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RESEARCH

Relationship Between the Incidence of Metabolic Syndrome and Breast Cancer

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Abstract

Purpose Breast cancer affects females from puberty onward, with incidence rates increasing with age. Although metabolic syndrome (MetS) has reportedly increased the incidence of almost all cancers, no clear consensus on the role of MetS in breast cancer development exists. We aimed to clarify the effects of MetS on breast cancer incidence.

Methods To investigate this relationship, we analyzed Japanese healthcare data of females from 2005 to 2020 and examined the incidence of breast cancer. MetS was evaluated based on the Japanese criteria or the NCEP ATP III guidelines at enrollment. Of 1,144,791 participants without missing data in our general public cohort, 32,775 with breast cancer at the beginning of the observation period were excluded; 54,330 participants with breast cancer were identified during the observation period.

Results Both pre-stage MetS and MetS, defined using the Japanese criteria, were associated with the less frequent incidence of breast cancer (hazard ratios [HRs], 0.90; 95% CI, 0.86–0.94; $p < 0.005$: HR, 0.83; 95% CI, 0.80–0.87; $p < 0.005$). Furthermore, MetS using NCEP ATP III was associated with the lower HR (0.87: CI, 0.84–0.90; $p < 0.005$), and the number of the factors from 1 to 5 was gradually associated with the lower HRs. Analysis according to age group revealed that this observation was the most prominent in the < 50-year-old group.

Conclusion MetS is associated with the less frequent breast cancer incidence in females, especially aged < 50 years.

Keywords Breast cancer · Metabolic syndrome · Big data · Early stage of metabolic syndrome · Age

Naoki Kimoto and Yohei Miyashita equally contributed to this study as principal investigators.

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Introduction

Cancer poses substantial economic and healthcare burdens worldwide [1]. Although early detection, prompt diagnosis, and innovative medical and surgical treatments have gradually mitigated various cancer types, cancer-related mortality has been high even in developed countries. In particular, breast cancer is the most frequently diagnosed cancer type among females worldwide, especially affecting those in their 30–50 s [2]. Cancers, including breast cancer, are reportedly primed by family history [3], genetic background [4], smoking [5–7], and type II diabetes mellitus (T2DM) [8]. We and several investigators have reported that metabolic syndrome (MetS) increases the risk of pancreatic cancer [9, 10], and we have shown that MetS increases the risk of almost all cancer types [11]. The overall incidence of cancers may be influenced by the molecular mechanisms of MetS, including (1) insulin, (2) adipokine, and (3) reactive oxygen species (ROS) [12]. Among almost all cancer types, breast cancer is special owing to its estrogen sensitivity. Estrogen is known to initiate or proliferate breast cancer [13, 14], and MetS or obesity increases estrogen production in adipose tissues [15] along with the basal secretion of estrogen from the ovary. Furthermore, MetS increases insulin resistance, leading to a high risk of breast cancer [16]. Several investigators have examined the relationship between the incidences of MetS and breast cancer, and a meta-analysis of nine articles encompassing 6417 cases of cancer revealed that MetS is associated with a moderately increased risk of postmenopausal breast cancer [17]. Furthermore, MetS reportedly increased the risk of breast cancer in females aged > 60 years, which is not confirmed in younger females in 4862 cases of breast cancer [18]. Conversely, MetS is a risk factor for breast cancer in females aged 40–80 [19] and ≥ 18 years [20]. Taken together, MetS, especially obesity, may increase breast cancer incidence, and age may serve as a critical threshold that determines whether MetS exacerbates or mitigates breast cancer risk; however, no clear evidence exists regarding the relationship between MetS and breast cancer, as the sample size of each study is relatively small, with < 50,000 participants, 2000 of whom have breast cancer. Such an investigation is valid; however, we needed a single and large cohort of one million females by age group.

Therefore, we planned to form a cohort of more than one million individuals from the general population and followed them for more than 10 years, and we decided to investigate the relationship between the occurrence of MetS or the early phase of MetS and the incidence of breast cancer.

Table 1 Characteristics of 1,112,016 subjects with complete data for identifying MetS and important risk factors

The parameters for the diagnosis of MetS and important risk factors	All data (N = 1,112,016)	Japanese criteria of MetS			NCEP/ATPI criteria of MetS	
		NonMetS (N = 1,013,480)	PreMetS (N = 45,984)	MetS (N = 52,552)	NonMetS (N = 1,019,413)	MetS (N = 92,603)
Age, median age	53 (46–60)	53 (46–61)	56 (50–64)*	59 (53–67)*+	52 (45–60)	59 (51–65)*
Smoker, *n* (%)	124,339 (11.2%)	111,144 (11.0%)	5943 (12.9%)*	7252 (13.7%)*+	111,146 (10.9%)	13,193 (14.2%)*
BMI, median BMI	21.1 (19.3–23.5)	20.7 (19.1–22.7)	28.0 (26.0–30.4)*	29.1 (26.9–32.0)*+	21.3 (20.0–24.2)	27.0 (24.8–29.5)*
Abd circumference, median cm	70.5 (76.0–83.0)	75.0 (70.0–81.0)	94.5 (92.0–99.0)*	96.0 (92.5–101.8)*+	76.3 (73.0–85.0)	91.0 (88.0–98.5)*
sBP, median mmHg	112 (103–124)	111 (102–122)	121 (112–128)*	136 (129–146)*+	112 (106–126)	135 (126–143)*
dBP, median mmHg	69 (62–77)	68 (61–76)	74 (68–81)*	84 (77–90)*+	69 (64–80)	82 (78–91)*
HbA1c, median %	5.4 (5.2–5.6)	5.4 (5.2–5.6)	5.6 (5.4–5.9)*	5.8 (5.6–6.2)*+	5.4 (5.2–5.6)	6.0 (5.5–6.2)*
Fasting glucose, median mg/dL	89 (84–95)	89 (84–94)	94 (89–102)*	100 (93–112)*+	89 (85–97)	110 (99–117)*
HDL-cholesterol, median mg/dL	70 (60–81)	71 (61–82)	60 (52–70)*	56 (48–66)*+	72 (53–75)	56 (41–57)*
LDL-cholesterol, median mg/dL	115 (95–137)	113 (94–135)	130 (110–151)*	137 (116–160)*+	116 (98–138)	138 (110–153)*
TG, median mg/dL	66 (49–93)	64 (48–88)	92 (70–118)*	133 (91–181)*+	72 (55–110)	159 (125–233)*

Values are median (interquartile ranges), and only values of "women" and "smoker" are number (percent). Both symbols of * and + indicate $p < 0.001$ between the NonMetS and Mets groups and between the preMetS and MetS groups, respectively. It should be noted that, due to variation in the timing of subject entry, the exact year of entry could not be specified. As our database comprises annual data from 2005 through 2020, subjects meeting the entry criteria were included irrespective of their year of entry

BMI body mass index, *Abd* abdominal, *sBP* systolic blood pressure, *dBP* diastolic blood pressure, *Hb* hemoglobin, *HbA1c* hemoglobin A1c, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *TG* triglyceride

Table 2 Characteristics of 696,142 subjects with complete data for subanalysis of temporal appearance of MetS

The parameters for the diagnosis of MetS and important risk factors	All data ($n=696,142$)	NonMetS ($n=620,663$)	Type of MetS		
			MetS-developed ($n=26,830$)	MetS-persistent ($n=29,051$)	MetS-recovered ($n=19,598$)
Age, median age	55 (49–63)	55.0 (48.0–62.0)	61.0 (54.0–68.0)*	62.0 (56.0–69.0)*	62.0 (55.0–69.0)*
Smoker, *n* (%)	71,462 (10.3%)	61,583 (9.9%)	3423 (12.8%)*	4002 (13.8%)*	2454 (12.5%)*
BMI, median BMI	21.1 (19.3–23.6)	20.8 (19.1–22.9)	25.3 (23.2–28.2)*	26.8 (24.3–30.1)*	24.8 (22.6–27.7)*
Abd circumference, median cm	76.5 (71–83.5)	75.2 (70.0–81.2)	87.5 (83.0–93.8)*	90.5 (85.5–97.8)*	86.5 (81.0–93.0)*
sBP, median mmHg	113 (103–125)	111.0 (102.0–122.0)	133.0 (124.0–141.0)*	136.0 (126.0–146.0)*	125.0 (117.0–135.0)*
dBP, median mmHg	69 (62–78)	68.0 (61.0–76.0)	81.0 (74.0–88.0)*	83.0 (75.0–90.0)*	77.0 (70.0–84.0)*
HbA1c, median %	5.4 (5.2–5.7)	5.4 (5.2–5.6)	5.7 (5.5–6.0)*	5.9 (5.6–6.4)*	5.7 (5.4–6.0)*
Fasting glucose, median mg/dL	70 (60–82)	89.0 (84.0–94.0)	102.0 (95.0–108.0)*	106.0 (99.0–117.0)*	96.0 (91.0–104.0)*
HDL-cholesterol, median mg/dL	116 (97–139)	72.0 (62.0–83.0)	56.0 (47.0–67.0)*	50.0 (44.0–61.0)*	59.0 (52.0–69.0)*
LDL-cholesterol, median mg/dL	68 (50–96)	114.0 (96.0–136.0)	134.0 (114.0–156.0)*	135.0 (114.0–158.0)*	132.0 (111.0–155.0)*
TG, median mg/dL	90 (84–96)	64.0 (49.0–87.0)	147.0 (91.0–181.0)*	157.0 (108.0–208.0)*	104.0 (79.0–132.0)*

Values are presented as medians (interquartile ranges), except for "smoker," which is expressed as number (percentage). $p<0.01$ compared with each value of the MetS-free group. It should be noted that, due to variation in the timing of subject entry, the exact year of entry could not be specified. As our database comprises annual data from 2005 through 2020, subjects meeting the entry criteria were included irrespective of their year of entry

BMI body mass index, *Abd* abdominal, *sBP* systolic blood pressure, *dBP* diastolic blood pressure, *Hb* hemoglobin, *HbA1c* hemoglobin A1c, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *TG* triglyceride

Methods

Study Design

This retrospective observational study adhered to the principles of the Declaration of Helsinki and the Japanese Ethical Guidelines for Clinical Research.

Participants

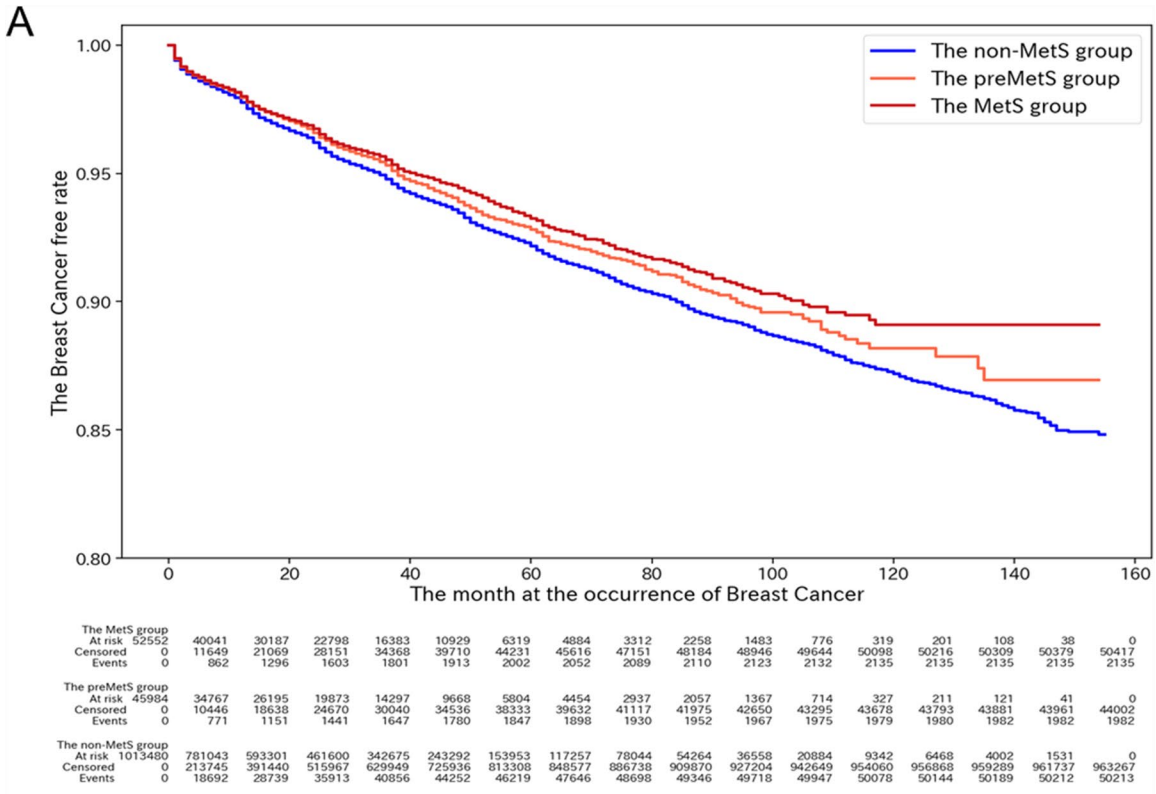
Our analyses were based on the data from healthcare insurance claims provided by JMDC (Japan Medical Data Center), Inc. (Tokyo, Japan). The database comprised standardized eligibility and claims data provided by health insurance societies for insured individuals from 2005 to 2020. It included the data of general corporation employees, their family members, and all medical treatments received by insured individuals at treatment facilities. While breast cancer can occur in men, our dataset did not include any male patients diagnosed with breast cancer. Accordingly, this study included only female participants.

Moreover, it included a comprehensive record of all the treatments administered to a patient. In this study, the decoding indexes stored by JMDC, Inc. were discarded, and the personal data were analyzed under unlinkable anonymization.

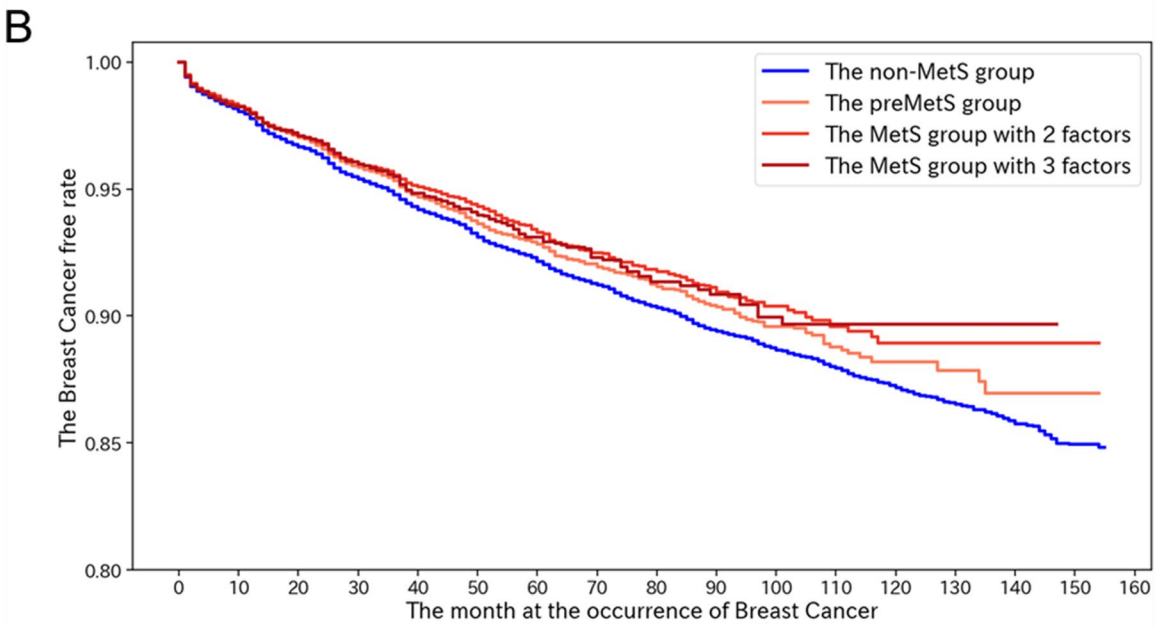
Definition of MetS

The Japanese criteria defined MetS as abdominal central obesity with an abdominal circumference at the umbilical levels of ≥ 85 and ≥ 90 cm for males and females, respectively, with two or more of the following factors: (1) elevated triglyceride and/or reduced high-density lipoprotein levels, (2) elevated blood pressure, and (3) elevated fasting glucose levels [21]. Premetabolic syndrome (preMetS) was defined as the presence of abdominal central obesity combined with one of the above-mentioned factors. Furthermore, the nonMetS group comprised participants not classified as having either MetS or preMetS.

Additionally, MetS was defined according to the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria [22], with the presence of ≥ 3 of the following factors: (1) serum triglycerides (TG) ≥ 1·69 mmol/L (150 mg/dL), (2) high-density lipoprotein (HDL)-cholesterol < 1·03 mmol/L (40 mg/dL) for men and < 1·29 mmol/L (50 mg/dL) for



The MetS group																	
At risk	52552	40041	30187	22798	16383	10929	6319	4884	3312	2258	1483	776	319	201	108	38	0
Censored	0	11649	21069	28151	34368	39710	44231	45616	47151	48184	48946	49644	50098	50216	50309	50379	50417
Events	0	862	1296	1603	1801	1913	2002	2052	2089	2110	2123	2132	2135	2135	2135	2135	2135
The preMetS group																	
At risk	45984	34767	26195	19873	14297	9668	5804	4454	2937	2057	1367	714	327	211	121	41	0
Censored	0	10446	18638	24670	30040	34536	38333	39632	41117	41975	42650	43295	43678	43793	43881	43961	44002
Events	0	771	1151	1441	1647	1780	1847	1898	1930	1952	1967	1975	1979	1980	1982	1982	1982
The non-MetS group																	
At risk	1013480	781043	593301	461600	342675	243292	153953	117257	78044	54264	36558	20884	9342	6468	4002	1531	0
Censored	0	213745	391440	515967	629949	725936	813308	848577	886738	909870	927204	942649	954060	956868	959289	961737	963267
Events	0	18692	28739	35913	40856	44252	46219	47646	48698	49346	49718	49947	50078	50144	50189	50212	50213



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At risk	1013480	781043	593301	461600	342675	243292	153953	117257	78044	54264	36558	20884	9342	6468	4002	1531	0
Censored	0	213745	391440	515967	629949	725936	813308	848577	886738	909870	927204	942649	954060	956868	959289	961737	963267
Events	0	18692	28739	35913	40856	44252	46219	47646	48698	49346	49718	49947	50078	50144	50189	50212	50213
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Censored	0	10446	18638	24670	30040	34536	38333	39632	41117	41975	42650	43295	43678	43793	43881	43961	44002
Events	0	771	1151	1441	1647	1780	1847	1898	1930	1952	1967	1975	1979	1980	1982	1982	1982
The MetS group with 2 factors																	
At risk	41100	31307	23592	17739	12682	8475	4904	3803	2577	1761	1165	608	250	165	88	32	0
Censored	0	9123	16496	22110	27022	31145	34644	35706	36905	37703	38290	38839	39194	39279	39356	39412	39444
Events	0	670	1012	1251	1396	1480	1552	1591	1618	1636	1645	1653	1656	1656	1656	1656	1656
The MetS group with 3 factors																	
At risk	11452	8734	6595	5059	3701	2454	1415	1081	735	497	318	168	69	36	20	6	0
Censored	0	2526	4573	6041	7346	8565	9587	9910	10246	10481	10656	10805	10904	10937	10953	10967	10973
Events	0	192	284	352	405	433	450	461	471	474	478	479	479	479	479	479	479

◂**Fig. 1** Kaplan–Meier curves of breast cancer incidence in the preMetS or MetS group (**A**), and Kaplan–Meier curves of breast cancer incidence in the MetS groups with two and three factors (**B**) based on the Japanese MetS criteria. In **A**, $p < 0.01$ between nonMetS and MetS groups, $p < 0.01$ between nonMetS and preMetS groups, and $p < 0.01$ between preMetS and MetS groups were observed. In **B**, $p < 0.01$ between preMetS group and MetS group with 2 factors, $p < 0.01$ between preMetS group and MetS group with three factors, and $p < 0.01$ between the MetS group with two factors and three factors were observed

women, (3) glucose ≥ 6·11 mmol/L (110 mg/dL) fasting or ≥ 7·77 mmol/L (140 mg/dL) non-fasting, or on treatment, (4) blood pressure (BP) ≥ 130/85 mm Hg or medication use, and (5) body mass index (BMI) ≥ 25·0 kg/m^2.

Study Protocol

Of the 1,144,791 females with complete baseline information, 32,775 with breast cancer at the beginning of the observation period were excluded, and breast cancer occurrence was evaluated (Table 1). Our results showed that 54,330 participants had breast cancer during the observation period according to the International Classification of Diseases 10th Revision (coded as C50.0 to C50.9).

After acquiring each dataset, we used the Kaplan–Meier analysis to compare breast cancer occurrence with and without MetS or preMetS. Furthermore, we calculated the hazard ratios (HRs) using Cox proportional hazard models between two and three groups. Moreover, we examined breast cancer incidence in the subgroups of females aged < 50 or ≥ 60 years and aged ≥ 50- and < 60- years old.

For another subanalysis, we enrolled 696,142 participants with well-followed metabolic states for > 3 years to investigate the effects of metabolic dynamics on breast cancer occurrence (Table 2). We classified the participants into four groups based on the presence or absence of MetS at baseline and after three years:

Participants with nonMetS were categorized into either MetS-developed (26,830 participants) or nonMetS (620,663 participants) groups on the basis of either MetS appeared or not-appeared. Participants with MetS were categorized into either the MetS-recovered (19,598 participants) or MetS-persistent (29,051 participants) groups on the basis of the conditions that MetS improved/disappeared or persisted for 3 years. These participants were followed until the end of the observation period or breast cancer onset.

Statistics

Time-to-event data were evaluated using Kaplan–Meier estimates and compared using the log-rank test for primary analyses. The entry time, that is, time = 0 for the Kaplan–Meier plots, varied. Censoring occurred when the patient died or was lost to follow up. We employed a complete case analysis (listwise deletion) for missing data, and a sensitivity analysis was not performed.

Cox proportional hazard models were employed for estimating HRs with the MetS or preMetS group assignment or combinations of the components with the MetS, preMetS, and nonMetS groups for calculating the p-values regarding the hypothesis testing between the groups. For those analyses involving multiple comparisons, we applied the Holm–Bonferroni correction [23] to adjust for the inflation of type I error.

The models were adjusted for smoking and age because the incidence of cancer is believed to be affected by these factors. After checking the interactions between the variables of age and smoking through likelihood ratio tests on regression coefficients of interaction terms, no interaction between smoking and age was noted to be significant.

All statistical analyses were performed using Python v310 and packages, including lifelines v0278 (https://github.com/nkimoto/PKMetS).

Results

The clinical characteristics of patients with and without preMetS or MetS are presented in Table 1. The results of the Kaplan–Meier analysis of the participants with and without MetS defined using the Japanese MetS criteria for breast cancer incidence are depicted in Fig. 1. As shown in Fig. 1A, along with progression from the nonMetS to MetS via preMetS, breast cancer was associated with less frequent incidence in a stepwise manner; as shown in Fig. 1B, MetS with two or three factors was associated with the less frequent incidence of breast cancer compared with preMetS/nonMetS. Both preMetS and MetS were associated with the less frequent incidence of breast cancer (HR, 0.90; 95% CI, 0.86–0.94; $p < 0.005$: HR, 0.83; 95% CI, 0.80–0.87; $p < 0.005$), and MetS with one, two, or three factors, as well as preMetS, was associated with the less frequent incidence of breast cancer (HR, 0.90; 95% CI, 0.86–0.94; $p < 0.005$: HR, 0.83; 95% CI, 0.80–0.87; $p < 0.005$: HR, 0.85; 95% CI, 0.78–0.94; $p < 0.005$). The results of the subanalysis for investigating the relationship between the presence of MetS or preMetS and breast cancer incidence by age group are shown in Fig. 2. In the < 50-year-old age group, both MetS (HR, 0.71: CI, 0.62–0.82; $p < 0.005$) and preMetS (HR, 0.69: CI, 0.61–0.79; $p < 0.005$) were associated with the less frequent incidence of breast cancer to the same extent. In the ≥ 50- and < 60-year-old age group, both MetS or preMetS (MetS: HR, 0.73: CI, 0.67–0.78; $p < 0.005$; preMetS: HR, 0.83: CI, 0.77–0.88; $p < 0.005$) were associated with less frequent incidence of breast cancer. In the ≥ 60-year-old age group, preMetS was associated with more frequent incidence

of breast cancer (HR, 1.07: CI, 1.00–1.15; $p < 0.05$), whereas MetS did not affect it (HR, 1.01: CI, 0.95–1.07; $p = 0.75$) compared with nonMetS.

The results of the Kaplan–Meier analysis indicated that participants with and without MetS, defined using the NCEP/ATP III criteria, had showed the association with less frequent breast cancer incidence (HR, 0.87: CI, 0.84–0.90; $p < 0.005$) (Fig. 3A). The negative relationship between the number of the factors of MetS and the incidence of breast cancer is shown in Fig. 3B. The HR for the incidence of breast cancer monotonically was associated with the less frequent incidence as the number of MetS factors increases: Particularly, for one factor, the HR was 0.95 (95% CI, 0.93–0.97; $p < 0.005$); for two factors, the HR was 0.90 (95% CI, 0.87–0.92; $p < 0.005$); for three factors, the HR was 0.84 (95% CI, 0.81–0.88; $p < 0.005$); for four factors, the HR was 0.83 (95% CI, 0.77–0.88; $p < 0.005$); and for five factors, the HR was 0.82 (95% CI, 0.71–0.94; $p < 0.005$).

Regarding the effects of changes in the status of MetS during the observation period, Kaplan–Meier analyses (Fig. 4) and log-rank test among the nonMetS, MetS-developed, MetS-persistent, and MetS-recovered groups revealed that even the temporal MetS status is associated with the less frequent incidence the risk of breast cancer. Compared with the nonMetS groups, the incidences of breast cancer were associated with the less frequent incidence in the MetS-developed (HR, 0.91; 95% CI, 0.85–0.98; $p < 0.01$), MetS-persistent (HR, 0.87; 95% CI, 0.81–0.93; $p < 0.005$), and MetS-recovered (HR, 0.88; 95% CI, 0.81–0.95; $p < 0.005$) groups. No differences in breast cancer incidences were observed among the MetS-developed, MetS-recovered, and MetS-persistent groups. Even though the differences in the Kaplan–Meier curves appear subtle, the large sample size may have contributed to the statistical significance. Taken together, these findings suggest that the temporary occurrence of MetS is associated with the less frequent breast cancer incidence.

Discussion

This study revealed that MetS is linked to the incidence of breast cancer in females with an average age of 53 years. Interestingly, in females aged < 50 years, MetS and preMetS are linked to the incidence of breast cancer compared with nonMetS, with preMetS exhibiting a protective effect comparable to that of MetS. In females aged 50–60 years, although either MetS or preMetS is linked to the incidence of breast cancer compared with nonMetS, preMetS seemed to exhibit a weaker effect than MetS. In contrast, in females aged ≥ 60 years, the effects of MetS on breast cancer were attenuated, and the breast cancer incidence in participants with either MetS or preMetS was high compared with that of participants with nonMetS, with no significant difference. Considering that females aged < 50 years may not yet have entered menopause, whereas most of those aged ≥ 60 years have already reached menopause, the observed significant age-dependent relationship between MetS (or preMetS) and breast cancer appears to be strongly mediated by menopausal status.

Cardiovascular Relevance of MetS in Relation to Breast Cancer

It is highly consistent that the patients with MetS are managed not only by endocrinologists but also by cardiologists, since numerous studies have reported that MetS is closely associated with the development of cerebrovascular and cardiovascular diseases [24–27]. In other words, MetS is considered a part of cardiovascular disease. In our previous work, we demonstrated that MetS is also linked to the incidence of various cancers [10, 11], suggesting that cardiologists treating the patients with MetS should pay attention not only to the risk of cerebrovascular and cardiovascular diseases but also to the potential development of cancer. In the present study, we further investigated the association with breast cancer, which had not been addressed in our prior research [10, 11], and found an intriguing result that, unlike previous reports, MetS appeared to be less frequently associated with the incidence of breast cancer. This finding suggests that cardiologists, when managing the patients with MetS, should also keep in mind the potential involvement of MetS in breast cancer development, even if such an association appears attenuated.

Differences and Similarities Between Previous and Present Results

In the cohort investigated in this study, MetS, including preMetS, was associated with a less frequent incidence breast cancer incidence overall. This finding contrasts with previous results from a meta-analysis of 97,277 females, which showed that MetS increased breast cancer incidence [20], suggesting that our findings differ from those of previous studies. However, a larger cohort study encompassing 287,320 females reported that although MetS increased breast cancer incidence in females aged > 60 years, this trend was not observed in younger females [18]. This hypothesis was also proved in a Japanese cohort [28]. The present study, with a cohort of 1,112,016 females, including 54,330 participants with breast cancer who can provide potential and definite power to analyze the relationship among MetS, breast cancer, and age, revealed a reversal in the relationship between MetS and breast cancer risk, especially in the < 60-year-old age group. Furthermore, this inverse

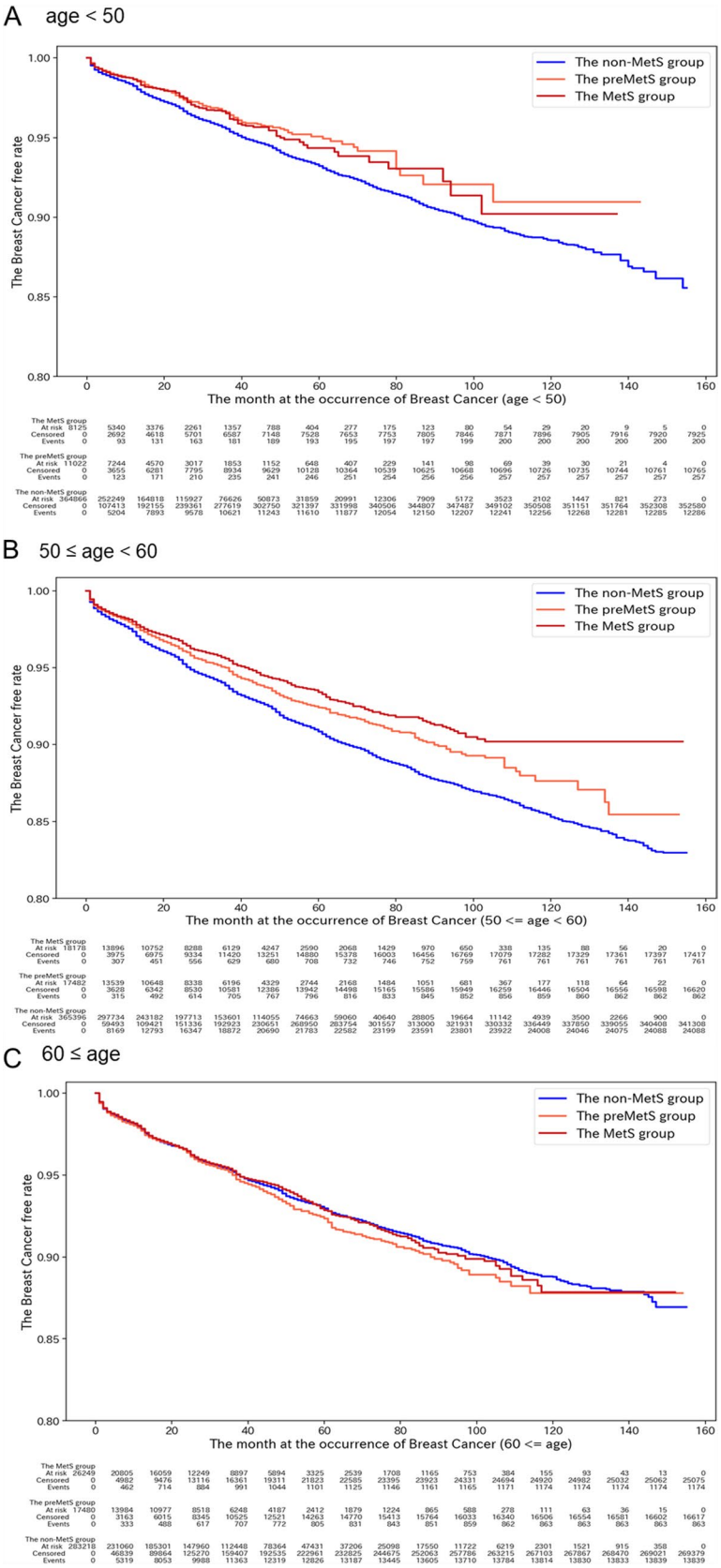
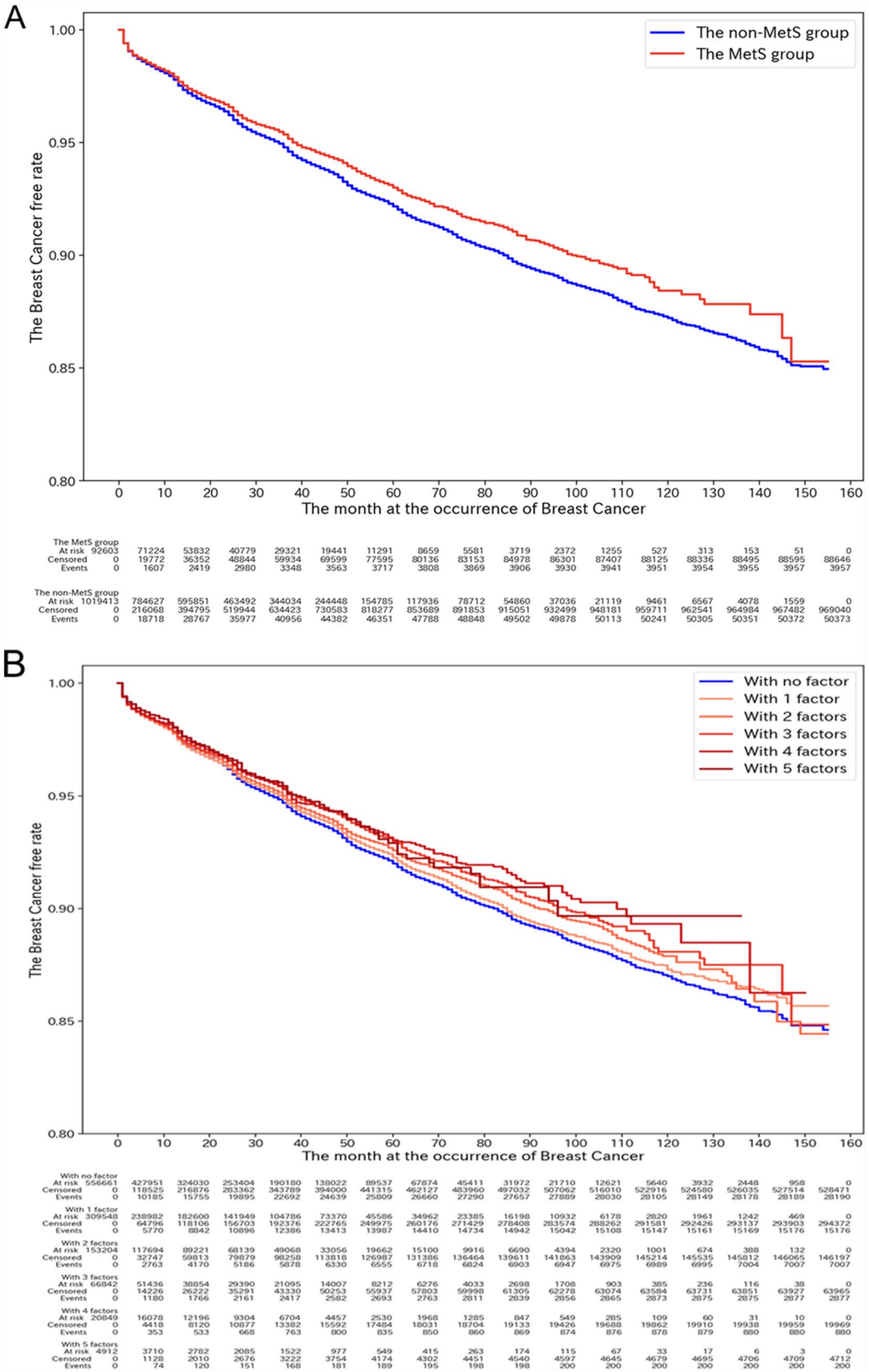


Fig. 2 Kaplan–Meier curves of breast cancer incidence according to < 50-, 50–60-, and > 60-year-old age groups. In age < 50 years old, $p < 0.01$ between nonMetS and MetS groups, $p < 0.01$ between the nonMetS and preMetS groups, and non-significant difference between the preMetS and MetS groups were observed. In 50 years old < age ≤ 60 years old, $p < 0.005$ between the nonMetS and MetS groups, $p < 0.001$ between nonMetS and preMetS groups, and $p < 0.05$ between preMetS and MetS groups were observed. In 60 years old < age, no significant differences were observed among the groups


A
The non-MetS group
The MetS group
The Breast Cancer free rate
1.00
0.95
0.90
0.85
0.80
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160
The month at the occurrence of Breast Cancer
The MetS group
At risk 92603 71224 53832 40779 29321 19441 11291 8659 5581 3719 2372 1255 527 313 153 51 0
Censored 0 19772 36352 48844 59934 69599 77595 80136 83153 84978 86301 87407 88125 88336 88495 88595 88646
Events 0 1607 2419 2980 3348 3563 3717 3808 3869 3906 3930 3941 3951 3954 3955 3957 3957
The non-MetS group
At risk 1019413 784627 595851 463492 344034 244448 154785 117936 78712 54860 37036 21119 9461 6567 4078 1559 0
Censored 0 216068 394795 519944 634423 730583 818277 853689 891853 915051 932499 948181 959711 962541 964984 967482 969040
Events 0 18718 28767 35977 40956 44382 46351 47788 48848 49502 49878 50113 50241 50305 50351 50372 50373
B
With no factor
With 1 factor
With 2 factors
With 3 factors
With 4 factors
With 5 factors
The Breast Cancer free rate
1.00
0.95
0.90
0.85
0.80
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160
The month at the occurrence of Breast Cancer
With no factor
At risk 556661 427951 324030 253404 190180 138022 89537 67874 45411 31972 21710 12621 5640 3932 2448 958 0
Censored 0 118525 216876 283362 343789 394000 441315 462127 483960 497032 507062 516010 522916 524580 526035 527514 528471
Events 0 10185 15755 19895 22692 24639 25809 26660 27290 27657 27889 28030 28105 28149 28178 28189 28190
With 1 factor
At risk 309548 238982 182600 141949 104786 73370 45586 34962 23385 16198 10932 6178 2820 1961 1242 469 0
Censored 0 64796 118106 156703 192376 222765 249975 260176 271429 278408 283574 288262 291581 292426 293137 293903 294372
Events 0 5770 8842 10896 12386 13413 13987 14410 14734 14942 15042 15108 15147 15161 15169 15176 15176
With 2 factors
At risk 153204 117694 89221 68139 49068 33056 19662 15100 9916 6690 4394 2320 1001 674 388 132 0
Censored 0 32747 59813 79879 98258 113818 126987 131386 136464 139611 141863 143909 145214 145535 145812 146065 146197
Events 0 2763 4170 5186 5878 6330 6555 6718 6824 6903 6947 6975 6989 6995 7004 7007 7007
With 3 factors
At risk 66842 51436 38854 29390 21095 14007 8212 6276 4033 2698 1708 903 385 236 116 38 0
Censored 0 14226 26222 35291 43330 50253 55937 57803 59998 61305 62278 63074 63584 63731 63851 63927 63965
Events 0 1180 1766 2161 2417 2582 2693 2763 2811 2839 2856 2865 2873 2875 2875 2877 2877
With 4 factors
At risk 20849 16078 12196 9304 6704 4457 2530 1968 1285 847 549 285 109 60 31 10 0
Censored 0 4418 8120 10877 13382 15592 17484 18031 18704 19133 19426 19688 19862 19910 19938 19959 19969
Events 0 353 533 668 763 800 835 850 860 869 874 876 878 879 880 880 880
With 5 factors
At risk 4912 3710 2782 2085 1522 977 549 415 263 174 115 67 33 17 6 3 0
Censored 0 1128 2010 2676 3222 3754 4174 4302 4451 4540 4597 4645 4679 4695 4706 4709 4712
Events 0 74 120 151 168 181 189 195 198 198 200 200 200 200 200 200 200

◂**Fig. 3** Kaplan–Meier curves of the incidence of breast cancer with and without MetS (**A**) and pancreatic cancer incidence among the six groups with 0–5 components of MetS (**B**) based on the modified NCEP/ATP III criteria. In **A**, $p < 0.005$ between nonMetS and MetS groups was observed. In **B**, significant differences were observed between the no factor group and the groups with 1, 2, 3, 4, and 5 factors ($p < 0.05$, $p < 0.05$, $p < 0.01$, $p < 0.01$, and $p < 0.01$, respectively)

association between breast cancer incidence and MetS occurrence became stronger as the number of MetS-related factors, including hypertension and dyslipidemia, beyond obesity alone, increased. Additionally, of note, this study showed that preMetS, considered an early stage of MetS, exhibited similar effects to those observed with MetS. This interesting phenomenon is observed in patients with T2DM. A more recent meta-analysis of 20 studies encompassing 30,407 cases of cancer revealed that females with diabetes (vs. females without diabetes) had a statistically significant 20% increased risk of breast cancer (1.20; 95% CI, 1.12–1.28). However, in the stratified analysis by menopausal status, diabetes was associated with a 16% increased breast cancer risk in postmenopausal females and a 9% reduced risk in premenopausal females [29].

These findings have profound clinical implications. However, understanding why such a discontinuous relationship between age and breast cancer incidence occurs with age is a major challenge in the present observation.

Age-Related Relationship Between MetS and Breast Cancer

Understanding the impact of MetS on breast cancer necessitates investigating its molecular mechanisms, which culminate in the effects of (1) insulin, (2) adipokine, (3) ROS, and (4) estrogen [12]. Insulin is a major anabolic hormone that stimulates cell proliferation. An indirect mechanism, including insulin-like growth factor (IGF)−1 stimulation, is believed to mediate the effects of insulin on cancer cell proliferation in vivo. IGF-1 receptor activation stimulates the p21 ras/MAPK pathway for cell proliferation and the PI3K/AKT cell survival pathway [30]. Furthermore, IGF-1 stimulates angiogenesis by increasing vascular endothelial growth factor production [31]. These findings may be related to breast cancer incidence. However, insulin, adipokine, or ROS may not explain the discontinuous relationship between age and breast cancer incidence that occurs with age.

Conversely, the levels of estrogen, which increases the incidence of breast cancer [13], may be changed throughout a female's life. Breast cancer is mainly influenced by estrogen, and estrogen levels remain high until 50 years old during the premenopausal period; however, they are known to significantly decrease once menopause is reached. In contrast, obesity, frequently observed in MetS, leads to estrogen production in the adipose tissue. After menopause, the primary source of estrogen production shifts from the ovaries to fat cells. Why, then, does MetS appear to reduce the risk of breast cancer before menopause, whereas following menopause, the relationship between MetS and breast cancer risk seems to have disappeared or reversed?

MetS, during the premenopausal period, is associated with increased anovulatory cycles [32, 33]. More frequent anovulatory cycles cause reduced estrogen production from the ovaries, which is hypothesized to lower the risk of breast cancer. This phenomenon is consistent with findings that breast cancer incidence shows less frequent not only in the MetS-persistent group but also in those who recover from MetS or develop it temporarily. In other words, even a transient premenopausal MetS occurrence may increase anovulatory cycles, thereby decreasing estrogen levels and potentially affecting breast cancer risk.

Study Limitations and Notable Features

One limitation of our study is the reliance on ICD-10 diagnosis codes to identify breast cancer cases, without pathological confirmation. While this may raise concerns regarding diagnostic accuracy, it is important to note that, in Japan, all cancer diagnoses are legally mandated to be reported to the national cancer registry under the Cancer Registry Act, and false registration is subject to legal penalties. Thus, cancer diagnoses are generally applied with considerable rigor. Nevertheless, the absence of direct pathological evidence remains a limitation and should be acknowledged. Additionally, we cannot rule out the possibility of residual confounding or unmeasured factors influencing the observed association between metabolic syndrome and breast cancer.

The relationship between MetS and cancers overall should be carefully concluded. Big data analyses may reveal subtle changes in the cohort. However, we observed that each factor responsible for MetS is independently associated with breast cancer, suggesting that MetS exhibits a stepwise effect on cancer risk modulation.

We also should consider the residual confounding or unmeasured variables that could explain the unexpected association between MetS and breast cancer. It is possible that differences in hormonal environments between individuals with and without MetS contribute to this association. Moreover, patients diagnosed with MetS are more likely to receive medical interventions and to engage in lifestyle modifications, including smoking cessation, alcohol restriction, and dietary control.

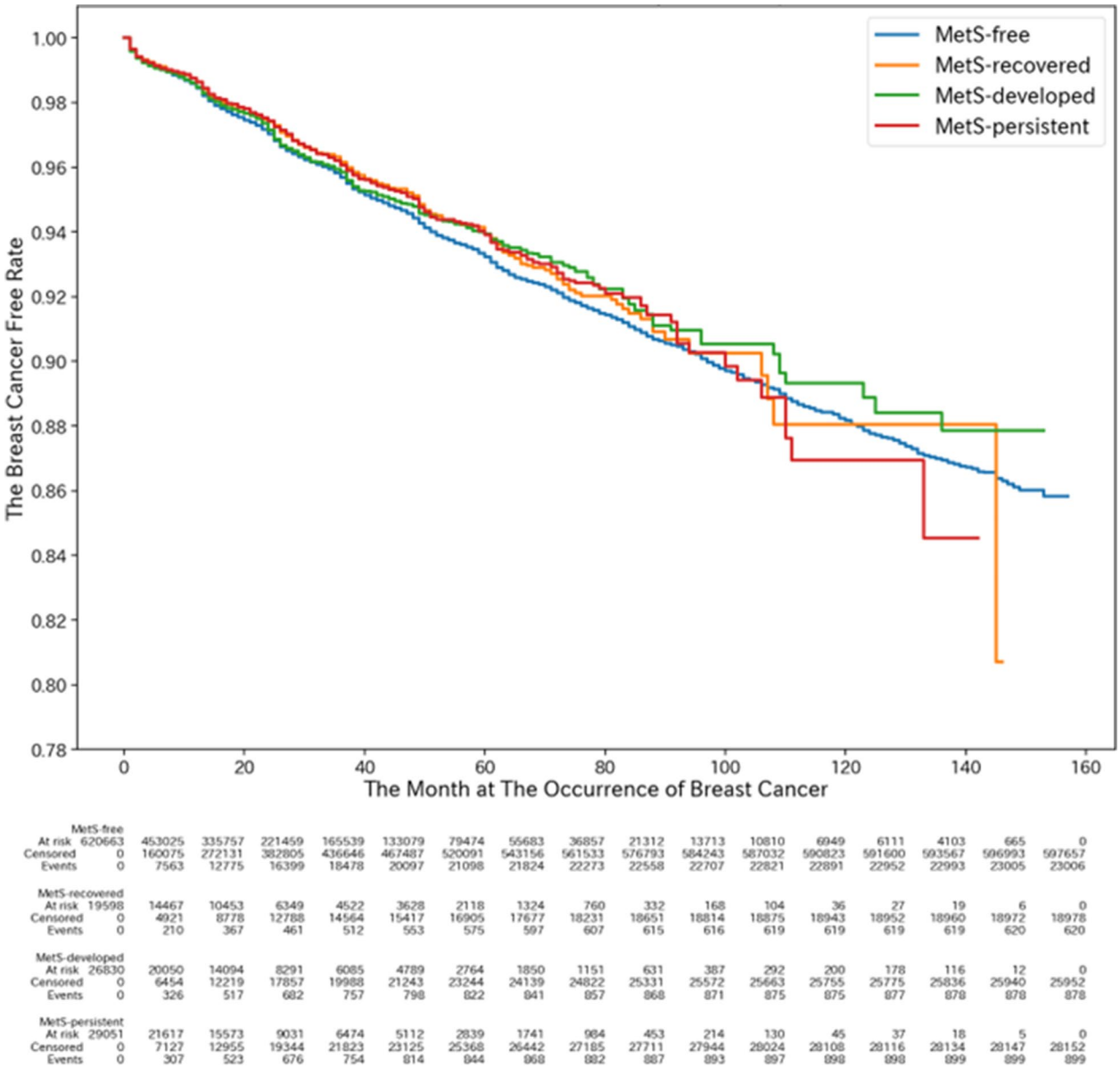


Fig. 4 Kaplan–Meier curves of the nonMetS-free and MetS-developed groups and the MetS-recovered and MetS-persistent groups for breast cancer incidence. Compared with the nonMetS groups, breast cancer incidences are less frequent in the MetS-developed ($p < 0.05$), MetS-recovered ($p < 0.05$), and MetS-persistent ($p < 0.01$) groups. No differences in breast cancer incidences are observed among the MetS-developed, MetS-recovered, and MetS-persistent groups

Racial differences may exist whether MetS regulates breast cancer incidence. In Japan, as the lifestyle has recently been westernized, cancers with high prevalence are becoming similar to those of Western countries, and the population with MetS has increased. As we employed a diagnostic method using the NCEP ATP III and Japanese criteria, our conclusion remains unchanged, suggesting that the present conclusion can be applicable worldwide.

As the study cohort was obtained from employees of general corporations and their family members, the average age of the participants may be younger than the average of the population in Japan. In 2020, the average age of the Japanese population was 48.9 years, which was similar to the average of the cohort of this study. The present cohort may lack older adult participants aged > 80 years; therefore, the relationship between MetS and breast cancer for females aged > 80 years may not be comparable with the present results.

For a therapeutic perspective, clinicians should recognize that women without MetS during the peri-menopausal period may show a lower likelihood of cerebrovascular and cardiovascular disease, whereas a tendency toward breast

cancer should not be overlooked. Furthermore, women with MetS who undertake excessive intentional weight reduction during the menopausal transition might warrant attention, as this could potentially affect their breast cancer risk.

Author Contribution The followings are the role of each author to this study: Study conceptualization and design: MK, NK, YM, ST; data curation, NK; data formal analysis: NK, YS, TW; project administration: YY, MY, YS, TW, ST; visualization: TA, YY, YS; figures and tables: NK, YM, TA, ST; writing and editing: MK. All authors have read and approved the manuscript and the agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Naoki Kimoto, Yohei Miyashita, and Masafumi Kitakaze have verified the underlying data of this study.

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Data Availability The data analyzed in this study are available from the corresponding author upon reasonable request, depending on the nature of the request.

Code Availability Not applicable.

Declarations

Disclaimer The Grants-in-Aid from Japan Heart Foundation played no role in the study design, data collection, data analysis, and data interpretation or in the writing of the manuscript. The corresponding author assumed full data access and made the final decision to submit for publication.

Ethics Approval This retrospective observational study was approved by the external Ethics Committee of the Kinshukai Medical Group (approval number: 2024–3).

Consent to Participate The Study Committee decided that based on the Japanese Clinical Research Guidelines, obtaining informed consent from patients selected for inclusion was not necessary as this was a retrospective observational study. Instead, we made a public announcement following the Ethics Committee's request and the Japanese Clinical Research Guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for Publication The authors affirm no use of any individual person's data in any form.

Conflict of interest Relationships to industry do not exist for N. K., Y. M., Y. Y., T. A., M. Y., T. W., and S. T. Y. S. reports personal fees from AstraZeneca, personal fees from Otsuka Pharmaceutical, personal fees from Nippon Boehringer Ingelheim, personal fees from Novartis Pharma, personal fees from Bayer, grants from Nippon Boehringer Ingelheim, grants from Abbott Medical Japan, and grants from Otsuka Pharmaceutical outside the submitted work. M. K. reports personal fees from Daiichi-sankyo, personal fees from Viatris, grants and personal fees from Ono, grants from Novartis, grants and personal fees from Tanabe-mitubishi, grants from Takeda, grants and personal fees from Astra Zeneca, grants and personal fees from Boehringer-ingelheim, grants from Kowa, personal fees from Otsuka, and personal fees from Eli Lilly outside the submitted work.

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