to poor prognosis. However, multivariate analysis revealed that steroid use was not a risk factor for recurrence.

Regarding the possibility of undertreatment for breast cancer, five out of seven patients who had indications for chemotherapy received standard chemotherapy, indicating an insignificant influence of undertreatment. The relatively poor prognosis in the collagen disorder group could be attributed to the biological characteristics of breast cancer tissues. Regarding background characteristics, the collagen disorder group had a higher proportion of patients with moderate or high lymphatic invasion and histological grade 3 disease than the control group. There was no significant difference in the proportion of patients with triple-negative and HER2-type breast cancer. In the collagen disorder group, eight of the 11 patients with recurrent breast cancer had Ki-67 LI values of ≥20%. Moreover, the collagen disorder group showed higher average and median Ki-67 LI values than the control group (Table III). Extensive studies have demonstrated the prognostic utility of Ki-67 LI values (17). Although the optimal cutoff value is yet to be established, values ≥30% and ≤10% can be considered high and low, respectively (18). A high Ki-67 LI value may be related to the malignant potential of breast cancer in patients with collagen disorders. However, our intergroup comparison of Ki-67 LI was restricted because older patients were not included in the control group; Ki-67 LI examination was not performed as a routine examination before July 2006, and it was not possible to collect formalin-fixed paraffin-embedded samples for Ki-67 LI because of the lack of prior research on this topic. These results can be verified if similar case and control data were collected in 2012 and afterward.

In conclusion, patients with breast cancer and collagen disorders have relatively high growth factors and relatively low RFS and OS rates. Thorough follow-up is necessary for patients with breast cancer who have collagen disorders and high Ki-67 value.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KM, AO, YI, AF, AS, AN, HY, HS, AA, MO, HI, TT and TS provided the clinical data included in the text, performed the literature search and data analysis, and confirm the authenticity of all the raw data. KM wrote the manuscript draft. AO, HI and TS contributed to the conceptualization of the work and interpreted and revised the laboratory test results included in this report. MO and TT revised the manuscript critically and modified the text. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Saitama Medical University International Medical Center (approval no. 2021-006; April 7, 2021). The requirement of informed consent was waived given the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

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