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ORIGINAL PAPER

Patterns of comorbidities in women with breast cancer: a Canadian population-based study

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Abstract

Purpose Improving the understanding of co-existing chronic diseases prior to and after the diagnosis of cancer may help to facilitate therapeutic decision making in clinical practice. This study aims to examine patterns of comorbidities in Canadian women with breast cancer.

Methods We conducted a retrospective cohort study using provincial linked administrative health datasets from British Columbia, Canada, between 2000 and 2013. Women diagnosed with breast cancer between 2005 and 2009 were identified. The index date was defined as the date of diagnosis of breast cancer. Subsets of the breast cancer cohort were identified based on the absence of individual type of comorbidity of interest within 5 years prior to breast cancer diagnosis. For each subset, cases were then individually matched by year of birth at 1:2 ratios with controls without a history of cancer and the individual type of comorbidity of interest within 5 years prior to the assigned index year, matching with the year of breast cancer diagnosis of the corresponding case. Baseline comorbidities were measured over a 1-year period prior to the index date using two comorbidity indices, Rx-Risk-V and Aggregated Diagnosis Groups (ADG). Cox regression model was used to assess the development of seven specific comorbidities after the index date between women with breast cancer and non-cancer women.

Results The most prevalent baseline comorbidity in the breast cancer cohort measured using the Rx-Risk-V model was cardiovascular conditions (39.0%), followed by pain/pain-inflammation (34.8%). The most prevalent category measured using the ADG model was major signs or symptoms (71.8%), followed by stable chronic medical conditions (52.2%). The risks of developing ischemic heart disease, heart failure, depression, diabetes, osteoporosis, and hypothyroidism were higher in women with breast cancer compared to women without cancer, with the hazard ratios ranging from 1.09 (95 CI% 1.03–1.16) for ischemic heart disease to 2.10 (95% CI 1.99–2.21) for osteoporosis in the model adjusted for baseline comorbidity measured using Rx-Risk-V score.

Conclusion Women with breast cancer had a higher risk of developing new comorbidities than women without cancer. Development of coordinated care models to manage multiple chronic diseases among breast cancer patients is warranted.

Keywords Breast cancer · Cancer epidemiology · Comorbidity · Morbidity index · Rx-Risk-V index · Aggregated diagnosis groups · Administrative databases

Introduction

Breast cancer is the most common cancer diagnosed in Canadian women with one in eight women estimated to develop breast cancer in their lifetime [1]. Approximately 26,300 women were diagnosed with breast cancer in 2017, accounting for 25% of all new cancer cases in women. Breast cancer mortality has declined steadily since the mid-1980s, from 32.0 deaths per 100,000 in 1986 to 17.9 deaths per 100,000 in 2015 [2], thanks to screening programs and improvement in cancer treatment [1, 2]. The overall five-year

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survival rate for breast cancer is now 87% [1]. This means that a growing number of women alive with a history of cancer (either cured or living with cancer) may require support to live with the consequences of a cancer diagnosis than in the past.

Comorbidity is highly prevalent in the overall cancer population, with 69% to 88% reporting at least one comorbid disease [3]. Studies conducted in Australia showed that women with breast cancer were at greater risk of developing other health conditions [4, 5] such as mental illness and cardiovascular diseases compared to women without cancer. Population-based studies conducted in Ontario, Canada have shown that the presence of comorbid diseases was associated with an increased risk of death among women with breast cancer [6, 7]. The financial burden of chronic diseases in Canada is substantial with approximately $68 billion spent annually on direct healthcare costs and $122 billion spent annually on indirect costs due to lost productivity and premature death [8]. The costs of cancer care have also risen progressively from $2.9 billion in 2005 to $7.5 billion in 2012 [9]. However, there is limited study of overall morbidity in patients with cancer. Improving the understanding of the patterns of co-existing chronic diseases prior to and after the diagnosis of cancer may help to facilitate therapeutic decision making and to develop novel strategies and models of care that address both comorbidity and cancer.

In Canada, medically necessary healthcare is required to be universal, comprehensive, affordable, accessible, and portable across provincial and territorial jurisdictions, for all citizens and permanent legal residents [10]. The provincial/territorial governments are the sole funders of all medically necessary care, and administrative health data are collected by the government in the course of its regular activities such as cancer control and the remuneration of hospitals, physicians, and other health services. These datasets are available in each province, have records of all person-specific publicly-funded healthcare events over many years, and are being increasingly used for health research purposes [11]. However, no standard approach or classification is available to derive morbidities from administrative data [12].

Cancer care involves not just specialized care but community care for timely diagnosis, management of side effects and other health conditions during treatment, and surveillance and care of cancer-related issues post-treatment [13]. However, there is currently limited information available on the burden of health conditions among the cancer population in British Columbia (BC) to inform health policy. The aim of this study was to examine the patterns of comorbidity and excess comorbidity in women with breast cancer using the BC linked health datasets. We used linked registry and clinical and administrative datasets to compare the development of seven chronic diseases between women with breast cancer and women with no history of cancer.

Methods

Data sources

Six BC-based databases were used in this study: (i) BC Cancer Registry/Breast Cancer Outcome Unit database [14], that recorded information about the case, death date (if applicable), the cancer diagnosis date and the characteristics of the breast cancer and treatment; (ii) BC Ministry of Health (BCMOH) Medical Services Plan (MSP) Registry [15] recorded annual information about the health insurance plan status for the clients and demographic information including sex, year of birth and socioeconomic quintile; (iii) BCMOH MSP claims database [16] provided information on primary care physician visits including visit date and the relevant diagnoses for the visit coded using the International Classification of Diseases (ICD) 9th revision three-digit codes; (iv) Canadian Institute for Health Information (CIHI) Discharge Abstract Database and same-day surgery data [17] provided information on BC hospital inpatient stays including admission date and diagnoses coded using the ICD 9th revision or ICD 10th revision-CA depending on the record year. Each record includes up to 25 acute and chronic diagnoses noted for the patient during hospitalization; (v) BCMOH PharmaNet database [18] provided records of all medications dispensed in the community pharmacies in BC. Drug identification number assigned by Health Canada is used to uniquely identify a particular drug by chemical, dosage, form and manufacturer and is linked to the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) codes that classify drugs according to the major organ and system of the human body; and (vi) BC Vital Statistics Agency provided records of Vital Statistics Deaths [19] for all deaths registered in BC.

Ethics approval was received for a large breast cancer research study funded by the federal government-supported Canadian Institutes of Health Research (CIHR TT7 128272) that includes this analysis, led by Mary McBride, Research Scientist at BC Cancer, from the BC Cancer/University of British Columbia Research Ethics Committee (certificate number: H13-02458). Approvals for data linkage, access, and use were obtained from all Data Stewards.

The six databases were linked at the individual level, using a person-based health record identifier, by Population Data BC (PopData; www.popdata.bc.ca), a multi-university facility that provides researchers access to BC-based collections of government-funded health care and population health data, and record linkage support [20]. The identifiers that were used for the linkage were replaced with a project-specific Study ID when the data were released to researchers for the approved research

project. This means that records for the same individual from one research project cannot be linked to another research project that uses the same records, to ensure confidentiality and privacy requirements are upheld.

Study population

Breast cancer cohort

Women who were BC residents diagnosed with breast cancer as defined in the ICD-O version 3 [21] between years 2005 and 2009 ($n=13{,}208$), aged 18 and over at diagnosis, were identified from the BC Cancer Registry (Supplementary Fig. 1). We applied the following exclusion criteria to obtain our study cohort: (i) women who did not have active health insurance coverage identified in the MSP Registry in the calendar year when breast cancer was diagnosed and five calendar years prior to the breast cancer diagnosis ($n=1009$) (as a five-year look-back period was used to exclude people with selected types of comorbidity of interest prior to breast cancer diagnosis for analysis of risk of individual comorbidity) and (ii) women who died on the same date as breast cancer diagnosis ($n=72$). We defined the index date as the date of breast cancer diagnosis for the cases. Subsets of the breast cancer were identified based on the absence of individual type of comorbidity of interest within 5 years prior to breast cancer diagnosis (Table 1).

Control group

Women who did not have any diagnoses of malignant cancer (ICD-9 codes: 140-172, 174-209; and ICD-10 codes: C00-C43, C45-C97) recorded in MSP claims and hospital databases and no anti-neoplastic agents (ATC codes L01AA01-L01XX41, excluding oral methotrexate and topical fluorouracil) recorded in the PharmaNet database throughout the study period were eligible for selection in the control group. The following inclusion criteria applied for the selection of control groups: (i) women with active health insurance coverage identified in the MSP Registry within five calendar years prior to the assigned index year matching with the year of breast cancer diagnosis of the corresponding cases; (ii) women without a death record in the assigned index year; and (iii) women without the individual comorbidity of interest measured over a 5-year period before the assigned index date. Each case was matched with two randomly selected controls with the same year of birth who met the eligibility criteria. An index date was assigned to the controls matching with the date of breast cancer diagnosis of the corresponding case. Separate control groups were selected for each of the seven types of comorbidity evaluated in our study (Table 1). This was to ensure that neither cases nor controls selected would have the individual type of comorbidity of interest within 5 years prior to the index date for the subsequent analysis of the risk of developing that morbidity as an outcome measure.

Outcomes of interest

Baseline comorbidity

The baseline comorbidity was measured using two comorbidity indices determined over a 1-year period prior to the index date, namely the Rx-Risk-V model [22], which derives morbidity from prescription drug datasets; and the Aggregated Diagnosis Groups (ADGs) [23], a morbidity classification that is part of the Johns Hopkins Adjusted Clinical Groups (ACG)® System. Rx-Risk-V comorbidity categories [22] were determined using the PharmaNet database and measured up to 42 drug categories using the WHO ATC

Table 1 Number of women with breast cancer and number of matched non-cancer control women for each type of comorbidity of interest evaluated in our study

Comorbidity	Women with breast cancer			Women without cancer
	Total number	Number of women with the comorbidity of interest at baseline (up to 5 years prior to the diagnosis of breast cancer)	Number of women without the comorbidity of interest at baseline included in the time-to-event analysis	Control group (1:2 ratio) without comorbidity of interest
Ischemic heart disease	12,127	1,597 (13.2%)	10,530 (86.8%)	21,060
Heart failure	12,127	576 (4.7%)	11,551 (95.3%)	23,102
Depression	12,127	4,146 (34.2%)	7,981 (65.8%)	15,962
Cerebrovascular disease†	12,127	395 (3.3%)	11,732 (96.7%)	23,464
Diabetes	12,127	1,806 (14.9%)	10,321 (85.1%)	20,642
Osteoporosis	12,127	1,937 (16.0%)	10,190 (84.0%)	20,380
Hypothyroidism	12,127	2,052 (16.9%)	10,075 (83.1%)	20,150

†The cohort without cerebrovascular disease in the 5 years before index date was used to assess the risk of being hospitalized for stroke after the index date in the time-to-event analysis

codes and selected drug identification numbers with indications specific for selected comorbidity of interest (Supplementary Table 1). The ADGs were determined using the MSP claims and hospital databases that measured up to 32 comorbidity clusters based on disease characteristics such as severity, duration, etiology, diagnostic certainty, and specialty care involvement [24]. In both comorbidity indices, cancer was excluded in the count.

Development of new comorbidity

We evaluated the risk of developing seven comorbidities of interest after the index date, namely ischemic heart disease, heart failure, depression, stroke, diabetes, osteoporosis, and hypothyroidism identified using ICD-9 codes in the MSP claims database, ICD-9 or ICD-10 codes in the hospital records and dispensing of selected medicines in the PharmaNet database (if applicable) for selected type of comorbidities (Supplementary Table 2). These comorbidities were selected as they contribute to a high disease burden in Canada [25–27] and their development may be associated with breast cancer treatment [4, 28].

All the cases and controls were followed up to 31 December 2013 or until the date of death or the last date of record available in the MSP claims, hospital and PharmaNet databases for those who did not have complete records up to year 2013, whichever occurred first. Maximum follow-up was 9 years. Those who developed the individual comorbidity of interest were followed up to the date when the comorbidity of interest was first recorded.

Statistical analysis

Cox regression model was used to compare the development of new comorbidities over time between women with breast cancer and women with no history of cancer. Death was treated as a competing risk (i.e., subjects could die before developing comorbidity of interest) to derive sub-distribution hazard ratios and 95% confidence intervals. We used stratified Cox regression model that accounted for the matched pairs between cancer and non-cancer control groups as matching by year of birth was done at index date. The model was adjusted for baseline comorbidity scores measured using Rx-Risk-V (model 1) or ADG (model 2). In the model for each specific type of comorbidity of interest, we adjusted for other selected comorbidities present in the 5 years prior to index date (baseline) that might have been associated with higher risk of developing the individual type of comorbidity of interest (relevant diagnosis and medication codes used to identify the covariates are listed in Supplementary Table 2). We also adjusted for neighborhood income quintile as an indication of socioeconomic status. The proportional hazard assumption was assessed by including the interaction between study groups and follow-up time in the model. If it was found that hazard ratios varied with time, we computed the sub-distribution hazard ratios separately for each year since cohort entry. All analyses were performed in SAS 9.4 (SAS Institute).

Results

Baseline characteristics of breast cancer cohort

A total of 12,127 women diagnosed with breast cancer between 2005 and 2009 were included in the analysis (Table 2). The majority of women were aged 50 years and above ($n = 9{,}748$, 80%) at the time of breast cancer diagnosis. Clinical attributes of the breast cancer cases (HER-2 status, hormone receptor status) were similar to other population-based breast cancer cohort [29]; data were not available for approximately 15% of patients not referred to a BC Cancer center. The distribution of neighborhood income quintile was fairly even across the five categories. Using the Rx-Risk-V classification, about 18% of women had five or more reported morbidities; using the ADG classification, about 30% of women had six or more reported morbidities. The most prevalent comorbidity measured using the Rx-Risk-V classification was cardiovascular conditions (39.0%), followed by pain or pain-inflammation (34.8%) and gastric acid disorders (18.4%). The most prevalent category measured using the ADG classification was major signs or symptoms (71.8%), followed by stable chronic medical conditions (52.2%) and uncertain signs or symptoms (51.2%). Further details on baseline characteristics of the cases and matched controls for each of the seven individual comorbidity of interest are presented in Supplementary Table 3.

Development of selected new comorbidities

The risks of developing ischemic heart disease, heart failure, depression, diabetes, osteoporosis, and hypothyroidism were higher in women with breast cancer compared to women with no history of cancer (Table 3). There was no significant difference overall between the two groups for stroke over the observation period. Further details on the number of incident cases for each of the seven individual comorbidity are presented in Supplementary Table 4. The highest hazard ratio observed was for osteoporosis (HR model 1, 95% confidence interval: 2.10, 1.99–2.21; HR model 2: 1.99, 1.89–2.09).

The hazard ratios adjusted using ADG scores (Model 2) were consistently lower than the hazard ratios adjusted using Rx-Risk scores (Model 1). The risk of ischemic heart disease was significantly greater in breast cancer women than in the non-cancer group in the model adjusted using Rx-Risk-V scores, while the risk of ischemic heart disease

Table 2 Baseline characteristics of the overall breast cancer cohort, $n = 12,127$

Characteristics	Number (%)
Age at breast cancer diagnosis	
≤ 40 years	495 (4.1%)
41–49 years	1,884 (15.5%)
50–59 years	2,903 (23.9%)
60–69 years	2,948 (24.3%)
70–74 years	1,189 (9.8%)
≥ 75 years	2,708 (22.3%)
Neighborhood income quintile	
1 (lowest)	2,311 (19.1%)
2	2,389 (19.7%)
3	2,406 (19.8%)
4	2,353 (19.4%)
5 (highest)	2,519 (20.8%)
Unknown	149 (1.2%)
Number of baseline comorbidities measured using Rx-Risk-V score†	
None	2,643 (21.8%)
1–2	4,532 (37.4%)
3–4	2,778 (22.9%)
≥ 5	2,174 (17.9%)
Number of baseline comorbidities measured using ADG score†	
0–3	4,790 (39.5%)
4–5	3,665 (30.2%)
6–7	2,131 (17.6%)
8–9	985 (8.1%)
≥ 10	556 (4.6%)
Most common comorbidities measured using Rx-Risk-V model at baseline†	
Any cardiovascular conditions	4,731 (39.0%)
Pain or pain/inflammation	4,218 (34.8%)
Gastric acid disorders	2,226 (18.4%)
Hyperlipidemia	1,962 (16.2%)
Depression	1,962 (16.2%)
Most common categories measured using ADG model at baseline†	
Sign/symptoms: major	8,702 (71.8%)
Chronic medical: stable	6,336 (52.2%)
Sign/symptoms: uncertain	6,203 (51.2%)
Sign/symptoms: minor	3,386 (27.9%)
Time limited: minor	3,110 (25.6%)
Stage of breast cancer	
1	4,944 (40.8%)
2	3,747 (30.9%)
3	1,508 (12.4%)
4	478 (3.9%)
Missing	1,450 (12.0%)
Hormone receptor status	
Positive	8,932 (73.7%)
Negative	1,581 (13.0%)
Unknown	1,614 (13.3%)
HER-2 status	
Positive	1,620 (13.4%)
Negative	8,618 (71.1%)
Unknown	1,889 (15.6%)

†Number and type of baseline comorbidities measured over one year prior to breast cancer diagnosis, excluding cancer in the count

Table 3 Incidence rates for each of the comorbidity of interest in women with breast cancer and in matched non-cancer women, and hazard ratios

Comorbidity of interest	Incidence cases and incidence rate per 100 person-years (95% CI)			Hazard ratio, cases versus control (95% CI)			
		Breast cancer cases	Control group	Crude hazard ratio	Model 1 Rx-Risk-V scores	Model 2 ADG scores	Also adjusted for neighborhood income quintile and presence of additional selected types of baseline comorbidities listed below that might be associated with higher risk of developing the individual type of comorbidity of interest
Ischemic heart disease†	Cases	1,329	2,414	1.11 (1.05–1.18)	1.09 (1.03–1.16)	1.04 (0.99–1.11)	Diabetes, hypertension, hyperlipidaemia, heart failure, transient ischemic attack, cerebrovascular disease, renal failure, atrial fibrillation/atrial flutter (AF), Chronic obstructive pulmonary disease (COPD)
	Follow-up[a]	55,297	120,484				
	Incidence rate	2.40 (2.28–2.54)	2.00 (1.95–2.09)				
Heart failure†	Cases	919	1,526	1.24 (1.16–1.32)	1.23 (1.14–1.32)	1.19 (1.11–1.28)	Diabetes, hypertension, hyperlipidaemia, ischemic heart disease, transient ischemic attack, cerebrovascular disease, renal failure, AF, COPD
	Follow-up[a]	63,513	137,597				
	Incidence rate	1.45 (1.36–1.54)	1.11 (1.05–1.17)				
Depression†	Cases	2,068	2,694	1.68 (1.60–1.76)	1.65 (1.57–1.73)	1.52 (1.44–1.59)	Diabetes, hypertension, ischemic heart disease, heart failure, transient ischemic attack, cerebrovascular disease, renal failure, COPD
	Follow-up[a]	37,108	88,262				
	Incidence rate	5.57 (5.34–5.82)	3.05 (2.94–3.17)				
Stroke†‡	Cases	219	392	1.12 (0.98–1.28)	1.05 (0.92–1.21)	1.05 (0.91–1.21)	Diabetes, hypertension, hyperlipidaemia, ischemic heart disease, heart failure, transient ischemic attack, renal failure, AF
	Follow-up[a]	65,754	142,553				
	Incidence rate	0.33 (0.29–0.38)	0.27 (0.25–0.30)				
Diabetes	Cases	1,199	2,058	1.16 (1.10–1.23)	1.15 (1.08–1.22)	1.11 (1.04–1.18)	Hypertension, hyperlipidaemia, ischemic heart disease, heart failure, transient ischemic attack, cerebrovascular disease, renal failure, COPD
	Follow-up[a]	54,905	119,532				
	Incidence rate	2.18 (2.06–2.31)	1.72 (1.65–1.80)				
Osteoporosis	Cases	2,026	2,124	2.11 (2.01–2.22)	2.10 (1.99–2.21)	1.99 (1.89–2.09)	COPD
	Follow-up[a]	49,698	116,980				
	Incidence rate	4.08 (3.90–4.26)	1.82 (1.74–1.89)				
Hypothyroidism	Cases	769	1,294	1.19 (1.10–1.28)	1.17 (1.09–1.26)	1.12 (1.04–1.21)	No
	Follow-up[a]	54,209	118,461				
	Incidence rate	1.42 (1.32–1.52)	1.09 (1.03–1.15)				

†Overall hazard ratio (hazard ratio varied over time: refer to Fig. 1a–d)

‡Excluded people with history of cerebrovascular disease in the 5 years prior to the index date in both cancer and control group to assess the risk of being hospitalized for stroke after the index date

[a]Follow-up in person-years

became non-significant from the fourth year onwards in the model adjusted using ADG scores (Fig. 1a). For three conditions, namely ischemic heart disease, heart failure, and depression (Fig. 1a, b, c), the risks were highest in the first year and declined over time but remained statistically significant for heart failure and depression at the ninth year. The risk of being hospitalized for stroke was highest in the first 6 months and became non-significant thereafter compared to non-cancer group (Fig. 1d).

Discussion

This study provided an overview on the patterns of comorbidities in women with breast cancer prior to breast cancer diagnosis and their risks of developing selected new comorbidities compared to women with no history of cancer. The majority of women in our study were diagnosed with breast cancer at the age of 50 years and above, which is consistent with the national data that 82% of the new breast cancer cases occur in that age range [30]. The most prevalent chronic disease measured using the Rx-Risk-V index at baseline was cardiovascular conditions, followed by pain or pain-inflammation and gastric acid disorders. We found an increased risk of developing ischemic heart disease, heart failure, depression, diabetes, osteoporosis, and hypothyroidism in women with breast cancer following cancer diagnosis compared to age-matched women without cancer.

The results of our study are consistent with the findings of the Australian studies that showed that women with hormone-dependent breast cancer were more likely to develop new comorbidities than women without cancer [4, 5]. However, the Australian studies had limitations as the presence of breast cancer and comorbidities could only be ascertained by using the administrative data on dispensing of selected medicines as proxy measures of diseases in the absence of clinical data. The Australian studies only included those with a hormone-dependent subtype of breast cancer, while our study included all breast cancer patients with 74% cases being hormone-dependent. Our results are also consistent with a United Kingdom database study which showed an increase in heart failure, coronary heart disease, osteoporosis, and

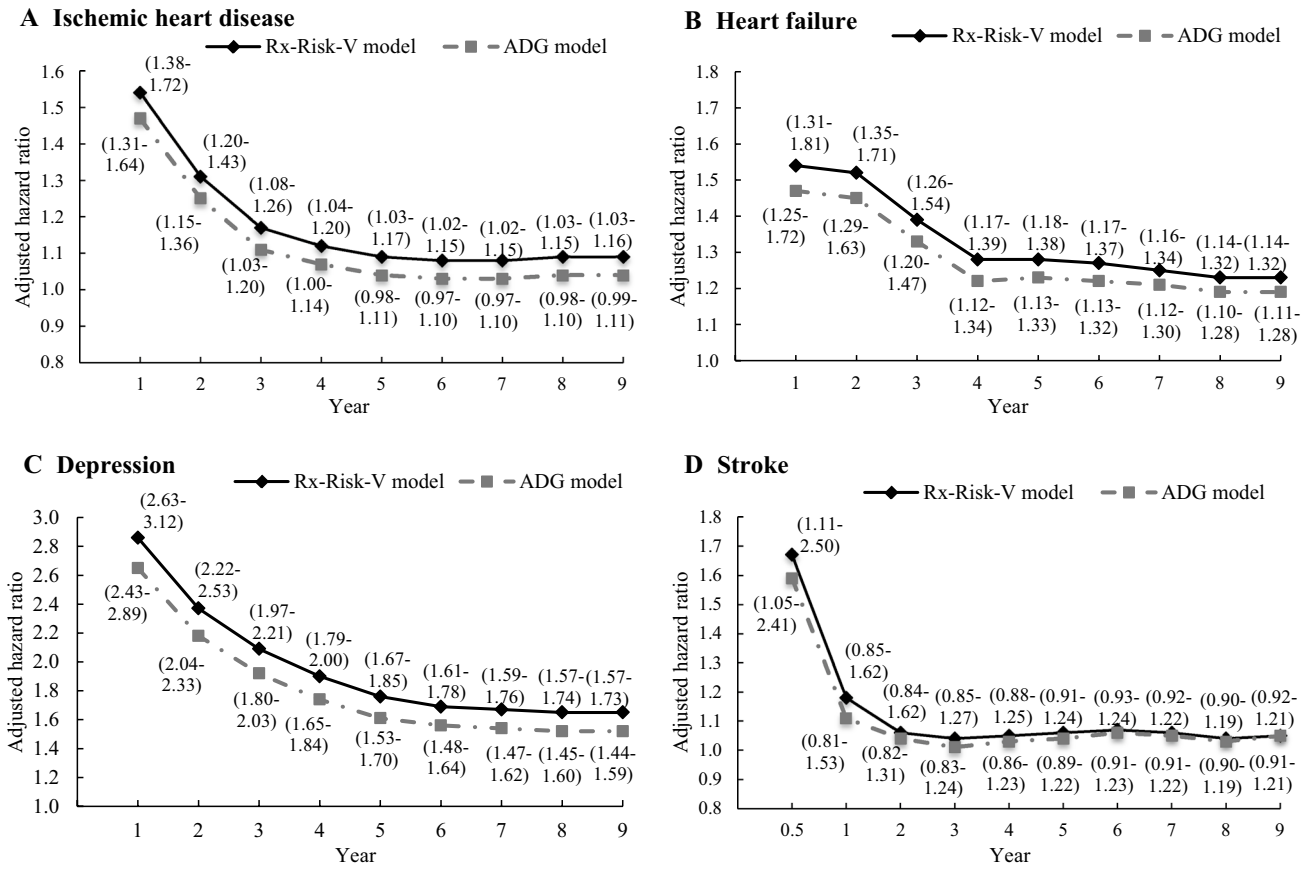

Fig. 1 Adjusted hazard ratios (with 95% confidence intervals in parentheses) for incidence of selected type of comorbidity in women with breast cancer versus women without cancer, stratified by type of comorbidity scores adjusted in the model. **a** Ischemic heart disease. **b** Heart failure. **c** Depression. **d** Stroke. Data were also adjusted for neighborhood income quintile and selected type of baseline comorbidity as listed in Table 3

hypothyroidism in women with breast cancer who have survived for at least 5 years compared to their matched counterparts without cancer [28]. In contrast, a study conducted in the United States showed that the rate of developing new comorbidities in older-diagnosed (aged 65 and above) Stage I and II breast cancer survivors 6–15 years after cancer diagnosis was similar to older women without breast cancer [31]. The ability to compare between studies was restricted by the differences in time period to capture comorbidities as our study measured the incidences of comorbidity from the date of breast cancer diagnosis, whereas both the UK and US studies measured the incidences of comorbidity in women with breast cancer who had survived for at least 5 years.

A higher risk of developing comorbidities in breast cancer survivors may be due to common risk factors shared between diseases. For example, diabetes and cardiovascular conditions including heart failure and ischemic heart disease share a number of risk factors with breast cancer such as physical inactivity, tobacco use, excessive alcohol intake, poor diet intake, and obesity [32–34]. The metabolic syndrome including elevated blood pressure, fasting glucose and waist circumference, and abnormal cholesterol level are other known risk factors for diabetes and cardiovascular diseases [35, 36]. The presence of metabolic syndrome has also been shown to be associated with an increased risk of breast cancer [35, 37].

The increased risk of developing new comorbidities may also be related to the effects of breast cancer treatment. Treatment with cancer drugs such as trastuzumab [38] and anthracyclines [39, 40] is associated with a higher risk of heart failure, while radiotherapy may increase risk of ischemic heart disease [41, 42]. Ovarian suppression as a result of chemotherapy or ovarian ablation therapy [43, 44] and treatment with aromatase inhibitors contribute to the development of osteoporosis [5, 43–45]. A Canadian study found a higher incidence of diabetes in women treated with adjuvant chemotherapy in the first 2 years of breast cancer diagnosis [46]. The use of chemotherapy results in oestrogen suppression that may promote development of diabetes, while the use of glucocorticoids as an antiemetic in patients receiving chemotherapy may cause acute hyperglycaemia [46]. The use of endocrine therapy may increase risk of diabetes [5, 47] and depression [48], although the findings are conflicting [48–50]. There are also mixed findings in the literature on the possible association between breast cancer and thyroid disorders. Several epidemiology studies demonstrated a higher risk for hypothyroidism [51–53] which may be associated with radiotherapy [52, 53], while others did not find a higher incidence of thyroid disorders in breast cancer patients [54].

It is also plausible that the increased risk of comorbidity observed in patients with breast cancer may be explained by the fact that they are being monitored more closely due to greater health care utilization [55, 56]. They may be more likely to be screened for cardiovascular risk factors and osteoporosis prior to the commencement of breast cancer treatment [57, 58]. Tests undertaken after the initial breast cancer diagnosis may identify pre-existing conditions that were previously undetected. A study published in the United Kingdom reported that morbidity incidence was greatest in the first 6 months of breast cancer diagnosis [59], while the occurrence of depression was highest during the first year of breast cancer diagnosis particularly in those on adjuvant chemotherapy [48]. A higher prevalence of depression in breast cancer patients may be associated with adverse effects of cancer treatments, hormonal changes or cancer-related disease burden such as fear of disease progression [48, 60, 61].

The slightly lower hazard ratios adjusted using ADG scores (Model 2) compared to results adjusted using Rx-Risk scores (Model 1) may be due to the differences in types of conditions captured in each comorbidity index. The ADG index included signs and symptoms and time-limited conditions that may be more prevalent in the breast cancer cohort [62, 63]. For example, cancer patients were more likely to consult general practitioners and to have more diagnostic investigations and hospital contacts prior to their cancer diagnosis compared to the population without cancer. This may partly explain our study results that women in the breast cancer cohort had a higher baseline ADG score, which is based on administrative records of these types of utilization. The ADG index has been validated in the Canadian setting to predict one-year mortality in a general ambulatory population [24]. However, the ADG index may be less transparent as the assignment of ICD codes to different categories is through a patented algorithm not based on specific diagnoses. This means that it may be difficult for researchers to fully explore the results as the individual morbidities in each of the ADG category are not explicitly described. In contrast, the Rx-Risk-V index focuses on chronic diseases that are identified through the dispensing of selected medication groupings. The Rx-Risk-V model has been validated in the Australian setting with one-year predictive mortality shown to be similar to that of Charlson Comorbidity Index [64, 65]. However, comorbidities without drug initiation are not captured using the Rx-Risk-V index. Our results showed that the variations between cancer and non-cancer groups for baseline comorbidities measured using Rx-Risk-V scores were lesser compared to those measured using ADG scores (Supplementary Table 3). In spite of these differences, the hazard ratios adjusted using either comorbidity scores indicated excess comorbidity, and yielded similar trends across the seven comorbidities evaluated in our study, suggesting that there is no gold standard approach to measure comorbidity in the cancer context and that each index may be reporting different relevant comorbidity components.

Measurement of comorbidity is useful both for health services policy and clinical practice. From a health services perspective, this information is helpful in identifying the extent and types of additional services that may be needed in the future for these patients. For the clinicians, this information provides clinical guidance on patient outcomes and care. These consequences of cancer and its treatment are being increasingly recognized, leading to the development of position statements on appropriate cancer patient follow-up to surveille and manage selected health conditions such as osteoporosis and cardiovascular diseases [32, 58]. Primary care physicians and other primary care team members have a vital role to play in the management of non-cancer comorbidities that may include both medical and lifestyle (i.e., diet and exercise) interventions [66]. There is growing evidence to support the incorporation of exercise as part of standard practice in cancer care [66, 67] as physical activity can lower the risk of osteoporosis and might be helpful in limiting the cardio-toxicity of cancer treatments. Primary care service providers such as exercise physiologists and physiotherapists can play an important role by prescribing exercise in line with clinical guidelines. Care coordination is therefore necessary to ensure cancer patients are able to access the services that they need and to facilitate communications between health professionals [66]. However, there is currently limited implementation and assessment of these strategies.

This study has some limitations. Firstly, MSP claims database only captured the first three digits of the ICD-9 codes and this results in lack of specificity. A more specific five-digit diagnosis code (ICD-9 733.01-733.09) was used to identify osteoporosis cases in the hospital records, whereas only a three-digit code (ICD-9 733) was used to identify the cases in the MSP claims database that may also capture pathologic fracture and other disorders of bone and cartilage as they share the same three-digit code [68]. This means that we may have overestimated the osteoporosis cases in both the cancer and non-cancer groups. Secondly, the mortality was higher in the cancer group compared to the non-cancer groups and this may affect their opportunity to develop the comorbidities of interest. Therefore, we accounted for death as a competing risk by modeling the sub-distribution hazard of developing a new comorbidity of interest. We also repeated the analysis by excluding women diagnosed with stage 4 breast cancer in an attempt to account for differential survival rates that may affect their chances of developing new comorbidity of interest. The hazard ratios showed similar patterns to our current results (individual results not shown). Thirdly, selection bias cannot be excluded as it is possible that people diagnosed with cancer may have greater healthcare contact compared to the non-cancer group. We restricted the selection of cancer and non-cancer groups to those with at least 5 years of active health insurance coverage before study entry to ensure both groups had similar chances in access to health services. Fourthly, we lacked information on several other risk factors for later health conditions such as body mass index and family history that may be associated with the development of selected types of comorbidity.

In conclusion, in our population-based database study, women diagnosed with breast cancer had a higher risk of developing selected new comorbidities in the first decade after diagnosis than women without a history of cancer. The findings have important implications for the development of coordinated care models to monitor for and manage multiple chronic diseases experienced by breast cancer survivors. As co-existing conditions may vary by breast cancer subtypes that were not accounted for in this study, further research into the mechanism of comorbidity development and longer-term morbidity would provide invaluable indicators for future health services and policy planning of this heterogeneous patient population.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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