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Original Article

Characteristics and prognosis of Japanese female breast cancer patients: The BioBank Japan project



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ABSTRACT

Background: Breast cancer is currently the most common type of cancer in Japanese females. Unlike most other types of cancer, breast cancer develops more frequently in middle-aged females than in elderly females.

Methods: Of all Japanese female breast cancer patients aged ≥ 20 years whom the BioBank Japan Project originally enrolled between 2003 and 2008, 2034 were registered within 90 days after their diagnosis. We described the lifestyle and clinical characteristics of these patients at study entry. Furthermore, we examined the effect of these characteristics on all-cause mortality.

Results: In the female patients registered within 90 days after diagnosis, the frequency of stage 0 or unclassified, stage I, II, III and IV were 11.4%, 47.9%, 37.0%, 2.9% and 0.8%, respectively. The proportion of histological types was 12.9% for non-invasive carcinoma (ductal carcinoma and lobular carcinoma), 81.0% for invasive carcinoma (papillotubular carcinoma, solid tubular carcinoma, scirrhous carcinoma and special types), 0.2% for Paget's diseases and 5.8% for others. Those positive for the estrogen and progesterone receptors accounted for 75.8% and 62.1% of all patients, respectively. Among 1860 female participants registered within 90 days, 218 participants died during 144,54 person-years of follow-up. More advanced stage, elevation of serum carcinoembryonic antigen and carbohydrate antigen 15-3 levels and absence of the estrogen receptor at study entry were crudely associated with an increased risk of all-cause mortality after adjustment for age.

Conclusions: This study showed the association of several clinical characteristics with all-cause mortality in female breast cancer patients.

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Introduction

Breast cancer is a common type of cancer in females worldwide, although the incidence rate varies by region.^{1,2} The incidence of breast cancer has increased globally,¹ with a remarkable increase witnessed in Japan.³ One explanation for this increasing

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trend in Japan may be exposure to the Westernized diet, characterized largely by its high fat content, and the subsequent development of obesity.^{4–6} Another explanation may be an increase in habitual alcohol consumption among middle-aged females.^{4,7} In Japan, breast cancer is currently the most common type of cancer in females.⁸ Unlike most other types of cancer, breast cancer develops more frequently in middle-aged females than in elderly females.⁸

Breast cancer is a determinant of mortality in females.^{1,9} According to the latest Japanese National Vital Statistics, 13,240 annual deaths are due to breast cancer in females, and breast cancer is the fifth leading cause of cancer-related death in Japanese females.¹⁰ Cancer stage and other clinical factors at diagnosis predict prognosis in breast cancer patients.¹¹ Recently, interest has increased in hormone receptors such as estrogen receptor (ER) and progesterone receptor (PgR) with regard to the therapeutic strategies and prognostic assessment of breast cancer.¹²

The BioBank Japan (BBJ) Project is a large patient-based biobank designed to implement personalized medicine for common diseases such as cancer and cardiovascular disease. Since the morbidity and mortality of breast cancer are much higher in females compared with males,^{8,10} it is worthwhile to examine sex-specific clinical characteristics and mortality of breast cancer patients. In this study, we attempted to investigate lifestyle and clinical characteristics of Japanese breast cancer patients and their prognosis, using the BBJ Project database.

Participants and methods

Study design and population

Details of the study design and protocol of the BBJ Project were described elsewhere.^{13,14} Briefly, the project enrolled patients with any of 47 common target diseases including breast cancer between June 2003 and March 2008, from 66 hospitals consisting of 12 cooperating medical institutions throughout Japan. This project collected clinical information and biological samples from participants annually until March 2013, regardless of whether the patients were newly diagnosed or treated cases. This project also followed up participants who had at least one of 32 diseases until 2014. The study protocol of the BBJ Project was approved by the research ethics committees of the Institute of Medical Science, the University of Tokyo, RIKEN Yokohama Institute and the 12 cooperating medical institutions. Written informed consent was obtained from all participants.

The BBJ Project originally enrolled 6336 breast cancer patients (46 males and 6290 females). In this report, we focused on the 6290 female participants; we excluded the 46 male participants because of the small number of participants. Of the 6290 female participants, 138 were excluded due to being aged less than 20 years having no data on smoking and alcohol drinking habits ($n = 2$) or missing data on the time from their diagnosis of breast cancer to study entry ($n = 136$). Accordingly, we described the overview of lifestyle factors and clinical profiles of the remaining 6152 female breast cancer patients. To describe the characteristics of possible newly diagnosed breast cancer patients, we selected 2034 female participants who were registered in the BBJ Project within 90 days after their diagnosis of breast cancer. Of these 2034 participants, 174 were excluded due to their refusal to participate in the follow-up survey ($n = 173$) or loss of follow-up ($n = 1$). Thus, 1860 female participants were included in the survival analyses to examine the prognosis and its risk factors in breast cancer patients.

Data collection

Clinical data were collected at study entry via interviews and medical records.¹⁵ The data included age at study entry, time from the diagnosis of breast cancer to study entry, height, weight, smoking habits, alcohol intake, past history, family history and clinical information at study entry including laboratory examination data (e.g., blood chemical markers and imaging data). Body mass index was calculated as weight in kilograms divided by height in meters squared. The blood chemical marker used in this report were serum carcinoembryonic antigen (CEA) level, carbohydrate antigen 15-3 (CA15-3) level and ER and PgR statuses. The stage of breast cancer was classified according to the Japanese Classification of Breast Cancer, the 15th edition (2004). In this report, the histological type of breast cancer was determined primarily based on the findings in surgically resected tissues, while missing histological data were complemented with the findings from biopsy or cytological samples.

Follow-up survey

Follow-up survival survey was conducted until 2014 to determine whether the status of each participant was alive, relocated, unidentified, or dead by confirming their residence cards. The new addresses of participants who relocated were also recorded in the next survival survey. The date of death was also recorded for deceased participants. The outcome assessed in this study was death due to all causes. Details of the follow-up survey were described elsewhere.^{14,16}

Statistical analysis

We performed a descriptive analysis of lifestyle and clinical characteristics of female breast cancer patients. The characteristics of interest were age at study entry, body mass index, smoking and drinking habits, comorbidities of mastopathy, family history of breast cancer, stage, histological type, serum CEA and CA15-3 levels and ER and PgR statuses. The frequency of each characteristic was calculated in female study participants after excluding those with missing data. This analysis was performed in all participants and participants who were registered in the BBJ Project within 90 days after their diagnosis of breast cancer. The same analysis was conducted after stratifying the participants by age at study entry (20–59 versus ≥ 60 years old) or invasive status. The non-invasive type group included ductal carcinoma and lobular carcinoma, while invasive type group included papillotubular carcinoma, solid tubular carcinoma, scirrhous carcinoma and special types.

We evaluated the prognosis of breast cancer in female participants registered within 90 days after their diagnosis. We calculated the 5-year relative survival rate by dividing the 5-year cumulative survival rate by the sex- and age-adjusted expected survival rate in our eligible female breast cancer patients. The 5-year cumulative survival rate was calculated, using the Kaplan–Meier method. The expected survival rate was calculated, using a survival-rate table of a reference Japanese cohort from the Cancer Registry and Statistics, Cancer Information Service, National Cancer Center, Japan,¹⁷ which was based on sex- and age-specific mortality rates and Gompertz–Makeham's law in abridged life tables, published annually by the Statistics and Information Department of the Ministry of Health, Labour and Welfare, Japan.¹⁸

We examined the impact of lifestyle and clinical characteristics on all-cause mortality in breast cancer patients registered within 90 days after their diagnosis. We used a Cox proportional hazards model to estimate the hazard ratios and 95% confidence intervals (CIs) for mortality for each characteristic category, with one

category set as the reference. The model was stratified by institution to account for variability in baseline hazards among the institutions. The model incorporated age at study entry (years as a continuous variable) and the entry year (2003, 2004, 2005, 2006, 2007 and 2008, setting year 2003 as the reference) in addition to each characteristic. We examined the association between BMI and mortality using a continuous variable, as well as the categorical variable. In this analysis, we excluded the participants with missing data or the group of small number of participants.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). All p values were two-tailed, and the significance level was set at $p < 0.05$.

Results

Characteristics of all participants with breast cancer

Among 6152 female breast cancer patients aged ≥ 20 years at the enrollment, the mean (standard deviation) age at study entry was 57.6 (11.9) years. The distribution of the participants according to age at study entry is illustrated in Fig. 1; age distribution was normal, with 55–59 years representing the peak age. The distribution of the participants according to the time from the diagnosis to study entry was as follows: 33.1% for ≤ 90 days, 19.9% for 91–365 days, 28.0% for 1–4 years, 12.6% for 5–9 years, 4.3% for 10–14 years, 1.3% for 15–19 years, 0.9% for ≥ 20 years. Table 1 summarizes other characteristics of the female breast cancer patients. Over 10% of female participants had a family history of breast cancer. Among the participants with stage information, approximately 40% were classified as stage I at study entry, while 2% were classified as stage IV. Invasive carcinoma was much more common than the non-invasive type. Of the invasive types, papillotubular carcinoma was the most common histological type followed by scirrhous carcinoma, solid tubular carcinoma and special types. Less than 10% had a serum CEA level of 5 ng/mL or higher, while approximately 5% had a serum CA15-3 level of 27 U/mL or higher. Approximately 70% were positive for ER and approximately 60% for PgR.

Characteristics of participants registered within 90 days after diagnosis

Of all female breast cancer patients aged ≥ 20 years, 2034 female participants were registered within 90 days after the diagnosis of breast cancer. The mean age (standard deviation) at study entry was 55.3 (12.0) years. Age distribution of these participants was shifted to younger as compared to the overall participants (Fig. 1). The frequency of ever drinker was higher in those registered within 90 days compared with the overall participants (Table 1). The frequency of stage 0 or I was higher in those registered within 90 days compared with the overall participants, with the lower frequency of stage II or III. As compared with the overall participants, the proportion of ductal carcinoma was higher in those registered within 90 days, while the proportion of papillotubular carcinoma was lower in those registered within 90 days. Other characteristics were similar for those registered within 90 days and the overall participants.

When these female participants were stratified by age at study entry, most of the clinical characteristics were similar for younger (aged 59 years or less) and older (aged 60 years or more) groups. The frequency of obesity was higher in the older age group compared with the younger age group, while the frequencies of ever smoker, alcohol drinker and PgR positivity were lower in the older, than younger, age group (Table 1).

When these female participants were stratified by invasive status, most of the clinical characteristics were similar for the non-invasive and invasive types (Table 2). Non-invasive carcinoma was more prevalent at a younger age, compared with the invasive type. Over half of the non-invasive cases were classified as stage 0, while approximately 90% of the invasive cases were classified as stage I or II. Those with invasive carcinoma had a higher frequency of obesity and a lower frequency of PgR positivity, compared with the non-invasive cases.

Prognosis of participants registered within 90 days after diagnosis

Among the 1860 female participants involved in the survival survey, the mean (standard deviation) follow-up period was 7.8

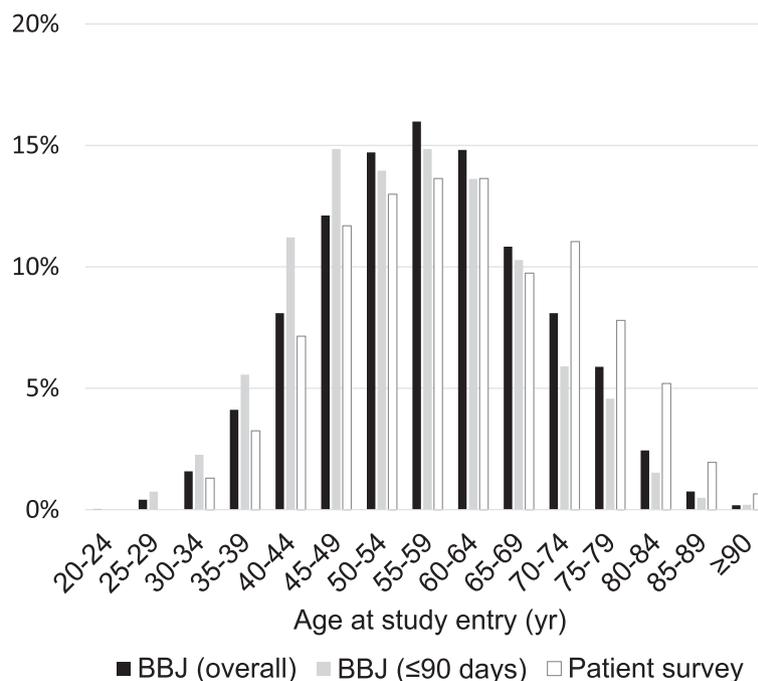


Fig. 1. Distribution of the female breast cancer patients according to age at study entry. Bars colored in black, gray and white represent patients in the BioBank Japan (BBJ) Project: (■) the overall participants and (■) those registered within 90 days after their diagnosis and (□) patients in the Patient Survey in Japan, 2005,¹⁹ respectively.

Table 1

Characteristics of the 6152 female breast cancer patients in the Biobank Japan Project. Data are also presented for the 2034 female breast cancer patients who were registered within 90 days after diagnosis and for patients grouped according to age at entry.

	Overall participants		Those registered within 90 days after diagnosis					
	Total (n = 6152)		Total (n = 2034)		Age at study entry			
	n	%	n	%	20–59 yr (n = 1290)		≥60 yr (n = 744)	
					n	%	n	%
Body mass index								
<18.5 kg/m ²	535	9.0	189	9.4	145	11.4	44	6.0
18.5–24.9 kg/m ²	4071	68.4	1387	69.2	926	72.7	461	63.2
≥25.0 kg/m ²	1347	22.6	427	21.3	203	15.9	224	30.7
Unknown	199		31		16		15	
Smoking habit								
Never	4759	78.3	1546	76.2	910	70.8	636	85.7
Ever (current/former)	1316	21.7	482	23.8	376	29.2	106	14.3
Unknown	77		6		4		2	
Alcohol drinking habit								
Never	3855	63.6	1176	58.1	640	49.8	536	72.3
Ever (current/former)	2207	36.4	849	41.9	644	50.2	205	27.7
Unknown	90		9		6		3	
History of mastopathy								
Absence	6083	98.9	2009	98.8	1272	98.6	737	99.1
Presence	69	1.1	25	1.2	18	1.4	7	0.9
Family history of breast cancer								
Absence	5459	88.7	1789	88.0	1142	88.5	647	87.0
Presence	693	11.3	245	12.0	148	11.5	97	13.0
Stage								
0	200	6.8	144	10.9	110	12.5	34	7.8
Unclassified	12	0.4	7	0.5	7	0.8	0	0.0
I	1188	40.2	633	47.9	434	49.2	199	45.4
IIA	911	30.8	413	31.3	258	29.2	155	35.4
IIB	382	12.9	76	5.8	43	4.9	33	7.5
IIIA	94	3.2	19	1.4	15	1.7	4	0.9
IIIB	86	2.9	15	1.1	6	0.7	9	2.1
IIIC	25	0.8	4	0.3	3	0.3	1	0.2
IV	59	2.0	10	0.8	7	0.8	3	0.7
Unknown	3195		713		407		306	
Histological type								
Non-invasive								
Ductal carcinoma	430	7.9	236	12.4	177	14.4	59	8.7
Lobular carcinoma	34	0.6	10	0.5	6	0.5	4	0.6
Invasive								
Papillotubular carcinoma	2081	38.2	596	31.3	382	31.1	214	31.7
Solid tubular carcinoma	798	14.7	262	13.8	160	13.0	102	15.1
Scirrhous carcinoma	1466	26.9	556	29.2	358	29.1	198	29.3
Special type	327	6.0	130	6.8	72	5.9	58	8.6
Paget's disease	12	0.2	4	0.2	1	0.1	3	0.4
Others	295	5.4	111	5.8	74	6.0	37	5.5
Unknown	709		129		60		69	
Serum CEA level								
<5 ng/mL	5437	92.9	1868	95.0	1198	96.1	670	93.1
≥5 ng/mL	417	7.1	98	5.0	48	3.9	50	6.9
Unknown	298		68		44		24	
Serum CA15-3 level								
<27 U/mL	5436	95.1	1897	97.2	1208	97.7	689	96.2
≥27 U/mL	283	4.9	55	2.8	28	2.3	27	3.8
Unknown	433		82		54		28	
Estrogen receptor status								
Positive	3110	71.7	1253	75.8	823	77.5	430	72.6
Negative	1226	28.3	401	24.2	239	22.5	162	27.4
Unknown	1816		380		228		152	
Progesterone receptor status								
Positive	2568	60.3	1021	62.1	704	66.6	317	54.1
Negative	1692	39.7	622	37.9	353	33.4	269	45.9
Unknown	1892		391		233		158	

Abbreviations: CA15-3, carbohydrate antigen 15-3; CEA, carcinoembryonic antigen.

(2.0) years in a total of 14,454 person-years of follow-up. During the follow-up period, 218 deaths were identified in the total period and 120 were identified during the 5 years of follow-up. Consequently, the 5-year cumulative survival rate was 93.5% (95% CI, 92.4–94.6). The 5-year relative survival rate was 96.2% (95% CI, 95.0–97.3).

Table 3 shows which clinical characteristics will affect all-cause mortality in female breast cancer patients. The risk of all-cause mortality increased with increasing age at study entry. In addition, more advanced stage, elevation of serum CEA and CA15-3 levels and absence of ER at study entry were crudely associated

Table 2
Characteristics of female breast cancer patients registered in the Biobank Japan Project within 90 days after diagnosis grouped according to invasive status.

	Invasive status			
	Non-invasive type (n = 246)		Invasive type (n = 1544)	
	n	%	n	%
Age at study entry				
20–29 yr	1	0.4	9	0.6
30–39 yr	29	11.8	111	7.2
40–49 yr	80	32.5	399	25.8
50–59 yr	73	29.7	453	29.3
60–69 yr	51	20.7	367	23.8
70–79 yr	11	4.5	170	11.0
80–89 yr	1	0.4	31	2.0
≥90 yr	0	0.0	4	0.3
Body mass index				
<18.5 kg/m ²	31	12.7	134	8.8
18.5–24.9 kg/m ²	175	71.7	1046	68.9
≥25.0 kg/m ²	38	15.6	339	22.3
Unknown	2		25	
Smoking habit				
Never	192	78.0	1174	76.3
Ever (current/former)	54	22.0	364	23.7
Unknown	0		6	
Alcohol drinking habit				
Never	142	57.7	891	58.0
Ever (current/former)	104	42.3	644	42.0
Unknown	0		9	
History of mastopathy				
Absence	243	98.8	1526	98.8
Presence	3	1.2	18	1.2
Family history of breast cancer				
Absence	219	89.0	1353	87.6
Presence	27	11.0	191	12.4
Stage				
0	99	51.3	37	3.6
Unclassified	4	2.1	3	0.3
I	57	29.5	532	51.7
IIA	31	16.1	348	33.8
IIB	1	0.5	69	6.7
IIIA	1	0.5	15	1.5
IIIB	0	0.0	15	1.5
IIIC	0	0.0	4	0.4
IV	0	0.0	7	0.7
Unknown	53		514	
Serum CEA level				
<5 ng/mL	233	96.3	1424	95.3
≥5 ng/mL	9	3.7	70	4.7
Unknown	4		50	
Serum CA15-3 level				
<27 U/mL	236	98.7	1449	97.3
≥27 U/mL	3	1.3	40	2.7
Unknown	7		55	
Estrogen receptor status				
Positive	154	74.4	1032	76.3
Negative	53	25.6	321	23.7
Unknown	39		191	
Progesterone receptor status				
Positive	138	67.0	826	61.5
Negative	68	33.0	518	38.5
Unknown	40		200	

Abbreviations: CA15-3, carbohydrate antigen 15-3; CEA, carcinoembryonic antigen.

with an increased risk of all-cause mortality after adjustment for age at study entry and entry year (Table 3).

Discussion

In this report, we described the lifestyle and clinical characteristics of Japanese female breast cancer patients involved in the BBJ Project. As compared to the results of female breast cancer patients in the Patient Survey in Japan, 2005 (Fig. 1),¹⁹ our registry contained a greater proportion of younger age distribution. Contrary to

expectation, those registered within 90 days had a higher frequency of stage 0 and I and a lower frequency of stage II and III, compared with the overall participants. These unreasonable results may have been due to missing data on stage and/or a possible selection bias. ER- and PgR-negative cases accounted for approximately 25% and 40% of those registered within 90 days after diagnosis, respectively, and were crudely associated with poorer prognosis.

The Japanese Breast Cancer Society (JBCS) Registry reported that the frequencies of stage 0, I, II, III and IV were 9.5%, 38.2%, 41.0%, 8.5% and 2.9%, respectively.¹¹ In addition, the JBCS Registry reported that the proportions of ER and PgR positivity were 75.7% and 62.3% among those registered in 2005, respectively.¹¹ Furthermore, with respect to histological type of breast cancer, the JBCS Registry reported proportions of 82.9%, 8.2% and 8.9% for invasive carcinoma, non-invasive ductal carcinoma and remaining types (including non-invasive lobular carcinoma and special and other types), respectively, among breast cancer patients registered in 2004.²⁰ Our results were in accordance with the results of this relevant registry.

The Japanese Association of Clinical Cancer Centers registered 21,322 female breast cancer patients between 2004 and 2007, and reported that the frequency of each cancer stage was 42.2% for stage I, 42.9% for stage II, 10.0% for stage III, 4.1% for stage IV and 0.8% for others or unknown.²¹ Our stage frequencies are comparable to those of that registry. The Japanese Association of Clinical Cancer Centers reported a 5-year relative survival rate of 92.9%.²¹ As expected from the similarities in stage frequency between the corresponding registry and our registry, our 5-year relative survival rate of female breast cancer patients was similar.

The JBCS Registry further demonstrated that more advanced stage was associated with poorer prognosis in breast cancer patients after a median follow-up period of 60.0 months.¹¹ A negative ER status tended to be associated with poorer prognosis, compared with a positive ER status, although prognosis was compared with respect to both ER and human epidermal growth factor receptor 2 statuses.¹¹ PgR negativity also tended to be associated with poorer prognosis, compared with PgR positivity, although this comparison was conducted only in ER-positive cases.¹¹ The effectiveness of endocrine therapy may explain better prognosis in ER- or PgR-positive cases compared with the respective negative cases.²² Our results were somewhat consistent with the results of that survival survey, although the association was not significant between PgR status and mortality in our patients. Along with patient characteristics evaluated in the JBCS Registry, our survival analysis also identified similar predictive factors for all-cause mortality in female breast cancer patients. In addition to cancer stage and hormone receptor status, we observed that elevation of serum CEA and CA15-3 levels was also crudely associated with poorer prognosis after adjustment for age and study entry year.

The strength of the present study was the enrollment of female breast cancer patients from many participating hospitals nationwide. On the other hand, the present study has several limitations. First, the survival analysis was conducted among cases registered within 90 days after their diagnosis, not definite incident cases. There might have been a bias resulting from selecting survival patients in our prognostic assessment. Therefore, the true prognosis of breast cancer may be worse than we observed. Second, we identified factors predicting all-cause mortality in breast cancer patients after adjustment only for age and entry year. These predictive factors may be interrelated, while other factors such as performance status and treatment may confound the associations we observed. Therefore, caution should be taken in interpreting our results. Finally, there were missing data on some variables in the BBJ Project database. The main reason for missing data was that the data were collected mostly from medical records in which limited clinical information was available. Another possible reason for missing data on cancer

Table 3

Age-adjusted hazard ratios for all-cause mortality in female breast cancer patients registered in the Biobank Japan Project within 90 days after diagnosis grouped according to characteristics, after a mean follow-up period of 7.8 years.

	Those registered within 90 days after diagnosis			Age-adjusted HR (95% CI)
	Participants	Cases	PYFU	
Age at study entry				
Additional 1 yr increase				1.04 (1.03–1.05)
Body mass index				
<18.5 kg/m ²	174	17	1323	1.03 (0.56–1.88)
18.5–24.9 kg/m ²	1271	141	9932	1.00 Reference
≥25.0 kg/m ²	386	48	3006	0.79 (0.53–1.18)
Additional 1 kg/m ² increase				0.98 (0.94–1.02)
Smoking habit				
Never	1416	172	10981	1.00 Reference
Ever (current/former)	439	46	3425	0.97 (0.64–1.46)
Alcohol drinking habit				
Never	1075	130	8248	1.00 Reference
Ever (current/former)	777	85	6146	1.06 (0.75–1.52)
Stage				
0 or unclassified	138	3	1051	0.65 (0.08–5.28)
I	582	38	4622	1.00 Reference
II	444	50	3528	1.28 (0.64–2.56)
III	33	8	237	16.06 (3.13–82.49)
IV	10	6	39	45.83 (10.83–193.89)
Invasive status				
Non-invasive	226	10	1785	1.00 Reference
Invasive	1414	182	11036	2.09 (0.91–4.77)
Serum CEA level				
<5 ng/mL	1726	173	13527	1.00 Reference
≥5 ng/mL	90	35	570	3.92 (2.56–6.00)
Serum CA15-3 level				
<27 U/mL	1753	181	13753	1.00 Reference
≥27 U/mL	51	27	243	5.16 (3.28–8.13)
Estrogen receptor status				
Positive	1149	104	9110	1.00 Reference
Negative	369	55	2795	1.55 (1.01–2.39)
Progesterone receptor status				
Positive	934	80	7399	1.00 Reference
Negative	576	77	4437	1.31 (0.86–1.98)

Abbreviations: CA15-3, carbohydrate antigen 15-3; CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; PYFU, person-years of follow-up. The hazard ratios were calculated using a Cox proportional hazards regression model stratified by institution and adjusted for age at study entry and entry year.

stage was that the data were collected through medical records regarding each component of the TNM classification (included in the Japanese Classification of Breast Cancer, the 15th edition (2004)), but not stage. Furthermore, some cancer patients admitted participating hospitals for only therapeutic procedures or follow-up after being diagnosed at other hospitals. The lack of data on stage may explain the unreasonable results regarding the frequency of stage among the overall participants and those registered within 90 days after diagnosis. However, it is unclear whether these reasons for missing data had a crucial effect on our results.

In conclusion, we evaluated the characteristics of female breast cancer patients in detail, and found that they are in excellent agreement with other nationwide registries of breast cancer patients. In the survival analysis, we found that some characteristics at study entry would be crudely associated with all-cause mortality in Japanese female breast cancer patients. Due to the potentially high generalizability of the breast cancer patients in the BBJ Project, this project can be expected to provide reliable and valuable evidence on breast cancer.

Conflicts of interest

All authors declare no conflicts of interest.

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Appendix

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