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ORIGINAL ARTICLE

Seven-plus hours of daily sedentary time and the subsequent risk of breast cancer: Japan Multi-Institutional Collaborative Cohort Study

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Abstract

This study aimed to investigate the association between daily sedentary time and the risk of breast cancer (BC) in a large Japanese population. The participants were 36,023 women aged 35–69 years from the Japan Multi-Institutional Collaborative Cohort Study. Cox proportional hazards analysis was used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for BC incidence in relation to time spent sedentarily (categorical variables: <7 and ≥7 hours/day [h/d]). Additionally, the associations of BC incidence to the joint effect of sedentary time with each component of physical activity, such as leisure-time metabolic equivalents (METs), frequency of leisure-time physical activity, and daily walking time, were examined. During 315,189 person-years of follow-up, 554 incident cases of BC were identified. When compared to participants who spent <7 h/d sedentary, those who spent ≥7 h/d sedentary have a significantly higher risk of BC (HR, 1.36; 95% CI, 1.07–1.71). The corresponding HRs among participants who spent ≥7 h/d sedentary with more physical activity, such as ≥1 h/d for leisure-time METs, ≥3 days/week of leisure-time physical activity, and ≥1 h/d of daily walking were 1.58 (95% CI, 1.11–2.25), 1.77 (95% CI, 1.20–2.61), and 1.42 (95% CI, 1.10–1.83), respectively, compared with those who spent <7 h/d sedentary. This study found that spending ≥7 h/d of sedentary time is associated with

Abbreviations: BC, breast cancer; BMI, body mass index; CIs, confidence intervals; hours/day, h/d; HRs, hazard ratios; ICD-10, International Classification of Diseases, Tenth Revision; IGF-1, insulin-like growth factor-1; IPAQ, International Physical Activity Questionnaire; J-MICC, Japan Multi-Institutional Collaborative Cohort Study; METs, metabolic equivalents; SHBG, sex hormone–binding globulin.

For Affiliation refer page on 620

the risk of BC. Neither leisure-time physical activity nor walking had a BC-preventive effect in those with ≥7 h/d of sedentary time.

KEYWORDS
Asian population, cancer prevention, physical activity, sitting time, women's health

1 | INTRODUCTION

Breast cancer (BC) is the most common cancer in Japanese women, as it is worldwide.[1,2] In 2019, 97,812 BC cases were newly diagnosed and accounted for 22.6% of all cancer cases in Japanese women. BC has also been the leading cause of cancer-related deaths in Japan: in 2020, 14,650 BC-related deaths were reported, accounting for 9.3% of all cancer-related deaths in that year. The incidence and death rates of BC have been increasing in recent decades, and the disease has become a public health priority.[1,3]

It is estimated that 33%–37% of cancers are potentially preventable through lifestyle changes and modifiable environmental factors known to be associated with cancers.[4–6] Epidemiological studies worldwide have revealed that physical activity can decrease the risk of BC, a concept that is gaining interest as a means of primary prevention.[7] Five percent of BC cases are attributable to physical inactivity in Japanese women.[8] Protective effects of physical activity against BC have also been reported in Japan; physical activity has been evaluated in terms of the exercise frequency, leisure-time physical activity, and daily walking time.[9–11] Physical activity is generally evaluated in terms of metabolic equivalents (METs)[12,13]; however, it is difficult to quantify the appropriate amount of physical activity for individuals because of differences in age, sex, and original muscle mass.

In the last decade, prolonged sedentary behavior (sitting or reclining posture) has drawn considerable concerns for having one of the most adverse effects on health worldwide. Among them, the median sedentary time of Japanese individuals is reported to be 7 hours/day (h/d), which is the longest worldwide.[14] Some systematic reviews and meta-analyses on the relationship between physical activity and health have revealed that sedentary behavior increases cardiovascular, cancer-specific, and overall death rates.[15–17] It was reported in Japan that sedentary time is associated with cardiometabolic disease and overall deaths.[18,19] The relationship between sedentary behavior and cancer incidence has been indicated in several countries, with the exception of Japan.[20] Meta-analyses have shown associations between BC and sedentary work[21] and sedentary behavior (including TV viewing)[22]; however few reports have shown an association with daily sedentary time. Only one study has been reported on BC and sedentary behavior in Japan, where a higher risk was observed in women mainly in a sitting posture at work.[10] There are currently no studies on the association between the daily sedentary time and BC incidence in Japan.

We aimed to evaluate the association between sedentary time and BC incidence and further examine the effects of physical activity (specifically, leisure-time METs, frequency of leisure-time physical activity, and daily walking time) on sedentary time and BC incidence in a large Japanese population.

2 | MATERIALS AND METHODS

2.1 | Study population

The present analysis was based on data from the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study, a large cohort study focusing on gene–environment interactions in lifestyle-related diseases, including cancer, among Japanese individuals.[23] The participants were individuals aged 35–69 years who were enrolled upon the following: (i) responding to study announcements in specified regions or companies, (ii) attending health checkup examinations conducted by local governments or employers, (iii) visiting health checkup centers, or (iv) visiting a cancer hospital. At the time of the baseline study (i.e., from February 2004 to March 2014), there were participants from 14 different regions in 12 peripherals. Participants completed questionnaires and provided blood samples.

Information on all enrolled participants was collected from baseline to December 31, 2017, using the dataset "ver.20210901." Mortality data were obtained from the Ministry of Health, Labour and Welfare of Japan[23] because registrations of death are mandated by the *Family Registration Law*. Information on cancer diagnosis was collected using population-based cancer registries, active patient notifications from major local hospitals, and reports from participants confirmed by checking medical records. The national cancer registry was also launched in January 2016 to obtain accurate nationwide cancer data of diagnosed cases in all hospitals across all 47 prefectures in Japan (*The Cancer Registry Promotion Act*, Ministry of Health, Labour and Welfare); these data were analyzed independently in this study. Death and cancer incidence data were coded according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (ICD-10), and *the International Classification of Diseases for Oncology, Third Edition* (ICD-O-3), respectively. The outcome in the present study was BC incidence, which was defined using ICD-O-3 codes C50.0–50.9. When participants moved out of their study region, they were excluded from follow-up at the time of their exit.

Among the 92,527 participants of the J-MICC Study, the following 56,504 were excluded from our study: 40,851 men; 4489 with a history of cancer or unknown; 2003 with incidence of cancers other than BC; 219 with BC incidence within the 1-year

follow-up; 2156 with missing sedentary time or body mass index (BMI) data, and 6786 with untracked cancer incidence. The remaining 36,023 women were included in the analysis (Figure 1). During the 315,189 person-years of follow-up, 554 incident cases of BC were identified.

All study participants provided written informed consent prior to enrollment. The study protocol was approved by the ethics committees of the Aichi Cancer Center (IRB No. H2210001A) and of the other institutions that participated in the J-MICC Study. This study was conducted in accordance with the principles of the Declaration of Helsinki.

2.2 | Data collection and measurements

At the time of enrollment, all participants completed a self-administered lifestyle questionnaire that included questions on age, height, weight, smoking and drinking habits, physical activity, personal and family medical history, menstrual and reproductive history, breastfeeding experience, and other lifestyle factors. The format for the questions on physical activity was adopted from the International Physical Activity Questionnaire (IPAQ).[24] Leisure-time physical activity was defined as when participants exercised on days off or had free time. It was categorized according to how intensely participants

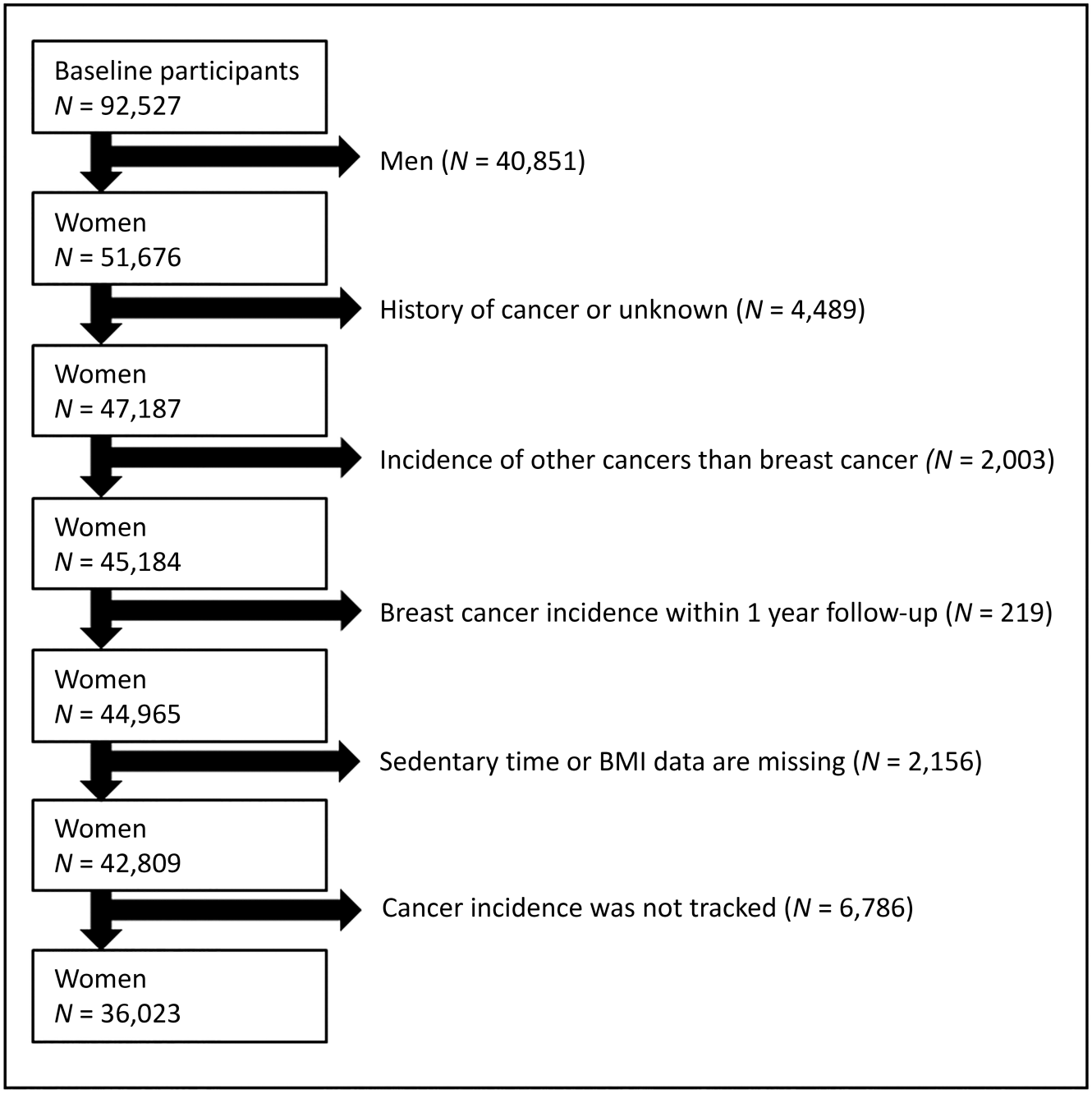

FIGURE 1 Flow chart of the study participants.

exercised (including three categories: exercise after which participants could still breathe, sufficient exercise for participants to be out of breathe but still able to talk, and sufficient exercise that participants were out of breathe and unable to talk), how often (including five categories: none, 1–3 days per month, 1–2 days per week, 3–4 days per week, and ≥5 days per week) and for how long (including six categories: <30 min, 30 to <60 min, 1 to <2 h, 2 to <3 h, 3 to <4 h, and ≥4 h). Leisure-time physical activity was measured as leisure-time METs.[12,13] METs-hours per day of leisure-time physical activity was estimated by multiplying the reported daily time spent engaged in each activity by the corresponding MET intensity and converting this value to a measure of a day. For daily physical activity, the IPAQ comprised the following: hard labor, walking, standing, and sitting times. Each time was categorized into one of the following eight categories: none, <1, 1 to <3, 3 to <5, 5 to <7, 7 to <9, 9 to <11, and ≥11 h/d. Sedentary behavior was defined as any waking behavior characterized by an energy expenditure of ≤1.5 METs in a sitting, reclining, or lying posture.[25,26] Accordingly, the sum of the daily time spent sleeping, performing hard labor, walking, and standing was subtracted from 24 h to calculate the daily sedentary time. Sedentary time was categorized into two types of categorical variables: <7 and ≥7 h/d and <7, 7 to <10, 10 to <13, and ≥13 h/d. BMI was calculated as weight (kg) divided by height squared (m^2).

2.3 | Statistical analysis

Continuous variables are expressed as mean and standard deviation, and categorical variables are expressed as numbers and proportions (%). To compare the baseline characteristics of the sedentary groups, a one-way analysis of variance and the χ^2 test were performed for continuous and categorical variables, respectively. For all participants, the person-years of follow-up were calculated using the time from enrollment until the diagnosis of BC, day of death from any cause, day of moving out of the study area, or the end of follow-up, whichever occurred first. Individuals who died or moved out were treated as censored. Cox proportional hazard models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the association between BC incidence and the daily sedentary time (<7 h/d was used as a reference). These models were adjusted for age, study area, BMI (<18.5, 18.5 to <25, or ≥25 kg/m^2), smoking (never, ever, or unknown), regular alcohol drinking (yes, no, former, or unknown), leisure-time METs (h/d), family history of BC (no, 1, ≥2, or unknown), menopausal status (premenopausal, postmenopausal, or unknown), age at menopause (<50, 50 to <55, ≥55 years, unknown, or premenopausal), age at menarche (≤12, 13–14, ≥15 years, or unknown), age at first birth (<30, ≥30 years, nulliparous, or unknown), number of births (nulliparous, 1 or 2, ≥3, or unknown), breastfeeding (yes, no, or unknown), and hormone therapy (yes, no, or unknown). To evaluate the effects of leisure-time physical activity in the groups that spent ≥7 h/d and <7 h/d being sedentary, we identified the following categorical variables: leisure-time METs (≥1, 0–1, 12 and 0 h/d), frequency of leisure-time physical activity (≥3 days/week, 1–2 days/week, and ≤3 days/month), and daily walking time (≥1 and <1 h). We performed a stratification analysis by age, BMI, alcohol consumption, and smoking status. All statistical analyses were performed using SPSS version 25 (IBM Japan, Tokyo, Japan), and $p < 0.05$ was considered statistically significant.

3 | RESULTS

Table 1 shows the baseline characteristics of the participants according to their sedentary time. Overall, 36,023 participants were included; the average age was 54.5 ± 9.36 years and the median follow-up time was 9.41 years. Among these, 7633 (21.2%), 9484 (26.3%), 9120 (25.3%), and 9786 (27.2%) participants spent <7, 7 to <10, 10 to <13, and ≥13 h/d being sedentary, respectively; the corresponding incidence rates (per 1000 person-years) were 1.39, 1.80, 1.93, and 1.81, respectively. The incidence rate (per 1000 person-years) for all participants was 1.76.

The results of the multivariable analysis (adjusted HR [95% CI]) are shown in Table 2. The HR was significantly higher among participants who spent ≥7 h/d being sedentary than among those who spent <7 h/d being sedentary (HR, 1.36; 95% CI, 1.07–1.71). When we categorized the sedentary time into the <7, 7 to <10, 10 to <13, and ≥13 h/d categories, the HRs were 1.00 (reference), 1.32 (95% CI, 1.01–1.72), 1.42 (95% CI, 1.09–1.84), and 1.34 (95% CI, 1.02–1.75), respectively. The trend *p*-value when divided into these four categories was 0.046 for all participants, 0.033 for premenopausal, and 0.348 for postmenopausal. The BC risk did not differ significantly with 1-h increments in the sedentary time in all of the aforementioned participants; therefore, 7 h was set as the cut-off value.

Using the group with <7 h/d sedentary and leisure-time METs ≥1 as a reference values, the HRs of the groups with leisure-time METs of ≥1, 0–1, and 0 h/d in the ≥7 h/d sedentary group were found to be 1.58 (95% CI, 1.11–2.25), 1.59 (95% CI, 1.10–2.30), and 1.47 (95% CI, 0.99–2.17), respectively. Using the groups with <7 h/d sedentary and leisure-time physical activity ≥3 days/week as a reference values, the HRs of the groups with leisure-time physical activities of ≥3 days/week, 1–2 days/week, and ≤3 days/month in the ≥7 h/d sedentary group were found to be 1.77 (95% CI, 1.20–2.61), 1.86 (95% CI, 1.22–2.83), and 1.72 (95% CI, 1.16–2.56). Using the groups with <7 h/d of sedentary time and daily walking time ≥1 as reference values, the HRs of the groups with daily walking times of ≥1 h and <1 h in the ≥7 h/d sedentary group were found to be 1.42 (95% CI, 1.10–1.83) and 1.38 (95% CI, 1.04–1.84), respectively. Although dose-dependence was observed in all participants, it was unclear in the premenopausal and postmenopausal groups (Table 3).

We performed a stratification analysis by age, BMI, alcohol consumption, and smoking status (Table S1). When age was categorized into quartiles (Q1: 35–46 years, Q2: 47–55 years, Q3: 56–62 years and Q4: 63–69 years) and analyzed, the trend *p*-value was 0.010 in the Q2 group. In the high BMI, no-drinking, and no-smoking groups, participants who spent ≥7 h/d being sedentary had a significantly higher HR.

TABLE 1 Characteristics of participants according to sedentary time

Sedentary time	All subjects	<7 h	7 to <10 h	10 to <13 h	≧13 h
Number of subjects	36,023	7633	9484	9120	9786
Age (years) mean ± SD	54.5 ± 9.36	54.4 ± 9.28	54.9 ± 9.36	54.7 ± 9.42	54.2 ± 9.37
Number of breast cancer	554 (1.5)	87 (1.1)	144 (1.5)	157 (1.7)	166 (1.7)
Person-years	315,189	62,522	79,785	81,341	91,541
Prevalence rate (per 1000 person-years)	1.76	1.39	1.80	1.93	1.81
BMI (kg/m^2)					
<18.5	3435 (9.5)	766 (10.0)	939 (9.9)	870 (9.5)	860 (8.8)
18.5 to <25	26,523 (73.6)	5603 (73.4)	7101 (74.9)	6777 (74.3)	7042 (72.0)
≥25	6065 (16.8)	1264 (16.6)	1444 (15.2)	1473 (16.2)	1884 (19.3)
Mean ± SD	22.2 ± 3.23	22.1 ± 3.23	22.1 ± 3.13	22.1 ± 3.16	22.4 ± 3.38
Smoking					
Never	30,772 (85.4)	6421 (84.1)	8132 (85.7)	7879 (86.4)	8340 (85.2)
Ever	5042 (14.0)	1112 (14.6)	1304 (13.7)	1214 (13.3)	1412 (14.4)
Unknown	209 (0.6)	100 (1.3)	48 (0.5)	27 (0.3)	34 (0.3)
Regular drinking					
No	21,289 (59.1)	4549 (59.6)	5527 (58.3)	5337 (58.5)	5876 (60.0)
Yes	14,032 (39.0)	7941 (38.5)	3800 (40.1)	3610 (39.6)	3681 (37.6)
Former	684 (1.9)	139 (1.8)	156 (1.6)	164 (1.8)	225 (2.3)
Unknown	18 (0.0)	4 (0.1)	1 (0.0)	9 (0.1)	4 (0.0)
Leisure-time METs (h/d)					
≥1	17,206 (47.8)	3601 (47.2)	4961 (52.3)	4528 (49.6)	4116 (42.1)
0–1	10,882 (30.2)	2174 (28.5)	2728 (28.8)	2750 (30.2)	3230 (33.0)
0	7935 (22.0)	1858 (24.3)	1795 (18.9)	1842 (20.2)	2440 (24.9)
Mean ± SD	1.94 ± 2.96	2.19 ± 3.52	2.15 ± 3.08	1.93 ± 2.75	1.55 ± 2.47
Frequency in leisure-time physical activity					
≥3 days/week	15,968 (44.3)	3351 (43.9)	4545 (47.9)	4199 (46.0)	3873 (39.6)
1–2 days/week	6323 (17.6)	1233 (16.2)	1698 (17.9)	1625 (17.8)	1767 (18.1)
≤3 days/month	13,732 (38.1)	3049 (39.9)	3241 (34.2)	3296 (36.1)	4146 (42.4)
Walking time (/day)					
≥1 h	25,788 (71.6)	6983 (91.5)	8214 (86.6)	6970 (76.4)	3621 (37.0)
<1 h	10,235 (28.4)	650 (8.5)	1270 (13.4)	2150 (23.6)	6165 (63.0)
Family history of breast cancer					
No	33,515 (93.0)	6939 (90.9)	8831 (93.1)	8550 (93.8)	9195 (94.0)
1	1479 (4.1)	341 (4.5)	409 (4.3)	368 (4.0)	361 (3.7)
≥2	66 (0.2)	13 (0.2)	13 (0.1)	21 (0.2)	19 (0.2)
Unknown	963 (2.7)	340 (4.5)	231 (2.4)	181 (2.0)	211 (2.2)
Menopasusal status					
Premenopausal	12,938 (35.9)	2702 (35.4)	3331 (35.1)	3247 (35.6)	3658 (37.4)
Postmenopausal	22,959 (63.7)	4896 (64.1)	6127 (64.6)	5844 (64.1)	6092 (62.3)
Unknown	126 (0.3)	35 (0.5)	26 (0.3)	29 (0.3)	36 (0.4)
Age at menopause (years)					
<50	7703 (21.4)	1705 (22.3)	1982 (20.9)	1950 (21.4)	2066 (21.1)
50 to <55	12,837 (35.6)	2702 (35.4)	3478 (36.7)	3311 (36.3)	3346 (34.2)
≥55	2226 (6.2)	444 (5.8)	615 (6.5)	536 (5.9)	631 (6.4)
Unknown	193 (0.5)	45 (0.6)	52 (0.2)	47 (0.5)	49 (0.5)

(Continues)

TABLE 1 (Continued)

Sedentary time	All subjects	<7 h	7 to <10 h	10 to <13 h	≧13 h
Mean ± SD	49.7 ± 4.56	49.6 ± 4.61	49.8 ± 4.51	49.7 ± 4.49	49.7 ± 4.65
Premenopausal	12,938 (35.9)	2702 (35.4)	3331 (35.1)	3247 (35.6)	3658 (37.4)
Age at menarche (years)					
≤12	11,998 (33.3)	2499 (32.7)	3098 (32.7)	3101 (34.0)	3300 (33.7)
13–14	17,879 (49.6)	3778 (49.5)	4794 (50.5)	4498 (49.3)	4809 (49.1)
15≤	5954 (16.5)	1300 (17.0)	1542 (16.3)	1477 (16.2)	1635 (16.3)
Unknown	192 (0.5)	56 (0.7)	50 (0.5)	44 (0.5)	42 (0.4)
Age at first live birth (years)					
<30	26,055 (72.3)	5825 (76.3)	6932 (73.1)	6538 (71.7)	6760 (69.1)
≥30	4950 (13.7)	1001 (13.1)	1444 (15.2)	1310 (14.4)	1195 (12.2)
Nulliparous	4637 (12.9)	727 (9.5)	1008 (10.6)	1182 (13.0)	1720 (17.6)
Unknown	381 (1.1)	80 (1.0)	100 (1.1)	90 (1.0)	111 (1.1)
Number of births					
Nulliparous	4638 (12.9)	727 (9.5)	1008 (10.6)	1182 (13.0)	1721 (17.6)
1 or 2	20,566 (57.1)	4196 (55.0)	5560 (58.6)	5363 (58.8)	5447 (55.7)
≥3	10,782 (29.9)	2702 (35.4)	2909 (30.7)	2565 (28.1)	2606 (26.6)
Unknown	37 (0.1)	8 (0.1)	7 (0.1)	10 (0.1)	12 (0.1)
Breastfeeding					
Yes	29,293 (81.3)	6460 (84.6)	7912 (83.4)	7436 (81.5)	7485 (76.5)
No	6707 (18.6)	1168 (15.3)	1570 (16.6)	1681 (18.4)	2288 (23.4)
Unknown	23 (0.1)	5 (0.1)	2 (0.0)	3 (0.0)	13 (0.1)
Hormone therapy					
Yes	4219 (11.7)	842 (11.0)	1103 (11.6)	1107 (12.1)	1167 (11.9)
No	31,621 (87.8)	6741 (88.3)	8348 (88.0)	7959 (87.3)	8573 (87.6)
Unknown	183 (0.5)	50 (0.7)	33 (0.3)	54 (0.6)	46 (0.5)

Note: Data are presented as mean ± SD or number (percentage).

4 | DISCUSSION

This is the first large-scale prospective cohort study to evaluate the association between daily sedentary time and BC incidence in Japanese women. Spending ≥7 h/d being sedentary was associated with a 36% increased risk of BC; the BC risk in 1-h increments of sedentary time did not differ significantly in all groups (Table 2). A recent meta-analysis revealed that sedentary behavior may increase BC risk by 21.6% and 8.26% in the Asian and North American populations, respectively.[22] Our results support this finding and suggest that Asians may be more susceptible to BC incidence on account of sedentary behavior. In Japan, some studies have been conducted on the effect of physical activity on BC incidence,[9–11,27–29] but no studies have evaluated the effect of the sedentary time duration on BC incidence. Only one cohort study reported that women whose work positions were mainly sitting had a higher risk (HR, 1.45; 95% CI, 1.01–2.12) when compared with those who mainly moved.[10] They classified the occupational postures as moving, mainly standing, and mainly sitting, and sedentary time was not analyzed. Therefore, our results (which were analyzed in terms of the daily sedentary time) are significant for the Japanese population, which spends the most time being sedentary among populations worldwide.[14] When the effects of leisure-time physical activity were examined in combination with the sedentary time, sedentary time was shown to outweigh the protective effects of physical activity and be a risk factor for BC (Table 3). As mentioned previously, it is difficult to quantify the appropriate amount of physical activity for individuals because of differences in age, sex, and original muscle mass; however, it is relatively simple to shorten the sedentary time, and this practice can be easily incorporated into daily life.

Sedentary behavior was defined as any waking behavior characterized by an energy expenditure of ≤1.5 METs in a sitting, reclining, or lying posture. Accordingly, we subtracted the total hours of sleeping and daily physical activity-defined hard labor, walking, and standing from the 24 h to calculate the daily sedentary time, including reclining postures. Using this method to calculate the sedentary time enabled us to convert it into a continuous variable. However, the present study did not use actigraph accelerometers to measure sedentary time, and thus, we cannot compare the validation of sedentary time. According to a study that used accelerometers to measure sedentary time, the proportion of sedentary time among Japanese women aged 40–64 years was 51.0% on working days and 60.5% on

TABLE 2 Associations between breast cancer incidence and daily sedentary time

	All			p for trend	Premenopausal			p for trend	Postmenopausal			p for trend
	Case/*n*	HR (95% CI)	*p*-value		Case/*n*	HR (95% CI)	*p*-value		Case/*n*	HR (95% CI)	*p*-value	
Total	554/36,023				174/12,938				379/22,959			
Daily sedentary time												
<7 h	87/7633	1.00 (ref.)			27/2702	1.00 (ref.)			59/4896	1.00 (ref.)		
≥7 h	467/28,390	1.36 (1.07–1.71)	0.010		147/10,236	1.42 (0.94–2.15)	0.100		320/18,063	1.37 (1.03–1.81)	0.031	
<7 h	87/7633	1.00 (ref.)			27/2702	1.00 (ref.)			59/4896	1.00 (ref.)		
7 to <10 h	144/9484	1.32 (1.01–1.72)	0.043	0.046	40/3331	1.25 (0.76–2.05)	0.375	0.033	104/6127	1.39 (1.01–1.92)	0.043	0.348
10 to <13 h	157/9120	1.42 (1.09–1.84)	0.010		45/3247	1.35 (0.83–2.19)	0.222		112/5844	1.47 (1.07–2.02)	0.019	
≥13 h	166/9786	1.34 (1.02–1.75)	0.035		62/3658	1.64 (1.03–2.60)	0.037		104/6092	1.22 (0.87–1.70)	0.251	
1 h increments in sedentary time		1.02 (1.00–1.04)		0.102		1.03 (1.00–1.08)		0.080		1.01 (0.98–1.04)		0.459

Note: Adjusted for age, body mass index, smoking, regular alcohol drinking, leisure-time metabolic equivalents, family history of breast cancer, menopausal status, age at menopause, age at first birth, number of births, breastfeeding, and hormone therapy.

Abbreviations: HR, hazard ratio; ref., reference.

non-working days for working women and 53.4% for non-working women.[30] Notably, the sedentary time in this study was underestimated by an amount equivalent to 3.2% of wearing time compared to devices used in other studies. Another study showed that the proportion of sedentary time for a wide range of Japanese men and women aged 20–88 years was 67.9%.[31] In this study, participants slept an average and median of 6.5 h. Assuming that 55%–60% of the 17.5 h (24 h minus sleeping time) was sedentary, this would be 9.6–10.5 h. The average sedentary time was 10.8 h and the median was 11 h, suggesting that the results were reasonable. The distribution of sedentary time showed unimodality.

From a mechanistic viewpoint, prolonged sedentary behavior results in decreased physical activity and low energy expenditure; these lead to a range of adverse health effects, including obesity, insulin resistance, increased sex hormones, and chronic inflammation.[32,33] BC incidence is closely associated with sex hormone imbalance. Physical activity decreases estrogen levels and increases sex hormone-binding globulin (SHBG) levels.[34–36] Exposure to estrogen increases BC risk; therefore, lowering estrogen levels with exercise lowers BC risk.[37–39] Circulating estrogen is transported to tissues bound to albumins and SHBG. Therefore, increased levels of SHBG indicate reduction of free estrogen, which has a suppressive effect on BC.[40] BC risk from reduced physical activity is not only limited to sex-hormone imbalances but is also driven by multiple interrelated biological pathways for insulin resistance and elevated insulin levels, chronic inflammation, oxidative stress, and adipokines.[41] In contrast, physical activity reduces insulin levels and insulin resistance; decreases fasting glucose, total insulin-like growth factor-1 (IGF-1), and HbA1c levels; and increases insulin-like growth factor binding protein-1 levels, which are inversely related to insulin.[41] Increased insulin and IGF-1 levels, which occur with physical inactivity and obesity, are involved in promoting tumor growth by inhibiting apoptosis and are associated with the incidence of common cancers (including BC).[42] Insulin and IGF-1 also stimulate the synthesis of sex steroids and inhibit the synthesis of SHBG.[43] Our results on the relationship between sedentary time and BC risk are supported by this sequence of mechanisms, considering decreased physical activity due to prolonged sedentary behavior.

When we categorized the sedentary time duration into <7, 7 to <10, 10 to <13, and ≥13 h/d, the *p* for trend was 0.046 in all participants and 0.033 in premenopausal participants; however, no significant differences in the trend were noted in postmenopausal participants (Table 2). A previous study investigated BC risk using daily TV-watching time as a marker for sedentary time; it found a positive association between BC risk and TV-watching time in premenopausal participants.[44] Occupational sitting time was further reported to be associated with an increased BC risk in women aged <55 years (who are considered premenopausal).[45] BC risk is suggested to increase in a dose-dependent manner in premenopausal women. However, there was no significant difference at 1-h increments in the sedentary time in this study (Table 2). Therefore, 7 h was set as the cut-off value.

TABLE 3 Associations between breast cancer incidence and daily sedentary time according to leisure time metabolic equivalents, frequency in leisure-time physical activity, and daily walking time

		All			*p* for trend	Premenopausal			*p* for trend	Postmenopausal			*p* for trend
		Case/n	HR (95% CI)	*p*-value		Case/n	HR (95% CI)	*p*-value		Case/n	HR (95% CI)	*p*-value	
Total		554/36,023				174/12,938				379/22,959			
Sedentary time	Leisure-time METs h/d												
<7 h	≥1	35/3601	1.00 (ref.)			7/1010	1.00 (ref.)			27/2572	1.00 (ref.)		
	0–1	31/2174	1.41 (0.87–2.29)	0.160	0.034	12/953	1.95 (0.76–4.96)	0.163	0.202	19/1212	1.39 (0.77–2.51)	0.268	0.074
	0	21/1858	1.11 (0.65–1.91)	0.700		8/739	1.43 (0.51–4.00)	0.495		13/1112	1.04 (0.54–2.02)	0.898	
≥7 h	≥1	226/13,605	1.58 (1.11–2.25)	0.012		55/3707	2.19 (1.00–4.83)	0.051		171/9864	1.53 (1.01–2.30)	0.044	
	0–1	148/8708	1.59 (1.10–2.30)	0.014		55/3797	2.10 (0.94–4.58)	0.070		93/4881	1.57 (1.02–2.43)	0.040	
	0	93/6077	1.47 (0.99–2.17)	0.054		37/2732	1.91 (0.85–4.30)	0.120		56/3318	1.44 (0.90–2.30)	0.125	
Sedentary time	Frequency in leisure-time physical activity												
<7 h	≥3 days/week	28/3351	1.00 (ref.)			7/882	1.00 (ref.)			20/2456	1.00 (ref.)		
	1–2 days/week	24/1233	2.21 (1.29–3.80)	0.004	0.025	7/482	1.95 (0.68–5.58)	0.212	0.250	17/744	2.67 (1.40–5.08)	0.003	0.039
	≤3 days/month	35/3049	1.28 (0.78–2.10)	0.326		13/1338	1.18 (0.47–2.99)	0.721		22/1696	1.45 (0.79–2.66)	0.232	
≥7 h	≥3 days/week	207/12,617	1.77 (1.20–2.61)	0.004		48/3337	1.85 (0.84–4.11)	0.129		159/9254	1.93 (1.21–3.09)	0.006	
	1–2 days/week	89/5090	1.86 (1.22–2.83)	0.004		29/1827	2.04 (0.89–4.67)	0.093		60/3242	1.98 (1.19–3.30)	0.008	
	≤3 days/month	171/10,683	1.72 (1.16–2.56)	0.008		70/5072	1.70 (0.78–3.70)	0.187		101/5567	1.93 (1.19–3.13)	0.008	
Sedentary time	Daily walking time (/day)												
<7 h	≥1 h	76/6983	1.00 (ref.)			22/2449	1.00 (ref.)			53/4500	1.00 (ref.)		
	<1 h	11/650	1.35 (0.72–2.55)	0.350	0.017	5/253	2.09 (0.79–5.55)	0.140	0.079	6/396	1.08 (0.47–2.50)	0.852	0.071
≥7 h	≥1 h	307/18,805	1.42 (1.10–1.83)	0.007		95/6704	1.58 (0.99–2.54)	0.055		212/12,047	1.41 (1.04–1.90)	0.029	
	<1 h	160/9585	1.38 (1.04–1.84)	0.025		52/3532	1.61 (0.97–2.68)	0.065		108/6016	1.33 (0.94–1.88)	0.106	

Note: Adjusted for age, body mass index, smoking, regular alcohol drinking, family history of breast cancer, menopausal status, age at menopause, age at menarche, age at first birth, number of births, breastfeeding, and hormone therapy.

Abbreviations: CI, confidence interval; HR, hazard ratio; ref., reference.

In a stratification analysis by age, BMI, alcohol consumption, and smoking, participants who spent ≥7 h/d being sedentary in the Q2 group (age: 47–55 years) and participants in the high BMI, no-drinking, and no-smoking groups had a significantly higher BC risk in this study (Table S1). Combining the results from the Q2 age group with the results from the premenopausal group (Table 2), premenopausal participants in their late 40s and early 50s may experience a dose-dependent increase in BC risk. An association between high BMI and BC risk has been reported previously[7]; lack of exercise is one of the causes of high BMI. Those with a high BMI may be recommended to limit their sedentary time to ≤7 h and perform exercises to lower the BMI. Previous studies have clearly noted that drinking and smoking increase BC risk[7]; a sedentary time of <7 h/d may be proposed as a further preventive measure in the non-drinking and non-smoking populations.

In Japanese cohort studies, protective effects of physical activity against BC have been reported; BC risk was lower (HR, 0.45; 95% CI, 0.25–0.78) in the most physically active group (whose members walked for ≥1 h/d and exercised for ≥1 h/week) than in the least active group (whose members who walked for <1 h/d and exercised for <1 h/week).[11] Furthermore, BC risk was also lower (relative risk, 0.73, 95% CI, 0.54–1.00) in the group with ≥3 days/week of leisure-time physical activity than in the group with ≤3 days/month of leisure-time physical activity.[9] In our study, leisure-time METs, leisure-time physical activity frequency, and daily walking time were stratified and verified in the same way as in these previous studies. Interestingly, the estimated risks did not decrease with increased leisure-time METs, frequency of leisure-time physical activity, or daily walking time in participants who spent ≥7 h/day being sedentary (Table 3). This result may seem to contradict the findings of previous studies that have clearly shown that leisure-time physical activity and daily walking have protective effects against BC.[9–11,46] However, ours is the first study to have evaluated leisure-time physical activity in combination with the sedentary time. Our study does not suggest the ineffectiveness of physical activity; rather, it suggests that sedentary time might be a stronger risk factor for BC than physical activity. Actually, the relationship between sedentary time and death also indicated that physical activity did not completely reduce the risk of death from sitting time.[47] The results from the stratification analysis (Table S1) in our study showed that the sedentary time might increase the risk of BC development or reduce the protective effects of physical activity depending on the condition. Furthermore, the effects of leisure-time physical activity or daily walking time on BC incidence among groups with <7 h/d of sedentary time are unclear (Table 3). Thus, studies with a larger number of cases are needed for further validation.

A major strength of our study is its prospective design and large sample size (approximately 36,000 women), which helped avoid selection bias that may occur in case-control studies. In addition, comprehensive baseline information, including major risk factors for BC (family history, menopausal status, menarche, childbirth, breastfeeding, and hormone therapy), enabled the control of potential confounders in the analysis when examining associations. This study is novel because there are no cohort studies investigating the association between the daily sedentary time and BC incidence in Japan.

Our study has several limitations that should be considered when interpreting its results. First, a self-administered questionnaire was used in the baseline survey to evaluate physical activity and other information. Although the use of questionnaires to assess physical activity is controversial, the IPAQ is widely accepted as an international physical activity surveillance instrument.[48] Self-reported measures might overestimate or underestimate the actual physical activity, but the information in this study was collected prior to diagnosis and should not have varied by the endpoint status. In addition, we did not use the accelerometers to verify each physical activity; thus, we were unable to examine discrepancies between the information obtained in the questionnaire and actual measurements. Second, we were unable to document changes in the risk factors, such as physical activity levels and other lifestyle factors, after the baseline survey was administered. Third, the samples were limited to a single ethnic group, and the findings may not be generalizable to other ethnic groups. Finally, our study is ongoing; thus, BC incidence might increase in the future. We will continue our research to further elucidate the effects of sedentary time and physical activity on BC in greater detail.

In conclusion, the habit of spending ≥7 h/d being sedentary is associated with a higher BC risk. In surveyed participants who spent ≥7 h/day being sedentary, the leisure-time physical activity and daily walking time tended to not have a suppressive effect on BC incidence. This finding suggests that the sedentary time might be a more influential factor than physical activity. Our results confirm the need to consider a shorter sedentary time of not more than 7 h/d to reduce BC risk among Japanese women.

AUTHOR CONTRIBUTIONS

Satomi Tomida: Conceptualization; formal analysis; writing – original draft. **Teruhide Koyama:** Conceptualization; formal analysis; writing – review and editing. **Etsuko Ozaki:** Investigation. **Naoyuki Takashima:** Investigation. **Midori Morita:** Investigation. **Koichi Sakaguchi:** Investigation. **Yasuto Naoi:** Investigation. **Yuichiro Nishida:** Investigation. **Megumi Hara:** Investigation. **Asahi Hishida:** Investigation. **Takashi Tamura:** Investigation. **Rieko Okada:** Investigation. **Yoko Kubo:** Data curation; investigation. **Jun Otonari:** Investigation. **Hiroaki Ikezaki:** Investigation. **Yohko Nakamura:** Investigation. **Miho Kusakabe:** Investigation. **Shiroh Tanoue:** Investigation. **Chihaya Koriyama:** Investigation. **Yuriko N. Koyanagi:** Investigation. **Hidemi Ito:** Investigation. **Sadao Suzuki:** Investigation. **Takahiro Otani:** Investigation. **Naoko Miyagawa:** Investigation. **Yukiko Okami:** Investigation. **Kokichi Arisawa:** Investigation. **Takeshi Watanabe:** Investigation. **Kiyonori Kuriki:** Investigation. **Kenji Wakai:** Funding acquisition; investigation; project administration; supervision; writing – review and editing. **Keitaro Matsuo:** Funding acquisition; investigation; project administration; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Kenji Wakai and Keitaro Matsuo are Editorial Board Members of *Cancer Science*. The authors have no conflicts of interest.

ETHICS STATEMENT

The ethics committees of the Aichi Cancer Center (IRB No. H2210001A) and of the other institutions that participated in the J-MICC Study. The study protocol of the J-MICC Study was approved by the Institutional Review Board of the Aichi Cancer Center (IRB No. H2210001A) and of the other institutions that participated in the J-MICC Study. All participants provided written informed consent before enrollment.

Approval of the research protocol by an Institutional Reviewer Board: N/A.

Informed Consent: N/A.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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