

Non-cancer risks among female breast cancer survivors: a matched cohort study in Japan

Chitose Kawamura,^{a,b} Krishnan Bhaskaran,^c Takaaki Konishi,^{d,e} Yasuaki Sagara,^f Hiroko Bando,^g Tomohiro Shinozaki,^h Shuko Nojiri,^{i,j} Motohiko Adomi,^k Angel Y. S. Wong,^c Nanako Tamiya,^{l,m,n} and Masao Iwagami^{c,l,m,n,o,*}



^aDepartment of Health Services Research, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Ibaraki, Japan

^bDepartment of Breast-Thyroid-Endocrine Surgery, University of Tsukuba Hospital, University of Tsukuba, Ibaraki, Japan

^cFaculty of Epidemiology and Population Health, Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

^dDepartment of Breast and Endocrine Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

^eDepartment of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, Tokyo, Japan

^fDepartment of Breast Surgical Oncology, Sagara Hospital, Social Medical Corporation Hakuikai, Kagoshima, Japan

^gDepartment of Breast and Endocrine Surgery, Institute of Medicine, University of Tsukuba, Ibaraki, Japan

^hDepartment of Information and Computer Technology, Faculty of Engineering, Tokyo University of Science, Tokyo, Japan

ⁱClinical Translational Science, Juntendo University School of Medicine Graduate School of Medicine, Tokyo, Japan

^jMedical Technology Innovation Center, Juntendo University, Tokyo, Japan

^kDepartment of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA

^lDepartment of Health Services Research, Institute of Medicine, University of Tsukuba, Ibaraki, Japan

^mHealth Services Research and Development Center, University of Tsukuba, Ibaraki, Japan

ⁿDigital Society Division, Center for Cyber Medicine Research, University of Tsukuba, Ibaraki, Japan

^oDepartment of Digital Health, Institute of Medicine, University of Tsukuba, Ibaraki, Japan

Summary

Background The number of breast cancer (BC) survivors has increased worldwide, but the landscape of their non-cancer disease risks remains unclear, especially among Asian women.

Methods In the JMDC claims database, which covers company employees and their family members in Japan, women aged 18–74 years with and without an incident BC were matched in a 1:4 ratio for age and entry timing to the database between January 2005 and December 2019. The risks for six cardiovascular diseases (myocardial infarction, heart failure, atrial fibrillation/flutter, ischaemic stroke, intracranial haemorrhage, and pulmonary embolism) and six non-cardiovascular diseases (major osteoporotic fractures, other fractures, gastrointestinal bleeding, urinary tract infection, infectious pneumonia, and anxiety/depression) were compared between the groups.

Findings Comparing 24,017 BC survivors and 96,068 matched women (mean age, 50.5 years, standard deviation, 8.7 years), the incidence rates of heart failure, atrial fibrillation/flutter, and all non-cardiovascular diseases were higher in the BC survivor group. The highest adjusted hazard ratio (HR) was noted for heart failure (3.99 [95% confidence interval 2.58–6.16]), followed by gastrointestinal bleeding (3.55 [3.10–4.06]), and anxiety/depression (3.06 [2.86–3.28]). The HRs in the first year were larger than those for 1–10 years for most outcomes, whereas the HRs for fracture outcomes were larger for 1–10 years.

Interpretation BC survivors in Japan showed an increased risk of many non-cancer diseases compared to women without BC. Most risks increased more steeply during the first year following diagnosis, whereas the risk of fractures increased later.

Funding Competitive research funding from Pfizer Health Research Foundation in Japan.

Copyright © 2025 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords: Breast cancer; Cardiovascular disease; Depression; Bleeding; Infection; Fracture

The Lancet Regional Health - Western Pacific 2025;56: 101519

Published Online 21 March 2025

<https://doi.org/10.1016/j.lanwpc.2025.101519>

*Corresponding author. Professor, Department of Digital Health, Institute of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki, Japan.

E-mail address: iwagami-tyk@umin.ac.jp (M. Iwagami).

Research in context

Evidence before this study

The risks of non-cancer diseases among female breast cancer survivors have been investigated. We searched PubMed on October 1, 2024, using the search terms (“cancer survivor” OR “breast cancer”) AND (“cardiovascular” OR “myocardial infarction” OR “heart failure” OR “arrhythmia” OR “atrial fibrillation” OR “stroke” OR “intracranial haemorrhage” OR “pulmonary embolism” OR “fracture” OR “gastrointestinal bleeding” OR “bleeding” OR “pneumonia” OR “urinary tract infection” OR “infection” OR “mental” OR “anxiety” OR “depression”), without restricting language or the start and end dates of the search, and conducted manual searches of reference lists from previous studies. We identified 34 studies that compared individuals with breast cancer to matched individuals without breast cancer (Appendix pp 1–9). We found that most studies on cardiovascular diseases were conducted in American or European countries and that there is a lack of data on other common diseases, such as bleeding and infections (Appendix p 10).

Added value of this study

In the present matched cohort study in Japan, breast cancer survivors showed an increased risk for heart failure and atrial fibrillation/flutter among major cardiovascular diseases, as well as major non-cardiovascular diseases including major

osteoporotic fractures, other fractures, gastrointestinal bleeding, infectious pneumonia, urinary tract infections, and anxiety/depression. This study also found that the risk of most outcomes is more likely to increase during the first year, while the risk of fractures tends to rise later. To the best of our knowledge, this is the first large-scale study from Asia that investigated the risk of individual cardiovascular diseases in breast cancer survivors compared with the general population. Moreover, this is the first study to show that breast cancer survivors have a higher risk of developing bleeding and infections.

Implications of all the available evidence

Breast cancer survivors, regardless of race or ethnicity, are at risk for a variety of non-cancer diseases, including both cardiovascular and non-cardiovascular diseases. For breast cancer survivors to live longer with a maintained quality of life, it is important for healthcare providers and patients to understand the risks of non-cancer diseases according to follow-up time (e.g., heart failure and anxiety/depression during the first year and fractures later) and to link them to screening (e.g., regular assessment of blood cholesterol, cardiac function, and bone density), prevention, and early treatment (e.g., statins, bisphosphonates, and counselling for anxiety/depression).

Introduction

In 2020, breast cancer (BC) was the leading cause of cancer among women worldwide, with the highest incidence in most countries.¹ Early detection and advancements in treatment strategies have increased survival rates for many patients with BC. For example, in the most recent data from Japan, the 5-year all-cause survival rates are 95.2% and 90.9% for patients with stage I and stage II, respectively.²

Accordingly, general health among BC survivors has become an increasing concern. As summarised in Appendix pp 1–9, American and European studies have suggested that BC survivors have an increased risk of several non-cancer diseases, such as heart failure and fractures.^{3–6} However, it remains controversial whether the risk of other diseases, such as myocardial infarction and stroke, also increases in BC survivors.^{3,4}

Moreover, several questions remain unanswered. First, the aforementioned studies were conducted in American or European countries and included only a limited number of individuals of Asian descent (Appendix p 10). Therefore, it remains unknown whether the risks of cardiovascular diseases are similarly heightened in Asian BC survivors. Second, regardless of ethnicity, there has been almost no data available on bleeding and infections comparing BC survivors with non-BC women, even though these are important diseases that require treatment and can sometimes be

life-threatening. Third, only a small fraction of previous studies has considered BC treatment in their analyses, although the risks of individual cardiovascular and non-cardiovascular diseases may differ among patients receiving different treatment regimens.

To address these significant knowledge gaps, this study sought to investigate the risk of 12 major non-cancer diseases among BC survivors in comparison to age-matched women. The diseases examined include six cardiovascular conditions (myocardial infarction, heart failure, atrial fibrillation/flutter, ischaemic stroke, intracranial haemorrhage, and pulmonary embolism) and six non-cardiovascular conditions (major osteoporotic fractures, other fractures, gastrointestinal bleeding, infectious pneumonia, urinary tract infections, and anxiety/depression). This analysis utilised a large, population-based claims database from Japan.

Methods

Study design

We conducted a matched cohort study using data from the JMDC claims database from January 2005 to June 2022.

Data source

JMDC Inc. (Japan Medical Data Center Co. until 2018) has obtained individual medical claims and annual

health checkup data from participating associations within the Japanese Health Insurance Societies for employee insurance, which cover companies with ≥ 700 regular employees or groups of companies totalling ≥ 3000 regular employees, as well as their dependants.⁷ In Japan, most people retire before the age of 65 years, and everyone aged ≥ 75 years is required to withdraw from employee insurance and join the long life medical care system.⁸ Therefore, the JMDC database mostly comprises details of people aged < 65 years, with an upper limit of 74 years. To date, several clinical and health-service studies have been conducted using the JMDC database.^{9–11} Since 2005, the number of participating health insurance associations, and therefore the number of insured individuals in the JMDC database, has consistently increased, reaching a cumulative total of > 14 million people when we obtained the studied data at the end of 2022. In addition to demographics and eligibility information, the JMDC database includes monthly data on inpatient and outpatient diagnoses recorded based on the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes, prescribed and dispensed medications (in both hospitals and clinics) coded using the World Health Organisation Anatomical Therapeutic Chemical classifications,¹² European Pharmaceutical Market Research Association codes, and procedures such as surgery, using original Japanese codes.

This study was approved by the Ethics Committee of the University of Tsukuba, Ibaraki, Japan (approval number 1839). The requirement for consent from individual participants was waived because the data were anonymised.

Study participants

The exposed group, or BC survivors, included women with incident BC, defined as a new diagnosis of BC (ICD-10 C50) between database inception (January 2005) and December 2019, who also received BC surgery (Japanese original procedure codes K476.1–K476.9) within 1 year of diagnosis. We selected December 2019 because the COVID-19 pandemic could have delayed BC diagnosis after January 2020 in Japan and led to misclassification of BC status. To ensure that the BC diagnosis was new, we excluded patients with possibly prevalent BC, defined as a diagnosis within 3 months of entering the JMDC database. We also excluded patients indicating metastatic BC, recurrent BC, sarcoma, or malignant phyllodes tumours using the Japanese original diagnosis codes, as they have different clinical courses from primary BC survivors. Moreover, we excluded patients with BC whose diagnosis and JMDC withdrawal occurred in the same month because their follow-up lengths were almost non-existent. The month of the first BC diagnosis was referred to as the ‘index month’ to indicate the start of follow-up.

For each BC survivor, we randomly selected four women with no history of BC at the index month, with

the same age (± 1 year) and the same timing (year and month) of entry to the JMDC database to ensure the same lengths of covariate definitions between the groups. The sampling was conducted without replacement, meaning that a woman could be selected for the matched cohort only one time.

Outcomes

We pre-defined algorithms to define the 12 outcomes, using ICD-10 codes; hospitalisation; medical procedures, such as surgery, ablation, and orthopaedic cast; and medication (Appendix pp 11–13) in reference to previous studies using the JMDC databases and validation studies using Japanese claims data.¹³ We examined six major cardiovascular diseases, including myocardial infarction (inpatient diagnosis and cardiac catheter or coronary artery bypass grafting), heart failure (inpatient diagnosis and cardiac echocardiography and diuretics or inotropic drugs), atrial fibrillation/atrial flutter (inpatient/outpatient diagnosis and catheter ablation or maze operation or antiarrhythmic drugs or anticoagulants), ischaemic stroke (inpatient diagnosis and catheter or surgical thrombus retrieval or thrombectomy or specific antithrombotic drugs including tissue plasminogen activator, antiplatelet drugs, or specific anticoagulants), intracranial haemorrhage (inpatient diagnosis and specific surgery or antihypertensive or specific nitrate drugs), and pulmonary embolism (inpatient diagnosis and pulmonary embolectomy or inferior vena cava filter placement or specific antithrombotic drugs) and six major non-cardiovascular diseases including major osteoporotic fractures (thoracolumbar and pelvic fractures, proximal humerus fractures, distal radius fractures, and femoral neck fractures; inpatient/outpatient diagnosis and orthopaedic surgery or orthopaedic procedures or orthopaedic cast), other fractures (all fractures except for major osteoporotic fractures; inpatient/outpatient diagnosis and orthopaedic surgery or orthopaedic procedures or orthopaedic cast), gastrointestinal bleeding (inpatient/outpatient diagnosis and endoscopic procedure), infectious pneumonia (inpatient/outpatient diagnosis and antibiotics or antifungal drug or antimycobacterial drugs or antiviral drugs), urinary tract infection (inpatient/outpatient diagnosis and antibiotics or antifungal drugs), and anxiety/depression (inpatient/outpatient diagnosis and anti-anxiety drugs or antidepressants). Anxiety and depression were grouped together as they are often recorded together or misclassified for reimbursement purposes in the Japanese claims system.

Covariates

Potential confounding factors between BC status and the studied outcomes included body mass index (BMI) (classified as < 18.5 kg/m², 18.5–24.9 kg/m², 25.0–29.9 kg/m², or ≥ 30.0 kg/m²), smoking history (non-smoker/ex-smoker or current smoker), drinking

habits (none, sometimes, or every day), and common lifestyle-associated diseases, including hypertension, diabetes, and dyslipidaemia. In both groups, information on BMI, smoking history, and drinking habits was obtained from the most recent annual health checkup data at or before the index month. Hypertension, diabetes, and dyslipidaemia were defined based on any history of prescriptions for these conditions from JMDC enrolment to the index month. Additionally, for fracture outcomes, we included patients treated for osteoporosis based on any history of prescriptions for osteoporosis before the index month.

Statistical analysis

We first summarised the baseline characteristics in each group and compared these between the groups using chi-squared tests for BMI, smoking status, drinking habits, comorbidities, and previous histories of each outcome. Yates' continuity correction was applied to estimate p-values for binary variables.

Subsequently, we calculated the crude incidence rate for each outcome in each group and the crude difference and ratio between the groups. For each outcome, both groups were followed-up from the index month to the earliest incidence of that outcome, withdrawal from the JMDC database (which suggests that the patient lost insurance due to death or ceasing to be an employee, or that the health insurance association no longer contributed to the JMDC database), June 2022, or 10 years from the index month. Additionally, if an individual in the matched cohort group was subsequently diagnosed with BC, she was censored in the month of the BC diagnosis because she would be included in the BC survivor group from that point forward.

For each outcome, patients with a record of that outcome in the same month as the index month or earlier (since entry into the database) were considered to have a past medical history and were excluded from that analysis. The mean look-back period was 3.90 years (SD 3.03 years) in both groups, because the index month and the timing of entry into the database were the same between matched women with and without BC. We plotted Kaplan–Meier survival curves for each outcome.

We then estimated adjusted hazard ratios (HRs) using stratified Cox regression models to account for the matching: model 1, without additional adjustment; model 2, adjusted for hypertension, diabetes, and dyslipidaemia, in addition to osteoporosis for major osteoporotic fractures and other fracture outcomes; model 3, further adjusted for BMI, smoking history, and drinking habits as a complete case analysis; and model 4, with multiple imputation for BMI, smoking history, and drinking habits. For multiple imputation, we used a chained equation method and created 50 filled-in complete data sets, using information from other variables (i.e., exposure status, hypertension, diabetes, dyslipidaemia, osteoporosis [only in the analysis of major

osteoporotic fractures and other fractures], and outcome status in each analysis).¹⁴

In a sensitivity analysis, both groups were followed-up from the month of the first BC surgery (and the same month for the matched women without BC), instead of the index month (month of first BC diagnosis) in the main analysis. In another sensitivity analysis, people with a look-back period <1 year (14.3% in both groups) were excluded from the analysis, because their past medical history might not have been sufficiently captured. As a subgroup analysis, we stratified patients by insurance status (women insured herself or women who are a dependent family member of an insured person), because their follow-up and/or censoring patterns may be different.

Further, after observing the Kaplan–Meier survival curves and corresponding log–log survival plots (i.e., log [–log S(t)] against t), we decided to estimate and report the incidence rates and HRs separately for <1 year and 1–10 years. This was because several outcomes showed evidently different trends between these two periods, consistent with the fact that most multidisciplinary treatments for BC (e.g., chemotherapy), except for hormone treatment, are completed within 1 year of diagnosis. In a post hoc analysis, we plotted the spline curves for the (crude) HR as a function of time since diagnosis, using flexible parametric models.^{15,16}

For additional analyses, we estimated adjusted HRs by treatment regimens during the first year following the index month, contingent upon having a sufficient outcome number. We categorised patients with BC into four chemotherapy groups: anthracycline, taxane, anthracycline and taxane, and no anthracycline or taxane (for heart failure outcomes, we utilised human epidermal growth factor receptor 2 [HER2]-targeted therapy in place of taxane). Similarly, by hormone therapy, patients with BC were divided into three groups: tamoxifen, aromatase inhibitors, and neither tamoxifen nor aromatase inhibitors. Patients receiving both tamoxifen and aromatase inhibitors (n = 348) were excluded from this analysis because of the small sample size and because these drugs may have opposite effects for some outcomes (e.g., bone protective effects of tamoxifen and decreases in bone density with aromatase inhibitors). Patients experiencing any event of interest or loss to follow-up within the first year were also excluded. For this analysis, we employed simple Cox regression rather than stratified Cox regression to compare BC patients receiving each treatment with non-BC women, adjusting for age, year of diagnosis, comorbidities (including osteoporosis for fracture outcomes), axillary dissection, radiotherapy, as well as the administration of anthracyclines and taxanes (using HER2-targeted therapy instead of taxanes for heart failure) when analysed by hormone therapy, and tamoxifen and aromatase inhibitors when analysed by chemotherapy.

All analyses were performed using STATA version 15.1 (Stata Corp, College Station, TX, USA).

Role of the funding source

We received competitive research funding from the Pfizer Health Research Foundation in Japan (<https://www.health-research.or.jp/>). The funder had no role in the study design, data collection, analysis, or interpretation.

Results

Between January 2005 and December 2019, we included a total of 24,017 BC survivors (mean age 50.5 years, standard deviation [SD] 8.7 years) and 96,068 women with no history of BC (mean age 50.5 years, SD 8.7 years), of whom 822 were later diagnosed with BC and therefore censored (Fig. 1). Table 1 presents the baseline characteristics of the groups. BC survivors showed a higher prevalence of hypertension and dyslipidaemia, as well as a greater number of previous outcomes (heart failure, major osteoporotic fractures, other fractures, gastrointestinal bleeding, infectious pneumonia, urinary tract infection, and anxiety/depression) compared to the matched cohort group. The treatment details of the BC

survivors during the first year are presented in Appendix p 14, suggesting a broadly similar distribution to that of the National Clinical Database-Breast Cancer Registry of Japan.¹⁷ The higher proportion of patients receiving chemotherapy in our study (23.9%) than the national data (15.2%–18.2%) may be due to the younger participant age in our study.

The mean follow-up period (maximum 10 years), if not censored for each outcome, was 3.25 years (SD, 2.46 years) in BC survivors and 3.22 years (SD, 2.48 years) in the matched cohort group. Table 2 shows the crude incidence rate for each outcome in each group, along with the differences and ratios between the groups. The incidence rates of heart failure, atrial fibrillation/flutter, and all non-cardiovascular diseases were higher in the BC survivors than in the matched cohort group, with the lower limit of the 95% confidence interval (CI) for their difference exceeding 0. The highest adjusted HR in the last model (model 4) was noted for heart failure (3.99, 95% CI 2.58–6.16), followed by gastrointestinal bleeding (3.55, 95% CI 3.10–4.06) and anxiety/depression (3.06, 95% CI 2.86–3.28).

Fig. 2 shows the Kaplan–Meier curves of the cumulative incidence for each outcome, while Appendix pp 15 and 16 presents the corresponding log–log survival

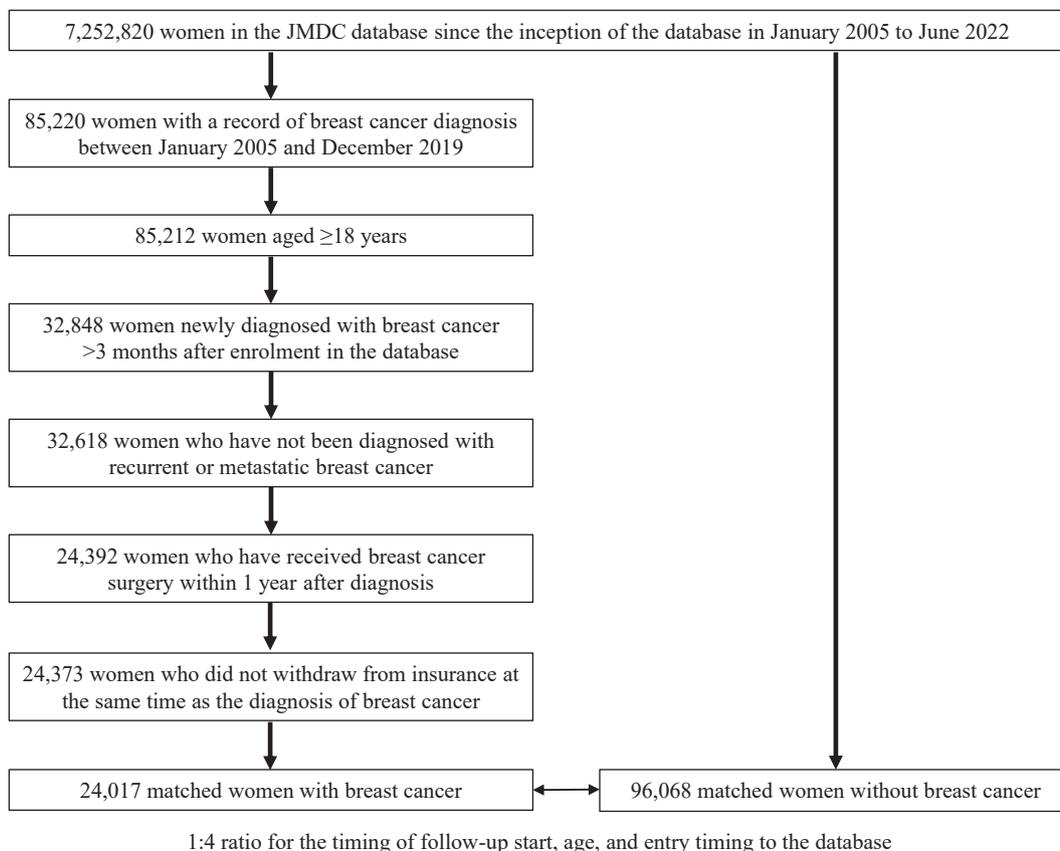


Fig. 1: Flow chart of matched cohort of women with and without breast cancer.

	Patients with breast cancer N = 24,017	Women without breast cancer N = 96,068	P-value
Age of follow-up start (years), mean (SD)	50.5 (8.7)	50.5 (8.7)	NA
Age of entry to the JMDC database (years), mean (SD)	46.6 (9.1)	46.6 (9.1)	NA
Body mass index, n (%)			<0.0001
Underweight (<18.5 kg/m ²)	2044 (8.5)	8118 (8.5)	
Normal weight (18.5–24.9 kg/m ²)	11,813 (49.2)	42,638 (44.4)	
Overweight (25–29.9 kg/m ²)	2532 (10.5)	8901 (9.3)	
Obese (≥30 kg/m ²)	699 (2.9)	2742 (2.9)	
Missing	6929 (28.9)	33,669 (35.1)	
Smoking status, n (%)			<0.0001
Non-smoker/ex-smoker	15,262 (63.6)	54,972 (57.2)	
Current smoker	1625 (6.8)	6727 (7.0)	
Missing	7130 (29.7)	34,369 (35.8)	
Drinking habits, n (%)			<0.0001
None	8793 (36.6)	33,411 (34.8)	
Sometimes	5078 (21.1)	17,893 (18.6)	
Every day	2406 (10.0)	7901 (8.2)	
Missing	7740 (32.2)	36,863 (38.4)	
Comorbidities, n (%)			
Diabetes	786 (3.3)	2933 (3.1)	0.083
Dyslipidaemia	2876 (12.0)	10,663 (11.1)	<0.0001
Hypertension	3157 (13.1)	11,539 (12.0)	0.0001
Osteoporosis	669 (2.8)	3038 (3.2)	<0.0001
Past medical history, n (%)			
Myocardial infarction	6 (0.02)	9 (0.01)	0.11
Heart failure	28 (0.12)	69 (0.07)	0.040
Atrial fibrillation/flutter	79 (0.33)	277 (0.29)	0.33
Ischaemic stroke	18 (0.07)	125 (0.13)	0.035
Intracranial haemorrhage	14 (0.06)	86 (0.09)	0.17
Pulmonary embolism	11 (0.05)	24 (0.02)	0.14
Major osteoporotic fractures	175 (0.73)	530 (0.55)	0.0016
Other fractures	630 (2.6)	1626 (1.7)	<0.0001
Gastrointestinal bleeding	341 (1.4)	652 (0.68)	<0.0001
Infectious pneumonia	755 (3.1)	2680 (2.8)	0.0035
Urinary tract infection	2900 (12.1)	10,612 (11.1)	<0.0001
Anxiety/depression	1760 (7.3)	5777 (6.0)	<0.0001

SD = standard deviation, NA = not applicable.

Table 1: Baseline characteristics of matched women with and without breast cancer.

plots. The incidences of all outcomes in the matched cohort group consistently increased over time. In contrast, the incidences of some outcomes, such as infectious pneumonia and anxiety/depression, increased more steeply during the first year of follow-up, whereas the incidence of major osteoporotic fractures and other fractures increased more steeply later in the follow-up period.

Results of the sensitivity analysis starting the follow-up from the month of the first BC surgery (and the same month for the matched women without BC) were very similar to those in the main analysis (Appendix pp 17 and 18). The results of another sensitivity analysis

excluding people with a look-back period of <1 year (14.3% in both groups) were similar to those of the main analysis (Appendix pp 19 and 20). The proportions of women who were insured herself (vs. women who are a dependent family member of an insured person) were 40.7% (9774/24,017) in the BC survivor group and 39.5% (37,954/96,068) in the matched comparison group. In the analysis stratified by insurance status, the results were similar between the two subgroups (Appendix pp 21–24).

Appendix pp 25–28 presents the results of survival analysis separately for <1 year and 1–10 years. The adjusted HRs in the last model (model 4), excluding those for myocardial infarction and pulmonary embolism (which could not be obtained because of the small number of outcomes), are summarised graphically in Fig. 3. The HRs for <1 year were larger than those for 1–10 years from the BC diagnosis for most outcomes, especially anxiety/depression (<1 year 5.98 [95% CI 5.43–6.60], and 1–10 years 1.48 [95% CI 1.34–1.63]). However, the HR was larger for 1–10 years than for <1 year for major osteoporotic fractures (<1 year 1.30 [95% CI 0.92–1.83], and 1–10 years 1.78 [95% CI 1.46–2.15]) and other fractures (<1 year 1.28 [95% CI 1.05–1.56], and 1–10 years 2.06 [95% CI 1.84–2.32]). Appendix pp 29 and 30 presents the spline curves for the (crude) HR as a function of time since diagnosis.

The additional analysis by treatment regimens was conducted for heart failure, atrial fibrillation/flutter, and all non-cardiovascular diseases, which showed a sufficient number of outcomes (Appendix pp 31–38). For chemotherapy, the point estimates of adjusted HRs for major osteoporotic fractures, other fractures, gastrointestinal bleeding, infectious pneumonia, and anxiety/depression in the anthracycline and taxane group, as well as that for heart failure in the anthracycline and HER2-targeted therapy group, were higher than in the other groups, although their 95% CIs were overlapping. For hormone therapy, the point estimates of adjusted HRs for major osteoporotic fractures and gastrointestinal bleeding were higher in the aromatase inhibitor group than in the other groups, although their 95% CIs were overlapping.

Discussion

Using a large Japanese claims database that includes over 24,000 women with BC, we illustrated the landscape of non-cancer risks among Japanese female BC survivors compared with the general population of women of the same age. Japanese BC survivors showed an increased risk of heart failure, atrial fibrillation/flutter, major osteoporotic fractures, other fractures, gastrointestinal bleeding, infectious pneumonia, urinary tract infections, and anxiety/depression compared to women without BC. The HRs at less than 1 year were higher than those at 1–10 years of follow-up for most

outcomes, especially anxiety/depression. However, the opposite trend was observed for fractures. We also found that the risk of certain outcomes could differ according to various treatment regimens for BC, although the analysis appeared to be underpowered even with this large database.

Previous American and European studies have suggested that the overall risk of cardiovascular diseases among patients with BC is high¹⁸; however, there is both agreement (e.g., heart failure) and controversy (e.g., stroke) regarding the risk associated with each type of cardiovascular disease. Consistent with previous studies, BC survivors in Japan were more likely to develop heart failure than age-matched women without BC, with even higher ratios than those reported in American and European studies.^{3,4,19–21} Although previous studies showed differing risks for other cardiovascular diseases,^{3,4,19–23} our study indicated a higher risk for atrial fibrillation/atrial flutter but no strong evidence for higher risk for myocardial infarction, ischaemic stroke, intracranial haemorrhage, or pulmonary embolism. Differences in results between studies may be attributable to variations in the age distributions of the study populations, the baseline risk of each outcome by country or ethnicity, and the stage of BC at detection. The overall study population was younger (mean age of 50.5 years) than most previous studies (Appendix pp 1–9), mainly because the database does not include individuals aged 75 years and older, all of whom are covered by the long life medical care system in Japan. It is possible that the Japanese in this population were less likely to experience cardiovascular events than individuals of similar age in other countries.

BC and cardiovascular diseases have several overlapping risk factors.^{24,25} Although cardiovascular diseases can be identified early, effectively managed, and in many cases prevented,²⁶ cardiovascular disease screening and management do not typically feature in routine long-term BC care.²⁷ It is important to ensure that regular checks for treatment-specific adverse events are performed (e.g., echocardiography to evaluate cardiac function in patients treated with anthracycline or HER2-targeted treatments) and that patients are encouraged to undergo medical screening (e.g., electrocardiogram or measurement of blood pressure), which is not usually performed routinely as part of BC care. Prevention and early treatment (e.g., statins, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers) are also possible.

Many studies have indicated that BC survivors have more osteoporotic fractures, both pre-and post-menopausal (Appendix pp 1–9). Osteoporosis due to aromatase inhibitors and chemotherapy-induced ovarian failure is an important risk factor for fractures in BC survivors.^{28,29} Although the participants in this study were relatively young, the risk for both osteoporotic and other fractures was higher among BC survivors, which

	Patients with breast cancer		Women without breast cancer		Crude rate difference (95% CI) (/1000 PY)	Crude rate ratio (95% CI)	Hazard ratio (95% CI)			
	No. of outcomes/No. of patients ^a (/1000 PY)	Incidence rate (95% CI) (/1000 PY)	No. of outcomes/No. of patients ^a (/1000 PY)	Incidence rate (95% CI) (/1000 PY)			Model 1	Model 2	Model 3	Model 4
Myocardial infarction	4/24,011	0.05 (0.02–0.13)	9/96,059	0.03 (0.02–0.06)	0.02 (–0.03 to 0.08)	1.75 (0.39–6.28)	1.35 (0.40–4.58)	NA	NA	NA
Heart failure	58/23,989	0.74 (0.58–0.96)	81/95,999	0.26 (0.21–0.33)	0.48 (0.28–0.68)	2.83 (1.98–4.01)	3.47 (2.39–5.04)	3.66 (2.45–5.46)	4.29 (2.04–9.02)	3.99 (2.58–6.16)
Atrial fibrillation/flutter	96/23,938	1.24 (1.01–1.51)	209/95,791	0.68 (0.60–0.78)	0.55 (0.29–0.82)	1.81 (1.41–2.32)	1.86 (1.43–2.40)	1.82 (1.40–2.37)	1.80 (1.19–2.71)	1.83 (1.40–2.40)
Ischaemic stroke	24/23,999	0.31 (0.21–0.46)	127/95,943	0.41 (0.35–0.49)	–0.11 (–0.25 to 0.04)	0.74 (0.46–1.16)	0.71 (0.45–1.12)	0.68 (0.43–1.09)	0.86 (0.42–1.79)	0.66 (0.41–1.08)
Intracranial haemorrhage	19/24,003	0.24 (0.16–0.38)	112/95,982	0.37 (0.30–0.44)	–0.12 (–0.25 to 0)	0.67 (0.39–1.09)	0.65 (0.39–1.09)	0.60 (0.35–1.01)	0.92 (0.38–2.22)	0.58 (0.34–1.01)
Pulmonary embolism	14/24,006	0.18 (0.11–0.30)	27/96,044	0.09 (0.06–0.13)	0.09 (0–0.19)	2.04 (0.99–4.04)	2.04 (1.04–3.98)	NA	NA	NA
Major osteoporotic fractures	239/23,842	3.10 (2.73–3.52)	546/95,538	1.79 (1.64–1.94)	1.31 (0.89–1.73)	1.73 (1.48–2.02)	1.63 (1.38–1.92)	1.64 (1.39–1.93)	1.49 (1.16–1.90)	1.63 (1.38–1.93)
Other fractures	643/23,387	8.58 (7.94–9.27)	1439/94,442	4.80 (4.55–5.05)	3.79 (3.08–4.50)	1.79 (1.63–1.97)	1.81 (1.64–2.00)	1.82 (1.65–2.01)	1.80 (1.57–2.07)	1.82 (1.65–2.01)
Gastrointestinal bleeding	455/23,676	5.99 (5.46–6.56)	517/95,416	1.70 (1.56–1.85)	4.29 (3.72–4.86)	3.53 (3.01–4.10)	3.56 (3.12–4.07)	3.55 (3.11–4.06)	3.17 (2.60–3.88)	3.55 (3.10–4.06)
Infectious pneumonia	950/23,262	13.0 (12.2–13.8)	1482/93,388	5.01 (4.76–5.27)	7.98 (7.11–8.85)	2.59 (2.39–2.81)	2.68 (2.45–2.92)	2.67 (2.45–2.92)	2.66 (2.33–3.04)	2.69 (2.47–2.94)
Urinary tract infection	2533/21,117	40.4 (38.8–42.0)	6338/85,456	24.3 (23.7–24.9)	16.0 (14.3–17.4)	1.66 (1.58–1.74)	1.69 (1.61–1.76)	1.68 (1.60–1.77)	1.66 (1.54–1.78)	1.68 (1.60–1.77)
Anxiety/depression	1700/22,257	25.0 (23.9–26.3)	2511/90,291	8.80 (8.46–9.15)	16.2 (15.0–17.5)	2.84 (2.67–3.03)	3.04 (2.85–3.25)	3.04 (2.84–3.25)	3.06 (2.78–3.38)	3.06 (2.86–3.28)

CI = confidence interval, PY = person-years, NA = not available (because the number of outcomes was too small). Model 1: without additional adjustment. Model 2: adjusted for hypertension, diabetes, and dyslipidemia, in addition to osteoporosis for the fracture outcome. Model 3: further adjusted for BMI, smoking history, and drinking habits as a complete case analysis. The sample size in each complete case analysis was 75,060 for heart failure, 74,912 for atrial fibrillation/flutter, 75,018 for ischaemic stroke, 75,050 for intracranial haemorrhage, 74,656 for major osteoporotic fractures, 73,512 for other fractures, 74,381 for gastrointestinal bleeding, 72,707 for urinary tract infection, 65,556 for infectious pneumonia, and 70,367 for anxiety/depression. Model 4: with multiple imputation for BMI, smoking history, and drinking habits. ^aPatients with a previous history of the outcome were excluded from the analysis.

Table 2: Incidence rate of each outcome in each group and its difference and ratio between the groups with and without breast cancer.

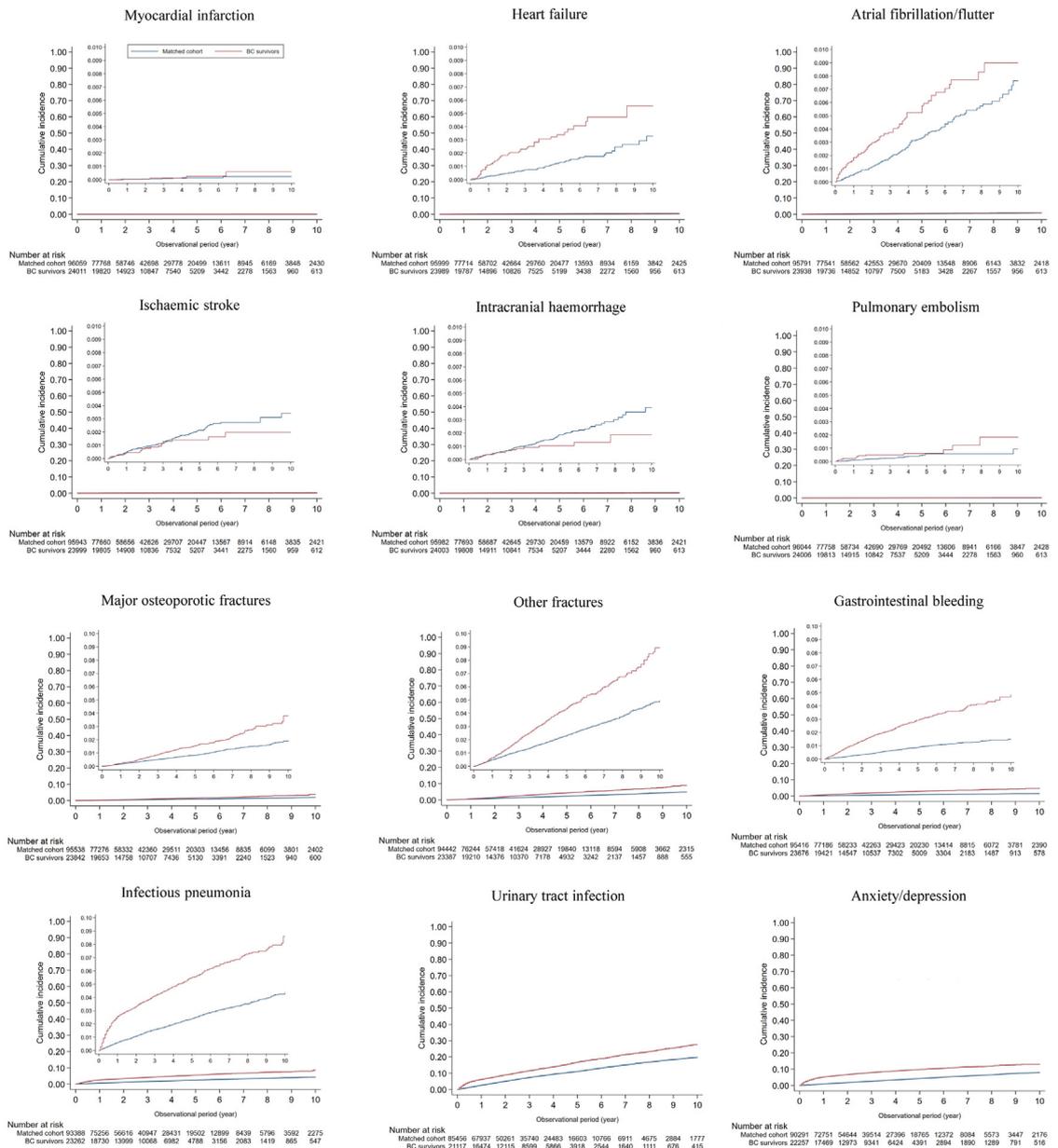


Fig. 2: Kaplan-Meier curves of the cumulative incidence among women with and without breast cancer for each outcome. BC = breast cancer.

is consistent with results from previous large population-based studies. It is important to consider whether bone density tests are performed regularly on those at higher risk (e.g., due to aromatase inhibitors or early menopause from chemotherapy) and whether patients with reduced bone density receive appropriate treatment, such as bisphosphonates and parathyroid hormone. Moreover, it has been reported that osteoporotic fractures in BC patients are not solely due to decreased bone density,³⁰ and it is important for

physicians not only to check bone density but also to encourage patients to quit smoking, eat a healthy diet, and adopt exercise habits, while informing them of their fracture risk to prevent osteoporotic fractures. For other fractures (e.g., rib fractures), as with osteoporotic fractures, it might be important to assess bone density, educate patients, and inform them of their fracture risk.

BC survivors have higher risks of mental health diseases, such as depression, anxiety, and stress-related disorders than non-BC women,³¹ and these risks are

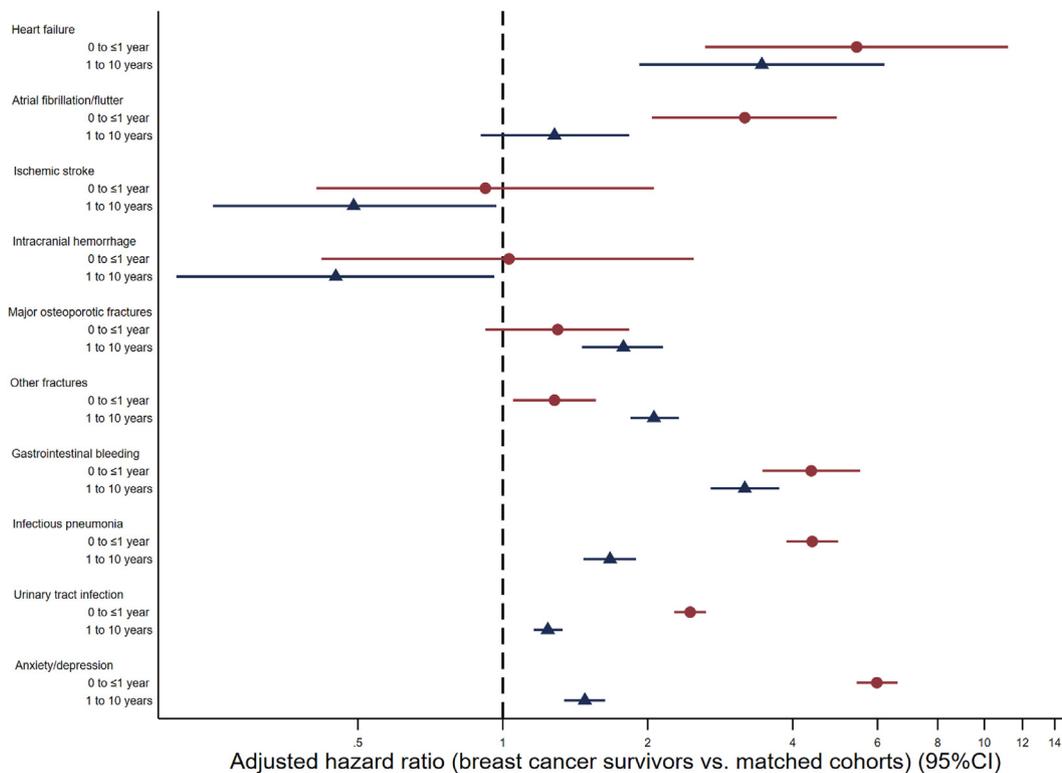


Fig. 3: Adjusted hazard ratios between women with and without breast cancer for each outcome during <1 year and 1-10 years from the index month. CI = confidence interval, BMI = body mass index. Note: The adjusted hazard ratios (95% CIs) are from the last model (model 4) adjusted for hypertension, diabetes, dyslipidaemia, osteoporosis (only for the fracture outcome), BMI, smoking history, and drinking habits, with multiple imputation for BMI, smoking history, and drinking habits (Appendix pp 25-28).

highest from diagnosis to approximately 1 year after diagnosis.^{5,32,33} Treatment with chemotherapy is also known to be a risk factor for mental health diseases.^{5,32} In our study, BC survivors had a higher risk of anxiety/depression than non-BC women, with the highest HR occurring within 1 year of diagnosis. One year after diagnosis, the HR (for the first incidence of anxiety/depression in the database) declined but remained higher than that of non-BC women. It is important for healthcare providers to keep in mind that BC patients are at high risk for anxiety or depression, even 1 year after treatment, and to consider psychosocial interventions as needed.

To the best of our knowledge, this is the first study to demonstrate that patients with BC have a higher risk of developing gastrointestinal bleeding and infections. Notably, the risk was high not only within the first year after the diagnosis of BC when treatment was intensive (e.g., chemotherapy) but also beyond 1 year. The increased risks of infections may suggest that BC survivors have decreased immunity associated with BC and/or side effects of BC treatments. Possible mechanisms for increased gastrointestinal bleeding include stress from BC, damage to the vessel wall due to side effects of BC treatment, the use of pain medications

such as non-steroidal anti-inflammatory drugs, increased use of antiplatelet drugs such as aspirin for cardiovascular disease, and side effects of antidepressants such as selective serotonin reuptake inhibitors.³⁴

This study had certain limitations. First, since the JMDC database mainly includes individuals aged <65 years (up to 74 years), the generalisability of our results to older individuals remains uncertain. We speculate that the absolute risk of each outcome would be higher in older BC survivors, while the relative risks (HRs) between those with and without BC could be lower in the older population, as non-BC women also experience various age-related diseases. Second, surveillance or ascertainment bias (i.e., patients with BC have more contact with the healthcare system and are therefore more likely to be identified as having certain diseases than those without BC) could partly explain the high HRs. However, most of the studied outcomes cause symptoms such as pain, negatively affect quality of life, or are life-threatening. Therefore, we expect that both insured women with and without BC would visit hospitals or clinics similarly if they had the condition, unlike asymptomatic diseases identified through examinations (e.g., liver and kidney diseases). Third, in terms of the possibility of misclassification of exposure status, we

defined BC cases based not only on diagnosis codes but also procedure codes for surgery (which must be accurate for reimbursement purposes). In addition, we excluded cases with diagnoses of metastatic or recurrent BC. Therefore, it is very unlikely that the exposure group included unexposed cases, whereas the unexposed group possibly included women with undiagnosed BC. If this was the case, this would dilute the observed associations towards the null, meaning that the true associations between the two groups would be even larger. Fourth, information regarding the BC stage was unavailable, which may have influenced some outcomes, such as anxiety/depression. Instead of the BC stage, we conducted additional analyses based on treatment regimens (chemotherapy and hormone therapy), which are expected to correlate with the BC stage and can serve as proxies. Fifth, this study focused on curable primary BC, and cases with recurrence or metastatic BC (suggesting stage IV) at the time of diagnosis were excluded. The life expectancy of patients with stage IV BC seems to be improving, and studies focussing on this patient group may be needed in the future. Sixth, there may be unmeasured or residual confounding factors, such as deprivation, diet, and exercise. Finally, this study focused on the presentation of overall and period-specific (<1 year and 1–10 years) HRs over several years of follow-up. These should be interpreted with caution, because if HRs vary over the follow-up period, as suggested by our supplementary analyses using flexible parametric models, the results may be sensitive to the duration of follow-up in the study.³⁵ In addition, the latter period-specific HRs may suffer from “built-in survivor bias”.³⁵

Conclusions

In this large claims database, female BC survivors in Japan had increased risks of heart failure, atrial fibrillation/atrial flutter, and non-cardiovascular diseases (major osteoporotic fractures, other fractures, gastrointestinal bleeding, infectious pneumonia, urinary tract infection, and anxiety/depression) compared with the general population of women of the same age. We found that the risk of most diseases increased during the first year after the BC diagnosis, while the risk of fractures increased later during the follow-up. It is important for healthcare providers and patients to understand the risks of these diseases and link them to screening, prevention, and early treatment.

Contributors

MI and CK designed the study, conducted data processing, analysed the data, and wrote the initial draft. MI was also responsible for the funding acquisition, project administration, and supervision. KB, TK, YS, HB, TS, SN, MA, AYSW, and NT substantially contributed to study design, interpretation of the data, and revision of the manuscript. MI and CK had access to raw data and verified the data. All authors approved the final version and had final responsibility for the decision to submit for publication.

Data sharing statement

We obtained data from JMDC Inc., and we did not obtain permission to share these data with other parties. Researchers who meet the criteria for access can acquire de-identified participant data from JMDC Inc. (<https://www.jmdc.co.jp/en/>).

Declaration of interests

KT has received grants from Kanzawa Medical Research Foundation and the Japan Kampo Medicines Manufacturers Association. SY has received honoraria from Pfizer Inc., AstraZeneca PLC, Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Eli Lilly and Company, Chugai Pharmaceutical Co., Ltd., MSD K.K., Nippon Kayaku Co., Ltd., Kyowa Kirin Co., Ltd., Sysmex Corporation, and Celltrion Healthcare Japan Co., Ltd. TS has received consultation fees from Takeda Pharmaceutical Co., Ltd. and TXP Medical Co., Ltd., and lecture fees from Chugai Pharmaceutical Co., Ltd., Novartis Pharma K.K., Pfizer Inc., SAS Institute Japan Ltd., CMIC Holdings Co., Ltd., and Santen Pharmaceutical Co., Ltd. Other authors declare no competing interests.

Acknowledgements

We thank Editage (www.editage.com) for the English language editing.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.lanwpc.2025.101519>.

References

- Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71(3):209–249.
- National Cancer Center. Hospital Cancer Registry - 5-year Observed Survival Rates 2014-2015 (in Japanese) [Internet]. Available from: <https://hbcrr-survival.ganjo.jp/graph?year=2014-2015&lapsed=5&type=c09#h-title>. Accessed January 28, 2025.
- Raisi-Estabragh Z, Cooper J, McCracken C, et al. Incident cardiovascular events and imaging phenotypes in UK Biobank participants with past cancer. *Heart.* 2023;109(13):1007–1015.
- Strongman H, Gadd S, Matthews A, et al. Medium and long-term risks of specific cardiovascular diseases in survivors of 20 adult cancers: a population-based cohort study using multiple linked UK electronic health records databases. *Lancet.* 2019;394(10203):1041–1054.
- Carreira H, Williams R, Funston G, Stanway S, Bhaskaran K. Associations between breast cancer survivorship and adverse mental health outcomes: a matched population-based cohort study in the United Kingdom. *PLoS Med.* 2021;18(1):e1003504.
- Buzasi E, Carreira H, Funston G, et al. Risk of fractures in half a million survivors of 20 cancers: a population-based matched cohort study using linked English electronic health records. *Lancet Healthy Longev.* 2024;5(3):e194–e203.
- Nagai K, Tanaka T, Kodaira N, Kimura S, Takahashi Y, Nakayama T. Data resource profile: JMDC claims database sourced from health insurance societies. *J Gen Fam Med.* 2021;22(3):118–127.
- Ministry of Health, Labour, and Welfare, Japan. Health and medical services, overview of health care insurance system [Internet]. Available from: https://www.mhlw.go.jp/english/wp/wp-hw4/dl/health_and_medical_services/P26.pdf. Accessed January 28, 2025.
- Li X, Ostropolets A, Makadia R, et al. Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: multinational network cohort study. *BMJ.* 2021;373:n1435.
- Iwagami M, Kumazawa R, Miyamoto Y, et al. Risk of cancer in association with ranitidine and nizatidine vs other h2 blockers: analysis of the Japan medical data center claims database 2005–2018. *Drug Saf.* 2021;44(3):361–371.
- Okada A, Hashimoto Y, Goto T, et al. A machine learning-based predictive model to identify patients who failed to attend a follow-up visit for diabetes care after recommendations from a national screening program. *Diabetes Care.* 2022;45(6):1346–1354.
- ATC/DDD index [Internet]. Available from: https://www.whocc.no/atc_ddd_index/. Accessed December 27, 2023.

- 13 Yamana H, Konishi T, Yasunaga H. Validation studies of Japanese administrative health care data: a scoping review. *Pharmacoepidemiol Drug Saf.* 2023;32(7):705–717.
- 14 White IR, Royston P. Imputing missing covariate values for the Cox model. *Stat Med.* 2009;28(15):1982–1998.
- 15 Royston P, Lambert PC. *Flexible Parametric Survival Analysis Using Stata: Beyond the Cox Model.* Stata Press; 2011.
- 16 Lambert PC, Royston P. Further development of flexible parametric models for survival analysis. *STATA J.* 2009;9(2):265–290.
- 17 Iwamoto T, Kumamaru H, Niikura N, et al. Survival trends and patient characteristics between 2004 and 2016 for breast cancer in Japan based on the National Clinical Database-Breast Cancer Registry. *Breast Cancer.* 2024;31(2):185–194.
- 18 Florido R, Daya NR, Ndumele CE, et al. Cardiovascular disease risk among cancer survivors: the atherosclerosis risk in communities (ARIC) study. *J Am Coll Cardiol.* 2022;80(1):22–32.
- 19 Abdel-Qadir H, Thavendiranathan P, Austin PC, et al. The risk of heart failure and other cardiovascular hospitalizations after early stage breast cancer: a matched cohort study. *J Natl Cancer Inst.* 2019;111(8):854–862.
- 20 Matthews AA, Peacock Hinton S, Stanway S, et al. Risk of cardiovascular diseases among older breast cancer survivors in the United States: a matched cohort study. *J Natl Compr Cancer Netw.* 2021;19(3):275–284.
- 21 Armenian SH, Xu L, Ky B, et al. Cardiovascular disease among survivors of adult-onset cancer: a community-based retrospective cohort study. *J Clin Oncol.* 2016;34(10):1122–1130.
- 22 Boekel NB, Schaapveld M, Gietema JA, et al. Cardiovascular disease risk in a large, population-based cohort of breast cancer survivors. *Int J Radiat Oncol Biol Phys.* 2016;94(5):1061–1072.
- 23 Jordan JH, Thwin SS, Lash TL, et al. Incident comorbidities and all-cause mortality among 5-year survivors of Stage I and II breast cancer diagnosed at age 65 or older: a prospective-matched cohort study. *Breast Cancer Res Treat.* 2014;146(2):401–409.
- 24 Mehta LS, Watson KE, Barac A, et al. Cardiovascular disease and breast cancer: where these entities intersect: a scientific statement from the American heart association. *Circulation.* 2018;137(8):e30–e66.
- 25 Okwuosa TM, Morgans A, Rhee JW, et al. Impact of hormonal therapies for treatment of hormone-dependent cancers (breast and prostate) on the cardiovascular system: effects and modifications: a scientific statement from the American heart association. *Circ Genom Precis Med.* 2021;14(3):e000082.
- 26 Guida JL, Agurs-Collins T, Ahles TA, et al. Strategies to prevent or remediate cancer and treatment-related aging. *J Natl Cancer Inst.* 2021;113(2):112–122.
- 27 Muhandiramge J, Zalcborg JR, van Londen GJ, et al. Cardiovascular disease in adult cancer survivors: a review of current evidence, strategies for prevention and management, and future directions for cardio-oncology. *Curr Oncol Rep.* 2022;24(11):1579–1592.
- 28 Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet.* 2015;386(10001):1341–1352.
- 29 Hadji P, Gnani M, Body JJ, et al. Cancer treatment-induced bone loss in premenopausal women: a need for therapeutic intervention? *Cancer Treat Rev.* 2012;38(6):798–806.
- 30 Fraenkel M, Geffen DB, Novack V, et al. Breast cancer survivors are at an increased risk for osteoporotic fractures not explained by lower BMD: a retrospective analysis. *NPJ Breast Cancer.* 2015;1:15010.
- 31 Suppli NP, Johansen C, Christensen J, Kessing LV, Kroman N, Dalton SO. Increased risk for depression after breast cancer: a nationwide population-based cohort study of associated factors in Denmark, 1998–2011. *J Clin Oncol.* 2014;32(34):3831–3839.
- 32 Yang H, Brand JS, Fang F, et al. Time-dependent risk of depression, anxiety, and stress-related disorders in patients with invasive and in situ breast cancer. *Int J Cancer.* 2017;140(4):841–852.
- 33 Hung YP, Liu CJ, Tsai CF, et al. Incidence and risk of mood disorders in patients with breast cancers in Taiwan: a nationwide population-based study. *Psychooncology.* 2013;22(10):2227–2234.
- 34 Francisco J, de Abajo LAG-R. Risk of upper gastrointestinal tract bleeding associated with selective serotonin reuptake inhibitors and venlafaxine therapy: interaction with nonsteroidal anti-inflammatory drugs and effect of acid-suppressing agents. *Arch Gen Psychiatry.* 2008;65(7):795–803.
- 35 Hernan MA. The hazards of hazard ratios. *Epidemiology.* 2010;21(1):13–15.