



Clinicopathological features of male patients with breast cancer based on a nationwide registry database in Japan

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Abstract

Background Male breast cancer (MBC) is rare; however, its incidence is increasing. There have been no large-scale reports on the clinicopathological characteristics of MBC in Japan.

Methods We investigated patients diagnosed with breast cancer in the Japanese National Clinical Database (NCD) between January 2012 and December 2018.

Results A total of 594,316 cases of breast cancer, including 3780 MBC (0.6%) and 590,536 female breast cancer (FBC) (99.4%), were evaluated. The median age at MBC and FBC diagnosis was 71 (45–86, 5–95%) and 60 years (39–83) ($p < 0.001$), respectively. MBC cases had a higher clinical stage than FBC cases: 7.4 vs. 13.3% stage 0, 37.2 vs. 44.3% stage I, 25.6 vs. 23.9% stage IIA, 8.8 vs. 8.4% stage IIB, 1.9 vs. 2.4% stage IIIA, 10.1 vs. 3.3% stage IIIB, and 1.1 vs. 1.3% stage IIIC ($p < 0.001$). Breast-conserving surgery was more frequent in FBC (14.6 vs. 46.7%, $p = 0.02$). Axillary lymph node dissection was more frequent in MBC cases (32.9 vs. 25.2%, $p < 0.001$). Estrogen receptor(ER)-positive disease was observed in 95.6% of MBC and 85.3% of FBC cases ($p < 0.001$). The HER2-positive disease rates were 9.5% and 15.7%, respectively ($p < 0.001$). Comorbidities were more frequent in MBC (57.3 vs. 32.8%) ($p < 0.001$). Chemotherapy was less common in MBC, while endocrine therapy use was similar in ER-positive MBC and FBC. Perioperative radiation therapy was performed in 14.3% and 44.3% of cases.

Conclusion Japanese MBC had an older age of onset, were more likely to be hormone receptor-positive disease, and received less perioperative chemotherapy than FBC.

Keywords Male breast cancer · National clinical database · Japanese

Introduction

Breast cancer is rare among men, while it is the most common cancer among women, with approximately 91,605 cases (excluding intraepithelial cancer) in 2017 [1]. In 2017, the Japanese Breast Cancer Society's Breast Cancer Registry reported 591 cases of male breast cancer (MBC), which continues to increase every year [2]. According to the Demographic Survey of the Ministry of Health, Labor and Welfare, the morbidity and mortality rates of both, MBC and female breast cancer (FBC) tend to increase; however,

the trend is more moderate in MBC than FBC [3]. On the other hand, the lack of the data and information of MBC is the issue.

In Japan, cancer statistics are evaluated based on regional cancer registries; however, MBC is not documented, and its clinicopathological features have not been examined. In addition, the evaluation of biomarkers such as estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) expression in the treatment of breast cancer is crucial yet lacking for MBC cases in Japan. According to previous reports from Western trials, MBC is characterized by older age and more hormone receptor-positive cases than FBC [4].

In 2011, the National Clinical Database (NCD), a nationwide system that links data collection to the first level of

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surgical specialization in the Japanese Surgical Board Certification System, adopted an annual web-based data collection system. In 2014, data on 1.6 million surgical procedures from more than 4,000 hospitals were collected [5]. Approximately 1.2 million cases are registered annually, representing more than 95% of the surgeries performed in Japan [6]. Many reports using the NCD have been published due to its reliable and abundant data [7–11]. Nevertheless, there are no large-scale reports on the clinicopathological characteristics of MBC in Japan. Understanding such characteristics is expected to be helpful for the treatment of this rare cancer. Thus, this study aimed to clarify the clinicopathological characteristics and identify the unmet needs of MBC cases in Japan.

Methods

Patient selection and data collection

We investigated patients diagnosed with breast cancer registered in the Japanese NCD between January 2012 and December 2018. This study was approved by the Institutional Review Board of the National Center for Global Health and Medicine (NCGM-G-003309-00) on September 6, 2019.

Robust patient variables, including age, sex, body mass index, performance status (PS), surgical procedure, family history, comorbidities, pathological factors, and perioperative systemic therapy, were obtained from the Japanese NCD.

ER and progesterone receptor (PgR) positivity were defined according to the ASCO/CAP 2010 guidelines [12], while HER2 positivity was defined according to the ASCO/CAP 2018 guidelines [13]. Subtypes were defined as follows: luminal type with HER2 negative, ER positive and/or PgR positive; luminal-HER2 type with HER2 positive, ER positive and/or PgR positive; HER2 type with HER2 positive, ER negative and PgR negative; triple negative breast cancer (TNBC) with HER2 negative, ER negative, and PgR negative.

Patients' backgrounds were analyzed in total populations. TNM classification, histology, family history, and systemic treatment were analyzed according to each subtype. Comorbidity was collected from 2016. Thus it is analyzed data between 2016 and 2018.

Statistical analysis

All statistical analyses were performed with SAS ver.9.4 (SAS Institute, Cary, NC, USA). Statistical comparisons of categorical variables were performed using chi-squared or Fisher's exact probability tests. Continuous variables were

compared using the Wilcoxon rank-sum test. Continuous variables are expressed using the median and interquartile range or average. Two-tailed *p* values < 0.05 were considered statistically significant.

Results

Patients

A total of 594,316 breast cancer cases, including 3780 cases of MBC (0.6%) and 590,536 cases of FBC (99.4%) were diagnosed between January 2012 and December 2018 in Japan (Table 1). The median ages at MBC or FBC diagnosis were 71 (45–86) and 60 years (39–83) ($p < 0.001$), respectively. Furthermore, 2.0% of the MBC cases and 5.6% of the FBC cases were under 40 years of age ($p < 0.001$). Bilateral disease was observed in 2.7% of the MBC cases and 9.7% of the FBC cases. Meanwhile, 97.0% of MBC cases and 90.1% of FBC cases were unilateral disease ($p < 0.001$). The median body mass index was higher in the MBC group than in the FBC group (23.1 vs. 22.3, $p < 0.001$). In addition, MBC cases tended to have higher clinical stages than FBC cases with resectable and/or locally advanced disease: 7.4 vs. 13.3% stage 0, 37.2 vs. 44.3% stage I, 25.6 vs. 23.9% stage IIA, 8.8 vs. 8.4% stage IIB, 1.9 vs. 2.4% stage IIIA, 10.1 vs. 3.3% stage IIIB, and 1.1 vs. 1.3% stage IIIC ($p < 0.001$). The frequency of de novo stage IV disease was similar between the two groups (2.1 vs. 2.0%). Over 95% of the cases in both groups underwent surgery (95.2 and 96.1%). Breast-conserving surgery was more frequent in FBC cases (14.6 vs. 46.7%, $p = 0.02$). Finally, axillary lymph node dissection with or without sentinel lymph node biopsy was more frequent in MBC cases (32.9 vs. 25.2%, $p < 0.001$).

Pathological feature

ER/PgR and HER2 statuses were available for 3003 (79.4%) MBC cases and 464,346 (78.6%) FBC cases. ER-positive disease was observed in 95.6% of MBC cases and 85.3% of FBC cases ($p < 0.001$). The PgR group had similar statistics between groups (90.4 vs. 72.9%, $p < 0.001$). The incidence of HER2-positive disease was 9.5% and 15.7% in MBC and FBC, respectively ($p < 0.001$). MBC exhibited larger tumors and more lymph node positivity ($p < 0.001$) but the same rate of M1 disease (1.4 vs. 1.3%, $p = 0.37$). Furthermore, invasive ductal carcinoma was more frequent in MBC cases (83.7 vs. 77.8%), and invasive lobular carcinoma was more frequent in FBC cases (1.3 vs. 4.6%) ($p < 0.001$). The distribution of the nuclear grade was similar between MBC and FBC cases (Table 2). Finally, the luminal subtype was more frequent in MBC cases (88 vs. 74%) (Fig. 1).

Table 1 Patients characteristics

		Male		Female		<i>p</i> value
<i>N</i>		3780		590,536		
Age	Median, 5–95%	71 (45–86)		60 (39–83)		<0.001
	<20	17	0.4%	996	0.2%	<0.001
	<40	62	1.6%	31,683	5.4%	
	<60	657	17.4%	252,212	42.7%	
	<80	2263	59.9%	253,507	42.9%	
	80 and above	781	20.7%	52,138	8.8%	
Bilateral disease	Unilateral	3668	97.0%	531,864	90.1%	<0.001
	Metachronous bilateral	36	1.0%	21,624	3.7%	
	Synchronous bilateral	63	1.7%	35,649	6.0%	
	Unknown	13	0.34%	1399	0.24%	
BMI kg/m ²	Median, 5–95%	23.1 (17.9–29.6)		22.3 (17.6–30.5)		<0.001
Clinical stage	Stage 0	280	7.4%	78,268	13.3%	<0.001
	Stage I	1407	37.2%	261,509	44.3%	
	Stage IIA	969	25.6%	141,311	23.9%	
	Stage IIB	334	8.8%	49,409	8.4%	
	Stage IIIA	70	1.9%	14,346	2.4%	
	Stage IIIB	381	10.1%	19,432	3.3%	
	Stage IIIC	40	1.1%	7716	1.3%	
	Stage IV	81	2.1%	12,012	2.0%	
	Unknown	218	5.8%	16,533	2.8%	
Surgery	Yes	3599	95.2%	567,434	96.1%	0.02
	No	53	1.4%	6613	1.1%	
	Biopsy only	127	3.4%	16,451	2.8%	
	Unknown	1	0.0%	38	0.0%	
Breast surgery	Mastectomy	2835	75.0%	273,062	46.2%	<0.001
	Breast-conserving surgery	552	14.6%	275,786	46.7%	
	Other/unknown	157	4.2%	10,121	1.7%	
	No breast surgery	55	1.5%	8465	1.4%	
Axillary surgery	SNB	1664	44.0%	345,504	58.5%	<0.001
	SNB and axillary dissection	257	6.8%	35,544	6.0%	
	Axillary dissection	985	26.1%	113,255	19.2%	
	No axillary surgery	437	11.6%	44,263	7.5%	
	Sampling	39	1.0%	9096	1.5%	
	Other/unknown	4	0.1%	1186	0.2%	
	Missing	1	0.03%	90	0.02%	

BMI body mass index, *SNB* sentinel lymph node biopsy

Family history of cancer and comorbidity

Patients with a family history of cancer were less likely to have MBC than FBC, regardless of the subtype ($p < 0.001$) (Tables 3). Missing/unknown family history was more frequent in patients with MBC compared with patients with FBC.

Comorbidities are recorded in Table 4. The proportion of patients with comorbidities was 57.3% for MBC and 32.8% for FBC ($p < 0.001$). The most frequent comorbidities of MBC were hypertension (35.1%), diabetes (14.7%), other

malignancies (11.7%), neuro/peripheral vascular disease (7.9%), and coronary artery disease (6.9%).

Systemic treatment

Neoadjuvant systemic therapy and adjuvant systemic therapy were less frequent in MBC cases than FBC cases (8.9 vs. 11.9%, $p < 0.001$; 82.7 vs. 86.3%, $p < 0.001$) (Table 5). Chemotherapy was less commonly administered in MBC cases (22.0 vs. 32.7%, $p < 0.001$), while endocrine therapy was more frequent in MBC cases (76.0 vs. 67.9%, $p < 0.001$).

Table 2 Pathological features

		Male		Female		<i>p</i> value
N		3003		464,346		
T	T0	10	0.3%	1625	0.3%	<0.001
	Tis	150	5.0%	45,176	9.7%	
	T1	1396	46.5%	235,664	50.8%	
	T2	987	32.9%	144,341	31.1%	
	T3	63	2.1%	13,883	3.0%	
	T4	362	12.1%	19,792	4.3%	
	Missing/unknown	35	1.2%	3863	0.8%	
N	Negative	2265	75.4%	381,398	82.1%	<0.001
	Positive	685	22.8%	78,561	16.9%	
	Missing	53	1.8%	4387	0.9%	
M	M0	2917	97.1%	453,465	97.7%	0.37
	M1	43	1.4%	5823	1.3%	
	Missing	43	1.4%	5055	1.1%	
Histology	Invasive ductal	2514	83.7%	361,052	77.8%	<0.001
	Invasive lobular	39	1.3%	21,421	4.6%	
	Others	447	14.9%	81,443	17.5%	
	Missing	3	0.1%	430	0.1%	
ER	Positive	2872	95.6%	387,500	83.5%	<0.001
	Negative	131	4.4%	76,802	16.5%	
	missing/not assessed	0	0.0%	44	0.0%	
PgR	Positive	2716	90.4%	338,617	72.9%	<0.001
	Negative	279	9.3%	125,050	26.9%	
	missing/not assessed	8	0.3%	679	0.1%	
HER2	Positive	284	9.5%	72,908	15.7%	<0.001
	Negative	2290	76.3%	333,601	71.8%	
	missing/not assessed	429	14.3%	57,837	12.5%	

ER estrogen receptor, PgR progesterone receptor, HER2 human epidermal growth factor-2

Fig. 1 Distribution of each subtype in MBC (a) and FBC (b)

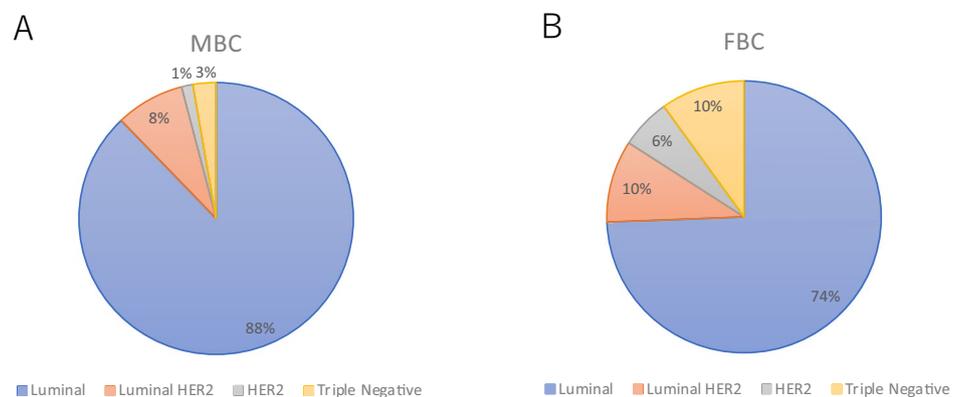


Table 3 Family history

	Male		Female		<i>p</i> value
N	3003		464,346		
Present	329	11.0%	63,058	13.6%	<0.001
Absent	2339	77.9%	366,917	79.0%	
Missing /unknown	335	11.2%	34,371	7.4%	

Specifically, the administration of chemotherapy in MBC vs. FBC cases according to subtype was 19.2 vs. 23.7% for Luminal, 47.1 vs. 60.4% for Luminal-HER2, 40.0 vs. 62.6% for HER2, 57.3 vs. 69.9% for TNBC. Meanwhile, endocrine therapy administration was similar in Luminal and Luminal-HER2 MBC and FBC cases (84.9 vs. 83.9%, 68.0 vs. 72.5%, respectively) (Table S4). Anthracycline, taxane, and

Table 4 Comorbidities

		Male		Female		<i>p</i> value
N		1781		276,341		
Comorbidities	Yes	1021	57.3%	90,602	32.8%	<0.001
	No	760	42.7%	185,734	67.2%	
	Missing	0	0.0%	5	0.002%	
Coronary artery disease	Present	123	6.9%	4999	1.8%	<0.001
Neuro/peripheral vascular disease	Present	140	7.9%	8265	3.0%	<0.001
Other malignancy	Present	209	11.7%	13,784	5.0%	<0.001
Congestive heart failure	Present	40	2.2%	2171	0.8%	<0.001
COPD	Present	40	2.2%	1067	0.4%	<0.001
Collagen disease	Present	10	0.6%	2564	0.9%	0.1
Liver disease	Present	67	3.8%	4053	1.5%	<0.001
Diabetes	Present	262	14.7%	19,893	7.2%	<0.001
Hypertension	Present	626	35.1%	60,932	22.0%	<0.001
Renal disease	Present	84	4.7%	3853	1.4%	<0.001

COPD chronic obstructive pulmonary disease

Table 5 Systemic treatment

		Male		Female		<i>p</i> value
N		3003		464,346		
Neoadjuvant systemic therapy	Received	Yes	266 8.9%	55,197 11.9%	<0.001	
	Not received	No	2730 90.9%	408,137 87.9%		
	Unknown	Missing	7 0.2%	1012 0.2%		
Adjuvant systemic therapy	Received	Yes	2484 82.7%	400,831 86.3%	<0.001	
	Not received	No	457 15.2%	53,250 11.5%		
	Unknown	Missing	62 2.1%	10,265 2.2%		
Treatment detail	Endocrine therapy	Yes	2282 76.0%	315,141 67.9%	<0.001	
	Chemotherapy	Yes	662 22.0%	151,839 32.7%	<0.001	
Chemotherapy regimen	Anthracycline	Yes	389 13.0%	96,962 20.9%	<0.001	
	Taxane	Yes	304 10.1%	83,444 18.0%	<0.001	
	anti-HER2	Yes	148 4.9%	47,249 10.2%	<0.001	

Table 6 Radiation therapy

	Male		Female		<i>p</i> value
N	3003		464,346		
Yes	430	14.3%	205,674	44.3%	<0.001
No	2499	83.2%	245,156	52.8%	
Missing	74	2.5%	13,516	5.5%	

anti-HER2 drug therapy was less frequent in MBC cases compared to FBC cases (13.0 vs. 20.9%, 10.1 vs. 18.0%, and 4.9 vs. 10.2%, respectively, $p < 0.001$).

Radiation therapy

Perioperative radiation therapy was performed in 14.3% of MBC cases and 44.3% of FBC cases (Table 6).

Discussion

To the best of our knowledge, this is the first study to report the real-world clinicopathological characteristics and treatment trends of Japanese male patients with breast cancer based on a nationwide registry database. Approximately, 600,000 patients with breast cancer were included in the study, and the frequency of male breast cancer was comparable to previous reports from Western countries at 0.6% [14, 15]. Furthermore, similar to previous reports from Western countries, the median age of MBC cases was more than 10 years higher than that of FBC cases [16–20]. The frequency of relatively advanced stage II or III breast cancer was higher in MBC than FBC, and this tendency was similar with pathological stages (Tables S1, S2a). This may be because males have much smaller breast tissue than females; thus, breast cancer in males easily invade the skin

and pectoral muscles [19, 21]. In addition, because males rarely visit breast oncologists due to a lack of understanding of breast cancer, they may believe that they do not have a risk of breast cancer. Nevertheless, the frequency of de novo stage IV disease was similar in MBC and FBC.

The breast-conserving surgery rate for MBC was 14.6%, which was lower than that of FBC but higher than that reported in Western countries. This may be due to tumors within 2 cm in size being relatively higher in Japanese MBC [4, 22]. Moreover, axillary lymph node dissection was more common in MBC, which may be due to the higher incidence of node-positive breast cancer in males. Additionally, similar to previous findings, MBC was more likely to be hormone receptor positive and less likely to be HER2 positive than FBC (Table S2b). The luminal subtype was the most common at 87.8%, which is consistent with previous reports [4, 23]. The frequency of the HER2-type and TNBC was slightly higher in our study than that of previous reports, suggesting that the biology may be different in Europe and the United States than in Japan [4, 23–25]. A positive family history of breast cancer was more common in FBC, while family history tended to be unknown in MBC cases (Table S3). Thus, clinicians may be taking insufficient family history of breast cancer for males.

Comorbidities were more common in the MBC group. Cardiovascular disease was the most frequent comorbidity, and the frequency of other malignancies was high (11.7%) in the patients with MBC (Table 4). In addition to the higher median age of MBC cases, hereditary tumor syndromes, such as hereditary breast and ovarian cancers, may be a cause of the higher rate of comorbidities and malignancies [25–27]. However, there were no data on detailed other malignancies in NCD.

Neoadjuvant systemic treatment was administered in less than 10% of MBC and FBC cases, and no significant difference of frequency was observed (Table S4). The frequency of endocrine therapy as a systemic treatment was similar between MBC and FBC cases; however, the frequency of chemotherapy with anthracyclines, taxanes, and anti-HER2 agents was lower in MBC. This suggests that patients' general condition, performance status, and/or cardiovascular complications may influence oncologists' decision-making with patients. The number of MBC cases who received radiotherapy was approximately one-third that of FBC cases, which could be because most MBC cases undergo mastectomy. Nevertheless, the proportion of patients who underwent BCS received radiation was slight in MBC. Furthermore, some patients eligible for post mastectomy radiation therapy, such as pN2 and pN3, also did not receive radiation. This may be related to older age and more comorbidities in Japanese MBC.

Real-world data analyses, such as the current study, boast a high number of patients. Our study included approximately

600,000 patients, which is much higher than of other retrospective studies. This high number of patients aids in the understanding of trends of clinicopathological features and treatment of MBC. Nevertheless, this study had several limitations. First, there was a risk of bias due to the retrospective nature of the study. Second, most databases, including the NCD, have missing data; thus, the true percentage of each value may not be reflected. Further analysis with a large cohort is required to obtain more reliable evidence. Addition to it, the NCD data are registered primarily by breast surgeons. Therefore, de novo stage IV data may be less available than the reality. Third, the NCD does not provide enough data on long-term survival, inhibiting the comparison of survival outcomes of MBC and FBC. Further studies should include additional histopathological and clinical data from the same cohort to obtain stronger conclusions, and such a study would be helpful in conducting clinical trials on MBC.

In conclusion, Japanese MBC had an older age of onset, were more likely to be hormone receptor-positive disease, and received less perioperative chemotherapy than FBC. This is the first comprehensive analysis using real-world data from a nationwide registry database in Japan of clinicopathological features and treatment trends in Japanese MBC cases. Further prospective studies are needed to evaluate the most suitable treatment strategy for MBC in Japan.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s12282-022-01378-6>.

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Author contributions AS, MN, and HK conceived and designed the study. HK analyzed data. AS interpreted data and wrote the manuscript. All authors approved the concept of this study and have read and made critical revision to the drafted manuscript. All read and approved the submission of the final version.

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Declarations

Conflict of interest Dr. Shimomura reports grants and personal fees from Chugai Pharmaceutical, grants and personal fees from AstraZeneca, grants and personal fees from Daiichi Sankyo, grants and personal fees from Eisai, grants from Taiho Pharmaceutical, grants from Mochida Pharmaceutical, personal fees from Pfizer, personal fees from Novartis, personal fees from Eli-Lilly, personal fees from Kyowa Kirin, personal fees from Takeda Pharmaceutical, and personal fees from MSD outside the submitted work. Dr. Kumamaru reports consulting fees from Mitsubishi-Tanabe Pharma, personal fees from Johnson and Johnson, personal fees from Pfizer, personal fees from Chugai Pharmaceutical outside the submitted work, affiliated with the department of Healthcare Quality Assessment at the University of Tokyo support-

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board of the National Center for Global Health and Medicine, Tokyo (NCGM-G-003309-01) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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