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Original article

Risk of cardiovascular disease after radiotherapy in survivors of breast cancer: A case-cohort study

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ABSTRACT

Background: The current investigation examined the association between chemotherapy and/or radiotherapy and subsequent risk of cardiovascular disease (CVD) in breast cancer survivors.
Methods: A case-cohort study was conducted, based on 2165 female breast cancer survivors recruited from "Leumit" healthcare fund, who were diagnosed with primary nonmetastatic invasive breast cancer between 2002 and 2012. A 20% random subcohort was sampled at baseline, and all CVD cases were identified. Adjusted hazard ratios (HRs) with 95% confidence intervals (CI) were estimated by weighted Cox proportional hazards models.
Results: Of 2165 breast cancer survivors, 466 developed CVD over a mean follow-up of 5.7 years. The crude cumulative incidence of CVD accounting for death as a competing risk was 33.6% (95% CI, 29.6–37.6%) at 13 years of follow-up. Lifestyle components, collected post-CVD incidence, indicated a higher prevalence of poor nutrition and physical inactivity in CVD patients. In multivariable analyses, CVD was positively associated with radiotherapy without chemotherapy compared to no radiotherapy or chemotherapy (HR, 2.94; 95% CI, 1.17–7.38; $p = .022$), outpatient visits (HR per average 10-annual visits, 1.86; 95% CI, 1.50–2.31; $p < .001$), employment transition between breast cancer diagnosis and treatment: job loss versus no change (HR, 29.62; 95% CI, 12.72–68.97; $p < .001$), and inversely associated with education (HR per 1-year increment, 0.84; 95% CI, 0.75–0.94; $p = .003$).
Conclusions: Radiotherapy administered as an adjuvant treatment for breast cancer elevates the risk of CVD. Preventive strategies should be directed to surveillance for radiotherapy-related CVD dysfunction. Efforts should also address lifestyle modifications and occupational rehabilitation in patients at a high risk of CVD.

Introduction

With enhanced breast cancer (BC) detection and treatment, more women are expected to outlive their malignancy in an aging population [1]. However, some may wind up 'winning the battle but losing the war' as they may be faced with debilitative and life-threatening treatment-associated cardiovascular toxicity that might compromise the quality of their survivorship and wreak havoc on their victory on cancer.

The cumulative incidence of treatment-related cardiovascular outcomes may be as high as 33% [2] and may manifest within several years after treatment [3,4], mainly as heart failure, coronary ischemia, arrhythmias, conduction abnormalities, or stroke [2,5–7]. Given that approximately 75% of BC survivors (BCS) worldwide are treated with adjuvant therapy (ATx), radiotherapy in particular [8], and the growing recognition of cardiovascular diseases (CVD) as a burgeoning global health issue held accountable for 30% of all deaths [9], even a minor increase in risk of CVD will have substantial health and economic impact on the individual and the society alike.

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The extant knowledge on the specific contribution of modern radiotherapy and chemotherapy agents in inducing CVD is limited and inconclusive. Most research that focused on the radiotherapy-associated cardiotoxicity, compared left- versus right-sided tumors, as correlating with the probability of the inclusion of parts of the heart in the radiation field [10]. However, using breast laterality as a surrogate to cardiac exposure to radiation instead of comparing radiotherapy with no radiotherapy may underestimate cardiac risk, inasmuch as only excess risk is estimated, whereas some risk may also be present in right-sided tumors, especially when internal mammary nodes are irradiated [3,6,11–13]. Beside the direct effect, radiotherapy may in parallel exert indirect cardiotoxic insult [14] through unfavorable behavioral changes, such as physical inactivity or weight gain, that is often overlooked in the pertinent literature. Furthermore, few studies separated radiotherapy effects from effects of chemotherapy agents [5] and even fewer incorporated established and novel CVD risk factors [14] into their analyses to fully appreciate the magnitude of risk, and to our knowledge, no prior study has examined the employment experience of BCS, which may be adversely affected by treatment and may profoundly impact the health of survivors. In an attempt to overcome these shortcomings, we conducted an investigation aimed to determine CVD association with ATx (chemotherapy and/or radiotherapy) in a cohort of BCS using comprehensive data on patient socio-demographic and clinical characteristics.

Methods

Study design and subjects

This study utilized a case-cohort design to estimate the association between ATx and CVD, which is an efficient approach to longitudinal studies, in which covariate data are examined in all cases and a representative sample of the parent cohort, 'the subcohort' [15].

Source cohort

We assembled a patient-based cohort to estimate long-term health-related adverse outcomes of treatment in survivors of BC. A detailed description of the cohort is provided elsewhere [16]. Briefly, subjects were female members of Leumit Health Services (LHS, a nonprofit Israeli healthcare fund covering around 10% of the total population), BCS for at least 1 year, who were treated for early-stage or regionally advanced primary invasive BC [*International Classification of Diseases, Ninth Revision* (ICD-9) code: 174.x] between January 1, 2002 and December 31, 2012. Localized and regional stages were selected to guarantee standardized treatment procedures and to avoid differential survival rates that may influence the opportunity to develop CVD [17].

Ineligibility criteria included in situ or metastatic BC, prevalent cases, or a previous history of any type of cancer. 2644 women matched the inclusion criteria, of whom 20% were randomly sampled at baseline to comprise the subcohort.

CVD parent cohort

The source cohort was further limited to BCS with no history of CVD before or during the first year following BC diagnosis. The rationale for the 1-year conditional CVD-free survival was to assure a sufficient period for completion of chemotherapy and/or radiotherapy. 479 (18%) women had prevalent CVD and were excluded. In total, 2165 BCS were included and observed until the occurrence of CVD (index date), death, LHS disenrollment, or the predetermined censoring date (May 31, 2016), whichever came first. Time at risk began 1 year after BC diagnosis.

Subcohort and cases

Data processing was restricted to the randomly selected subcohort of 421 BCS and all those who developed CVD during the study period (n = 466). A fraction of the CVD incident cases was part of the subcohort (n = 78). Of the 809 eligible candidates for the administration of a constructed questionnaire, 177 women were not contacted due to death of participant and loss to follow-up in one. The remaining 632 women, representatives of BCS who were alive at the time of the study (n = 1730), were contacted and all completed the survey questionnaire (Fig. 1).

Data collection

LHS pharmacy claims, procedures, and diagnoses billing databases were used to obtain information on chemotherapy, radiotherapy, and CVD, respectively. Information on potential confounders was extracted from LHS and the Israel National Cancer Registry (INCR) administrative databases along with a questionnaire. These data sources have been described in detail and validated in a previous report [18].

Exposure to adjuvant therapy

Inasmuch hormone therapy has not been clearly related to CVD [14], the present study focused on radiotherapy and chemotherapy. For means of single effect isolation, ATx was classified into four mutually exclusive treatment categories: (1) radiotherapy without chemotherapy (+RT/−CTX), (2) chemotherapy without radiotherapy (−RT/+CTX), (3) radiotherapy and chemotherapy (+RT/+CTX), (4) no radiotherapy, no chemotherapy (−RT/−CTX).

Chemotherapy was administered to 58% of the 632 cases and the subcohort, within 3 months following BC diagnosis, and for a median duration of five months (interquartile range [IQR], 3–7 months). The treatment protocol was predominantly anthracycline-based (92%), of whom 22% received trastuzumab as well, while only 3% of chemotherapy users received trastuzumab without anthracyclines.

Radiotherapy was delivered to 82% of CVD cases and subcohort noncases, within 8 months postdiagnosis, and for a median duration of 6 weeks (IQR, 5–7 weeks). In at least 80% of patients exposed to +RT/+CTX, radiotherapy timing was within 1–4 months after chemotherapy completion. Computed tomography (CT)-based 3D treatment planning was utilized in more than 96% of patients receiving radiotherapy for accurate heart volume and dose calculation.

Both radiotherapy and chemotherapy were completed before the diagnosis of CVD in all cases, with more than 80% of users completing treatment at least 1 year before the index date.

Outcome measure

The primary outcome was CVD-free survival, which was defined as the time from study entry (1 year after BC diagnosis) to a first diagnosis of ischemic heart disease (IHD, ICD-9: 410–411, 413–414), congestive heart failure (CHF, ICD-9: 428), arrhythmias and conduction disorders (ICD-9: 426–427), or cerebrovascular diseases (CeVD, ICD-9: 430–438). Identification of incident cases was based on LHS electronic encounter codes, which were shown to have high accuracy using a previously validation algorithm based on imaging reports, cardiac interventions, procurement of CVD medications, and review of medical records. The positive and

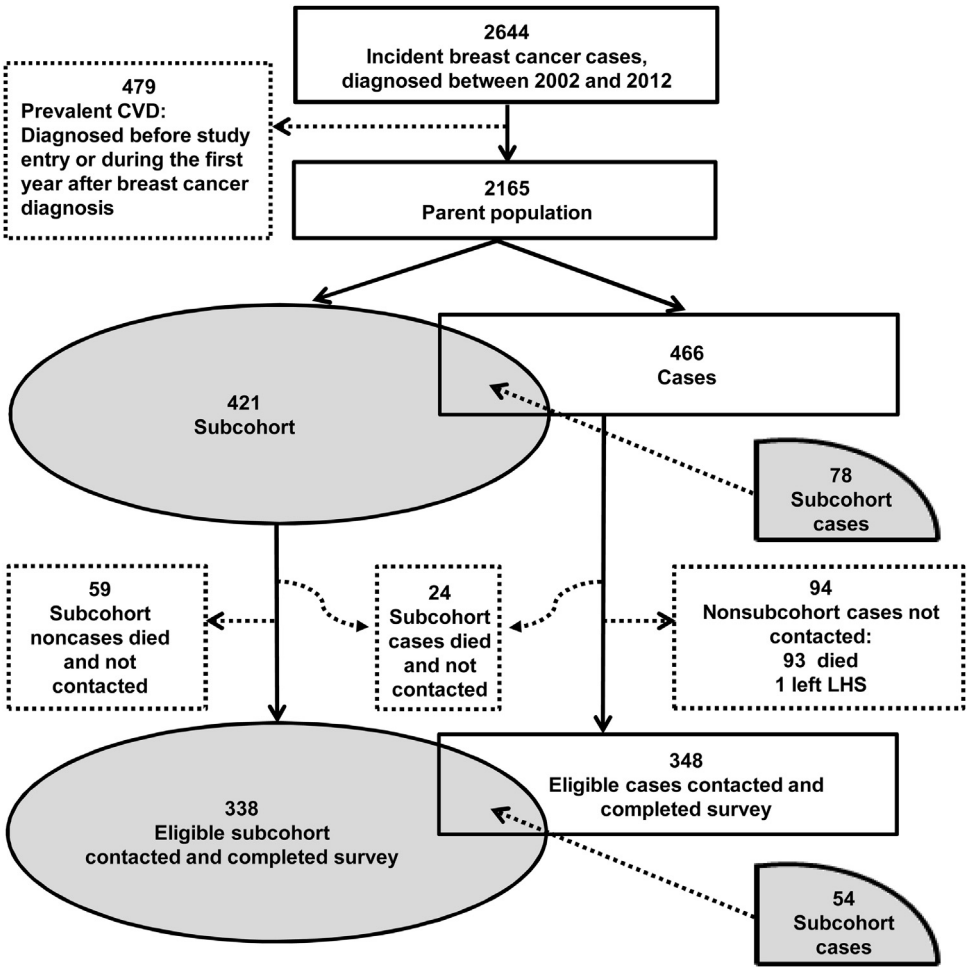

Fig. 1. Flow diagram of study participants. CVD, cardiovascular disease; LHS, Leumit Health Services.

negative predictive values were 95.8% [95% confidence interval (CI), 79.8–99.3], and 99% (95% CI, 94.3–99.8), respectively [18]. Additionally, cause-specific mortality retrieved from the National Registry of Death Causes was reviewed, and for patients who died from acute CVD events but had no prior documentation in LHS registries, the date of death was considered as the date of new CVD diagnosis.

Covariates

Information extracted from the INCR included: BC diagnosis date, age at diagnosis, clinical stage at diagnosis, breast laterality, type of surgery, axillary lymph node dissection, and immigration status. Supplementary information on the region of residence, mean household income (derived from census data based on subject's residence), comorbid conditions at the time of BC diagnosis, receipt of ATx, lymph node involvement, health services utilization, cardiac monitoring, and all-cause mortality were abstracted from LHS registries. The questionnaire, which was delivered in 2016 only to the subcohort and to BCS diagnosed with CVD, captured data on ethnicity, cohabitation status, education, BC diagnosis procedure, menopausal status at BC diagnosis, family history of CVD, work history, and lifestyles.

Statistical analysis

Cumulative incidence function was used to estimate the crude incidence of CVD outcomes among the parent CVD population in the presence of death as a competing risk [19]. The oversampling of cases typical of the case-cohort design was accounted for in the analyses by weighting according to Miettinen [20], with weights of 1 and inverse subcohort sampling probability given to cases and the subcohort, correspondingly.

To quantify the effect of ATx on CVD risk, multiple weighted Cox proportional hazards analyses were constructed with incremental adjustments to estimate the extent of CVD risk that could be explained by variations in factors. Analyses were performed by use of a SAS macro adapted from the MORGAM project [21], which computes the weighted estimates together with a robust standard error. Deviation from the proportional hazards assumption was detected by both inspecting Schoenfeld-type scaled residuals of each covariate included in the model, and testing correlation of these residuals with event time [22]. The assumption of proportionality was not violated with use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB); therefore, all analyses were stratified by this variable, unless otherwise specified. Impact measures of attributable risk fraction (ARF), and population attributable fraction (PAF) using Miettinen's formula [23] for adjusted estimates were assessed.

Multiple sensitivity analyses were performed to address potential limitations in observational administrative and reported information, including a propensity score analysis to assess the possibility of bias resulting from confounding by indication, since older patients suffering from preexisting comorbidities may be less likely to receive chemotherapy than other patients [5,10,24]. Fur-

Table 1
Patient characteristics by cardiovascular disease.

Characteristic	Total CVD cases % (SE)	Noncases % (SE)	Weighted HR (95% CI)	
			Crude model[a]	*p*
Number	348	284		
Demographics				
Mean attained age, years (SE)	65.61 (0.49)	61.41 (0.55)	NA	
Ethnicity (Arab vs non-Arab)[b]	6.90 (1.36)	7.39 (1.55)	1.61 (0.80–3.24)	.184
Cohabitation status (unmarried vs married)[c]	42.53 (2.65)	30.63 (2.74)	1.09 (0.75–1.59)	.646
District of residence				
Northern	20.98 (2.18)	19.37 (2.35)	1.41 (0.85–2.34)	.180
Central	30.17 (2.46)	32.75 (2.79)	0.95 (0.63–1.42)	.792
Jerusalem	13.22 (1.82)	15.85 (2.17)	0.81 (0.47–1.39)	.446
Southern			1.00 [reference]	
Immigration status (non-Israel born vs Israel born)	69.25 (2.48)	48.24 (2.97)	1.49 (1.04–2.15)	.031
Education level				
Below 10 years	65.80 (2.54)	33.45 (2.80)	2.30 (1.48–3.56)	<.001
11–12 years	10.06 (1.61)	17.25 (2.24)	1.13 (0.67–1.91)	.637
13+ years	24.14 (2.30)	49.30 (2.97)	1.00 [reference]	
Breast cancer characterization				
Breast cancer Dx year				
2002–2005	47.99 (2.68)	27.11 (2.64)	1.15 (0.74–1.80)	.529
2006–2009	35.34 (2.56)	40.14 (2.91)	0.83 (0.54–1.27)	.382
2010–2012	16.67 (2.00)	32.75 (2.79)	1.00 [reference]	
Mean age at breast cancer Dx, years (SE)	60.50 (0.49)	53.56 (0.55)	NA	
Age distribution at breast cancer Dx, years				
≤39	4.02 (1.05)	12.68 (1.98)	NA	
40–49	14.94 (1.91)	26.41 (2.62)		
50–59	28.74 (2.43)	31.69 (2.76)		
≥60	52.30 (2.68)	29.23 (2.70)		
Breast cancer stage (regional vs local)	36.78 (2.59)	42.25 (2.93)	0.91 (0.65–1.28)	.590
Lymph node involved	36.49 (2.58)	42.25 (2.93)	0.90 (0.64–1.27)	.541
Breast cancer laterality				
Right	46.26 (2.67)	48.24 (2.97)	1.00 [reference]	
Left	53.45 (2.68)	50.35 (2.97)	0.91 (0.65–1.28)	.593
Bilateral	0.29 (0.29)	1.41 (0.70)	0.22 (0.02–2.06)	.183
Breast cancer Dx procedure				
Clinical breast exam/mammography	75.29 (2.31)	54.93 (2.95)	1.87 (1.27–2.77)	.002
Self-detection	24.71 (2.31)	45.07 (2.95)	1.00 [reference]	
Breast cancer treatments				
Surgery	98.28 (0.70)	99.30 (0.50)	0.80 (0.17–3.87)	.781
Hormone therapy	82.18 (2.05)	81.69 (2.30)	1.24 (0.82–1.88)	.317
Adjuvant therapy				
Radiotherapy without chemotherapy	36.21 (2.58)	28.87 (2.69)	1.43 (0.83–2.46)	.199
Chemotherapy without radiotherapy	5.75 (1.25)	6.34 (1.45)	0.99 (0.45–2.16)	.977
Radiotherapy and chemotherapy	43.10 (2.66)	53.52 (2.96)	1.21 (0.71–2.07)	.477
No radiotherapy, no chemotherapy	14.94 (1.91)	11.27 (1.88)	1.00 [reference]	
Chemotherapy regimen				
Anthracycline without trastuzumab	36.21 (2.58)	42.96 (2.94)	0.93 (0.63–1.38)	.720
Trastuzumab without Anthracycline	2.01 (0.75)	1.41 (0.70)	1.80 (0.72–4.46)	.206
Anthracycline and trastuzumab	8.91 (1.53)	12.32 (1.95)	0.87 (0.50–1.51)	.628
Other	1.72 (0.70)	3.17 (1.04)	0.65 (0.23–1.84)	.413
No chemotherapy	51.15 (2.68)	40.14 (2.91)	1.00 [reference]	
Reproductive and medical history				
Parity (at least one child birth vs nulliparous)	90.52 (1.57)	92.25 (1.59)	0.90 (0.51–1.60)	.719
Menopausal status at breast cancer Dx (postmenopausal vs premenopausal)	79.89 (2.15)	58.10 (2.93)	1.13 (0.66–1.93)	.669
Family history of CVD	6.03 (1.28)	4.23 (1.19)	1.24 (0.67–2.28)	.496
Comorbidity at time of breast cancer Dx				
Hypertension	48.56 (2.68)	27.46 (2.65)	1.60 (1.07–2.42)	.024
Hyperlipidemia	39.94 (2.63)	32.04 (2.77)	1.20 (0.84–1.70)	.314
Diabetes	15.23 (1.93)	8.45 (1.65)	1.38 (0.83–2.30)	.213
Depression	6.61 (1.33)	4.93 (1.29)	2.10 (1.03–4.27)	.041
Health service utilization				
Mean outpatient visits per year, quartile (median)[d]				
1 (12.3)–lowest	12.93 (1.80)	27.46 (2.65)	1.00 [reference]	
2 (18.9)	15.80 (1.96)	27.46 (2.65)	0.98 (0.57–1.69)	.949
3 (23.7)	29.02 (2.43)	21.83 (2.45)	2.80 (1.69–4.64)	<.001
4 (35.5)–highest	42.24 (2.65)	23.24 (2.51)	4.00 (2.46–6.50)	<.001

Table1 (*Continued*)

Characteristic	Total CVD cases % (SE)	Noncases % (SE)	Weighted HR (95% CI)	
			Crude model[a]	*p*
Consumption of cardioprotective drugs[e]				
Dexrazoxane	0.29 (0.29)	2.46 (0.92)	0.21 (0.02–1.76)	.149
ACEI/ARB	51.72 (2.68)	30.99 (2.75)	1.05 (0.69–1.61)	.813
Statins	47.70 (2.68)	35.21 (2.84)	1.08 (0.76–1.55)	.670
Anti-diabetic medications	23.85 (2.29)	16.55 (2.21)	1.04 (0.68–1.60)	.849
Cardiac monitoring claims[f]				
0	25.57 (2.34)	28.52 (2.68)	1.00 [reference]	
1–3	50.29 (2.68)	45.77 (2.96)	1.38 (0.91–2.10)	.130
≥4	24.14 (2.30)	25.70 (2.60)	1.01 (0.64–1.59)	.956
Employment				
Employment before breast cancer Dx				
Full-time job	33.91 (2.54)	53.52 (2.96)	0.87 (0.56–1.35)	.522
Part-time job	10.06 (1.61)	5.63 (1.37)	1.61 (0.81–3.20)	.177
Retired	6.90 (1.36)	10.21 (1.80)	0.29 (0.17–0.52)	<.001
Looking after family or home	49.14 (2.68)	30.63 (2.74)	1.00 [reference]	
Employment transition between Dx and treatment (job loss vs no change)[g]	28.45 (2.42)	6.34 (1.45)	8.19 (4.09–16.42)	<.001
Lifestyle at time of survey (post-CVD Dx)				
Mean BMI, kg/m^2 (SE)	28.80 (0.23)	27.84 (0.23)	1.02 (0.99–1.05)	.301
Weight change since breast cancer Dx				
Weight increased	29.31 (2.44)	47.89 (2.97)	0.59 (0.38–0.92)	.020
Weight decreased	48.85 (2.68)	32.39 (2.78)	0.98 (0.62–1.54)	.928
Same weight	21.84 (2.22)	19.72 (2.36)	1.00 [reference]	
Tobacco use				
Ever	4.89 (1.16)	10.56 (1.83)	0.78 (0.39–1.55)	.477
Former	10.63 (1.65)	8.45 (1.65)	1.68 (0.95–2.97)	.074
Never	84.48 (1.94)	80.99 (2.33)	1.00 [reference]	
Alcohol intake (ever vs never)	0.29 (0.29)	0.70 (0.50)	0.40 (0.04–4.13)	.445
Physical activity	42.24 (2.65)	61.62 (2.89)	0.59 (0.42–0.83)	.003
Physical activity frequency				
≥4 per week	1.44 (0.64)	5.63 (1.37)	0.21 (0.07–0.59)	.003
3 per week	14.08 (1.87)	22.18 (2.47)	0.57 (0.36–0.91)	.018
1–2 per week	12.07 (1.75)	25.35 (2.58)	0.44 (0.28–0.71)	.001
1–2 per month	15.23 (1.93)	9.51 (1.74)	0.97 (0.55–1.69)	.903
≤1 per month	57.18 (2.65)	37.32 (2.87)	1.00 [reference]	
Healthy diet (no. of fruits and vegetable servings per day)				
0	24.71 (2.31)	2.82 (0.98)	24.31 (11.43–51.71)	<.001
1–2	67.24 (2.52)	63.73 (2.86)	3.19 (1.97–5.16)	<.001
≥3	8.05 (1.46)	33.45 (2.80)	1.00 [reference]	

CVD, cardiovascular diseases; SE; standard error; HR, hazard ratio; NIS, new Israeli shekel; Dx, diagnosis; SEER, Surveillance, Epidemiology, and End Results; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, BMI; body mass index; NA, not applicable. Weights: cases = 1; noncases = 1 sampling fraction of noncases, where sampling fraction of noncases = subcohort full cohort without cases = 284/(1730 − 348). Percentages may not sum to 100, due to rounding.

[a] Unadjusted model; sampling weight: 1730/338 = 5.118.

[b] Arab females were contrasted to non-Arab females (Jews and others).

[c] Unmarried category comprised all women not married or living with a spouse, i.e. divorced, separated, widowed, or single.

[d] Outpatient visits included all physician visits regardless of specialty; measured as average visits per year from date of breast cancer diagnosis till the end of follow-up.

[e] At least three dispensed prescriptions of drugs within an interval of 6 months during follow-up.

[f] Cardiac monitoring defined as the number of claims for myocardial scintigraphy, echocardiography, electrocardiography, computed tomography, or exercise test, from date of breast cancer diagnosis until a diagnosis of CVD or end of follow-up.

[g] Transition referred to women who made an unfavorable change in their employment status (job loss) during primary adjuvant therapy, as compared to women who resumed working, looking after family or home, or being retirees.

thermore, to address the potential introduction of survival bias, as those who died were excluded from analyses, missing values on questionnaire confounders were imputed by means of the SAS multiple imputations procedure. To contend with a possible sampling bias resulting from the inclusion of patients ≥80 years, who may manifest elevated cardiovascular risk profile regardless of treatment received, we reran analysis restricted to patients younger than 80 years [10]. Lastly, to appraise the effect of radiotherapy alone, women who received chemotherapy were excluded from analysis. Details of the statistical methods used are provided in Appendix 1.

Results

Total CVD population

Of 2644 women diagnosed with BC between 2002 and 2012, 2165 met the inclusion criteria.

A random subcohort of 421 BCS contributed 2432 person-years over a mean time of follow-up of 5.7 years. By extrapolation, 12,507 person-years were accrued in the CVD patient cohort, during which 466 BCS developed CVD (204 IHD, 42 CHF, 88 CeVD, and 132 arrhythmias and conduction disorders), yielding an incidence

density rate (IDR) of 37.3 (95% CI, 34.0–40.8) per 1000 person-years. The directly calculated IDR using summed person-years of observation for the CVD parent population (12,415 person-years) presented equivalent results (IDR, 37.5; 95% CI, 34.2–41.1 person-years), reinforcing the representativeness of the random subcohort. The crude cumulative incidence of CVD in the presence of death as a competing risk was 33.6% (95% CI, 29.6–37.6%) at 13 years of follow-up. Among the 2165 eligible BCS cohort, 435 died during follow-up; CVD was infrequently listed as the primary cause of death (6.7% of deaths).

Subcohort and CVD cases

Patient characteristics

A total of 632 subcohort and CVD cases alive at the time of the study were included in the analysis. The mean age at diagnosis was 55.0 years (SE, 0.45 years), and the mean time at CVD risk was 6.3 years (SE, 0.12 years). Overall, participants were predominantly non-Arabs (92.7%) and married (67.0%). Characteristics of CVD cases and noncases are detailed in Table 1. At baseline, CVD cases were more likely to be older, less educated, and to have a higher prevalence of preexisting CVD comorbid risk factors than subcohort noncases. During treatment, CVD cases were more likely to be treated with +RT/−CTX for their BC diagnosis and to make an unfavorable transition in their employment status. Over the course of follow-up, CVD cases generally made more frequent outpatient visits and consumed more cardioprotective drugs intended for comorbidity management but less dexrazoxane (a cardioprotective agent against chemotherapy-induced cardiotoxicity). Lifestyle components, collected post-CVD incidence, indicated a higher prevalence of poor nutrition and physical inactivity in CVD patients. Nevertheless, CVD cases were more successful in controlling their weight than noncases.

Risk of CVD in relation to treatment

For women treated with chemotherapy, there was no evidence of an increase in the incidence of any cardiovascular disease compared to −RT/−CTX (Table 2). For women given radiotherapy alone (+RT/−CTX), the incidence rate ratio of CVD was, however, increased (1.33; 95% CI, 0.96–1.84; $p = 0.084$), mainly due to increases in IHD, arrhythmias and conduction disorders, and CeVD, although the estimate did not achieve statistical significance.

In multivariable models initially adjusted for 'traditional' covariates, including BC characteristics, treatment, and comorbid risk factors, ATx was statistically insignificantly associated with risk of CVD. However, in adjusted analysis for socio-demographics and BC characteristics, +RT/-CTX was associated with a significantly greater risk of CVD than −RT/−CTX. The risk of CVD further increased following adjustment for medical history, health service utilization, and was most pronounced after controlling for employment. The results of the comprehensive model indicated that +RT/−CTX-treated BCS were almost threefold likely to experience CVD than ATx nonusers (HR, 2.94; 95% CI, 1.17–7.38; $p = .022$), rendering 24% of all CVD cases in the parent cohort attributable to +RT/−CTX (Table 3). Baseline characteristics that were independent predictors of CVD included education, BC diagnosis year, outpatient visits, and employment transition between diagnosis and therapy (Table 4).

Radiotherapy was the prominent factor associated with job loss during the acute stage of treatment, whereas the contribution of chemotherapy was only marginal. During the permanent stage of survivorship after completion of initial treatment, most radiotherapy-treated women who previously terminated their jobs did not return to work (Fig. 2).

Table 2
Crude incidence of cardiovascular diseases among breast cancer survivors alive at the time of the study, according to primary adjuvant treatment.

ATx	Ischemic heart disease			Arrhythmias and conduction disorders			Congestive heart failure			Cerebrovascular diseases			Total cardiovascular diseases		
	No. of cases	IDR	IDRR (95% CI)	*p*	No. of cases	IDR	IDRR (95% CI)	*p*	No. of cases	IDR	IDRR (95% CI)	*p*	No. of cases	IDR	IDRR (95% CI)	*p*	No. of cases	IDR	IDRR (95% CI)	*p*
+RT/−CTX	50	17.93	1.24 (0.76–2.09)	.399	38	13.63	1.39 (0.77–2.59)	.286	6	2.15	0.55 (0.17–1.79)	.310	32	11.47	1.95 (0.95–4.31)	.069	126	45.18	1.33 (0.96–1.84)	.084
−RT/+CTX	11	13.22	0.92 (0.43–1.87)	.830	8	9.62	0.98 (0.39–2.29)	.977	1	1.20	0.31 (0.01–2.07)	.276	0	0.00	0.00 (0.00–0.70)	.020	20	24.04	0.71 (0.41–1.17)	.182
+RT/+CTX	80	13.55	0.94 (0.59–1.54)	.779	38	6.43	0.65 (0.36–1.22)	.174	13	2.20	0.56 (0.22–1.60)	.255	19	3.22	0.55 (0.25–1.27)	.149	150	25.40	0.75 (0.55–1.09)	.073
−RT/−CTX	22	14.42	1.00 [reference]		15	9.83	1.00 [reference]		6	3.93	1.00 [reference]		9	5.90	1.00 [reference]		52	34.09	1.00 [reference]	

ATx, adjuvant therapy; RT, radiotherapy; CTX, chemotherapy; IDR, incidence density rate per 1000 person-years lived in the total cohort (extrapolated from the random subcohort data; sampling weight: 1730/338 = 5.118); IDRR, incidence density rate ratio; CI, confidence interval.

Table 3
Hazard ratios (95% confidence intervals) for incident cardiovascular diseases, by adjuvant therapy.

ATx	No. of CVD cases	Person-years	IDR	IDRR (95% CI)	p	Weighted hazard ratio (95% CI)												ARF (%)	CF	PAF (%)
						Model 1	p	Model 2	p	Model 3	p	Model 4	p	Model 5	p	Model 6	p			
+RT/−CTX	126	2789	45.18	1.33 (0.96–1.84)	.084	1.43 (0.83–2.46)	.199	1.52 (0.83–2.77)	.174	2.14 (1.11–4.13)	.022	2.30 (1.17–4.50)	.016	2.60 (1.19–5.72)	.017	2.94 (1.17–7.38)	.022	65.99	0.36	23.76
−RT/+CTX	20	832	24.04	0.71 (0.41–1.17)	.182	0.99 (0.45–2.16)	.977	1.18 (0.49–2.88)	.711	1.30 (0.50–3.38)	.598	1.32 (0.48–3.66)	.590	1.72 (0.53–5.58)	.370	2.77 (0.78–9.83)	.114			
+RT/+CTX	150	5906	25.4	0.75 (0.55–1.03)	.073	1.21 (0.71–2.07)	.477	1.52 (0.82–2.80)	.185	1.91 (0.93–3.94)	.080	2.07 (1.01–4.25)	.048	2.64 (1.17–5.95)	.019	2.29 (0.91–5.80)	.080			
−RT/−CTX	52	1526	34.09	1.00 [reference]		1.00 [reference]		1.00 [reference]		1.00 [reference]		1.00 [reference]		1.00 [reference]		1.00 [reference]				

ATx, adjuvant therapy; CVD, cardiovascular diseases; RT, radiotherapy; CTX, chemotherapy; IDR, incidence density rate per 1000 person-years lived in the total cohort (extrapolated from the random subcohort data; sampling weight: 1730/338 = 5.118); IDRR, incidence density rate ratio; CI, confidence interval; ARF, attributable risk fraction; CF, case fraction (number of exposed cases divided by the overall number of cases); PAF, population attributable fraction (PAF = CF × ARF).
Model 1: Unadjusted.
Model 2: Adjusted for conventional covariates: surgery, hormone therapy, laterality, stage, year of breast cancer, and medical history of hypertension, hyperlipidemia, and diabetes.
Model 3: Adjusted for socio-demographics (ethnicity, cohabitation status, residence, immigration status, education) and breast cancer characterization and treatment (breast cancer clinical stage and laterality, lymph node involvement, surgery, hormone therapy, breast cancer diagnosis procedure, year of breast cancer).
Model 4: Adjusted for socio-demographics, breast cancer characterization and treatment, reproductive and medical history (parity, menopausal status at breast cancer diagnosis, family history of cardiovascular diseases, hypertension, hyperlipidemia, diabetes, depression).
Model 5: Adjusted for socio-demographics, breast cancer characterization and treatment, reproductive and medical history, and health services utilization (outpatient visits, use of dexrazoxane, statins, and antidiabetic drugs, cardiac monitoring claims); stratified by angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs).
Model 6: Comprehensive: Adjusted for socio-demographics, breast cancer characterization and treatment, reproductive and medical history, health services utilization, employment status before diagnosis, and transition in employment; stratified by ACEIs/ARBs. Education, parity, clinical stage, outpatient visits, cardiac monitoring claims, and year of breast cancer were modeled in all analyses as continuous variables to avoid losing information.

We assessed cardiac surveillance during follow-up to explore whether different therapies were subjected to more precipitated monitoring for CVD complications [25]. Chemotherapy-treated BCS had significantly more cardiotoxicity monitoring claims than did BCS who did not receive chemotherapy (Fig. 3).

In confirmatory analyses, no appreciable differences with primary results were observed (Table 5). The propensity score findings indicated that selection bias for ATx was not a driving factor for the observed association, although older women and those with preexisting hyperlipidemia and diabetes were less likely to receive chemotherapy (data not shown).

Discussion

The aim of this study was to examine the association between chemotherapy and/or radiotherapy and subsequent risk of CVD in BCS. Our main results corroborated recent epidemiologic evidence of radiotherapy as increasing risk of CVD [26]. The finding of enhanced CVD risk as early as 1-year posttreatment reinforces and extends the results of several imaging-based studies of cardiac perfusion scans before and after radiotherapy that support the suggestion of an early onset of radiotherapy-induced CVD injury [27,28]. A previous report demonstrated increased coronary events starting within the first 5 years after exposure to radiotherapy and beyond [3], further substantiating our results.

The lack of an association between BC laterality and CVD is in line with other reports that found no excess risk between left- and right-sided tumors [29–31], and may be ascribed to the witnessed permeation of modern radiotherapy approaches in clinical practice that, unlike the outdated techniques, generally lead to lower doses to the heart [5]. Two recent studies of heart disease incidence following radiotherapy and anthracyclines have found, however, a significant increase in heart disease in left-sided compared with right-sided BC despite the use of modern radiotherapy techniques in most of the treated women [32,33]. Preexisting CVD comorbid risk factors were not accounted for in these studies, which could differ between left-sided and right-sided BC and would likely explain the observed lower proportions of anthracyclines and other chemotherapy in left-sided BC. All in all, presence or absence of excess risk cannot rule out background risk, particularly when there exists no threshold beneath which radiotherapy dose is safe [3], justifying the more appropriate use of nonirradiated patients in this investigation as the control group [12].

Several studies that compared radiotherapy with no radiotherapy and found no increased CVD morbidity [8,13] did not consider contributing factors other than age, BC characteristics and treatments, or preexisting comorbidity. Imbalances in unmeasured confounders may lead to measurement error in estimates if left uncontrolled [34]. Truthfully, only when we adjusted for underappreciated yet meaningful determinants of CVD, such as education, BC diagnosis procedure, outpatient visits, or employment, did the association show statistical significance. Greater educational attainment is believed to equip individuals with sufficient cognitive skills, personal control, and economic resources to drive them to pursue a preventive healthy lifestyle [35], and in turn, would have the impact to avert the grueling morbidity associated with treatment. Lower education has been shown to be closely related to advanced-staged BC [36], affecting thereby treatment choices. Similarly, a disease with aggressive features is more often detected by clinical breast examination than by self-detection [37]; practicing of the latter inculcates health alertness and well correlates with tertiary education [38] and younger age [39]. Women with preexisting risk factors, who are at higher risk of treatment-related adverse outcomes, may have increased screening opportunities for CVD due to more frequent physician visits.

Table 4
Comprehensive Cox hazards model for incident cardiovascular disease.

Characteristic	Weighted HR (95% CI)	
	Adjusted model[a]	*p*
Demographics		
Ethnicity (Arab vs non-Arab)	0.53 (0.16–1.78)	.306
Cohabitation status (unmarried vs married)	0.73 (0.41–1.29)	.277
District of residence		
Northern	1.52 (0.66–3.48)	.327
Central	1.56 (0.83–2.93)	.166
Jerusalem	1.44 (0.63–3.31)	.391
Southern	1.00 [reference]	
Immigration status (non-Israel born vs Israel born)	0.71 (0.35–1.44)	.336
Education (for each additional year)	0.84 (0.75–0.94)	.003
Breast cancer characterization		
Breast cancer diagnosis year (for each additional year)	0.83 (0.75–0.92)	.001
Breast cancer stage (regional vs local)	0.96 (0.50–1.85)	.898
Lymph node involved	0.77 (0.16–3.67)	.748
Breast cancer laterality		
Right	1.00 [reference]	
Left	0.90 (0.55–1.49)	.693
Bilateral	0.57 (0.05–7.02)	.661
Breast cancer Dx procedure		
Clinical breast exam/mammography	2.22 (1.10–4.50)	.027
Self-detection	1.00 [reference]	
Breast cancer treatments		
Surgery	0.50 (0.05–4.61)	.539
Hormone therapy	0.62 (0.34–1.14)	.122
Adjuvant therapy		
Radiotherapy without chemotherapy	2.94 (1.17–7.38)	.022
Chemotherapy without radiotherapy	2.77 (0.78–9.83)	.114
Radiotherapy and chemotherapy	2.29 (0.91–5.80)	.080
No radiotherapy, no chemotherapy	1.00 [reference]	
Reproductive and medical history		
Parity (for each additional child birth)	1.00 (0.89–1.13)	.946
Menopausal status at breast cancer Dx (postmenopausal vs premenopausal)	1.05 (0.44–2.52)	.912
Family history of CVD	1.02 (0.32–3.25)	.973
Comorbidity at time of breast cancer Dx		
Hypertension	1.62 (0.87–3.02)	.132
Hyperlipidemia	1.56 (0.91–2.68)	.110
Diabetes	1.31 (0.51–3.39)	.576
Depression	1.53 (0.47–5.01)	.478
Health service utilization		
Outpatient visits (for average 10-annual visits)	1.86 (1.50–2.31)	<.001
Consumption of cardioprotective drugs		
Dexrazoxane	0.52 (0.08–3.62)	.512
Statins	0.72 (0.41–1.27)	.261
Anti-diabetic medications	1.44 (0.62–3.39)	.399
Cardiac monitoring claims (for each additional claim)	0.88 (0.77–1.00)	.054
Employment		
Employment before breast cancer Dx		
Full-time job	0.51 (0.21–1.21)	.128
Part-time job	0.19 (0.06–0.66)	.009
Retired	0.37 (0.15–0.89)	.027
Looking after family or home	1.00 [reference]	
Employment transition between Dx and treatment (job loss vs no change)	29.62 (12.72–68.97)	<.001

CVD, cardiovascular diseases; HR, hazard ratio; Dx, diagnosis.
[a] Adjusted model; sampling weight: 1730/338 = 5.118; stratified by angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

To our knowledge, our study is the first to link employment transition with cancer treatment and CVD. Job cessation has been attributed to the difficulty in maintaining a full-time schedule that meets with the cancer pressing needs, or a reevaluation in women's perception of life priorities [40], but also to the development of chronic pain that disrupts occupational routines of survivors in and outside the home [16,41]. Despite its benefits in reducing tumor burden, radiotherapy has been established as a significant risk factor of chronic pain [16,42], particularly due to impaired upper body flexibility and development of painful brachial and lumbosacral plexopathies [43]. The pathophysiology of radiation-induced neuropathies is incompletely understood. A

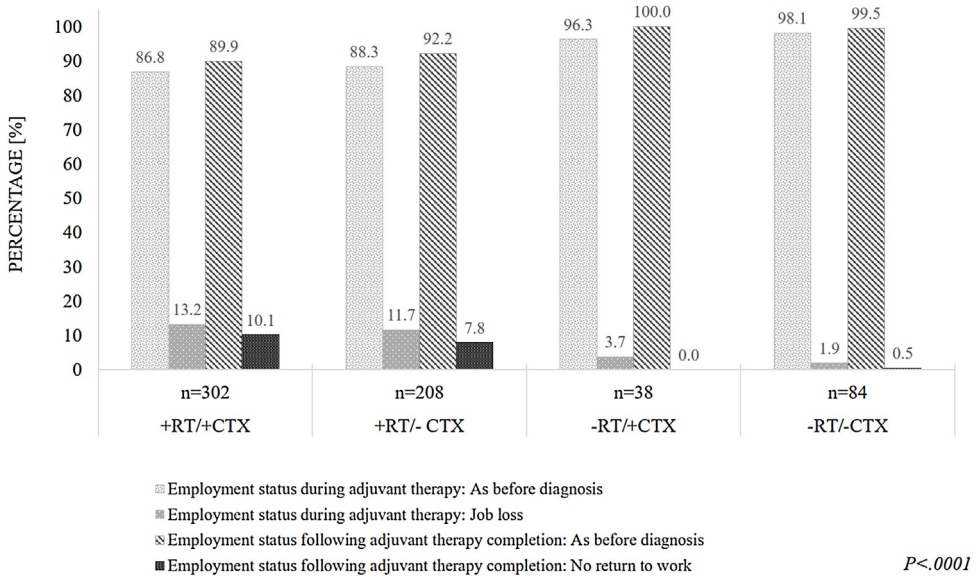

Fig. 2. Employment transition between breast cancer diagnosis and two-time points: (1) during treatment (acute stage), and (2) following treatment completion (permanent stage), by adjuvant therapy. CTX, chemotherapy; RT, radiotherapy.

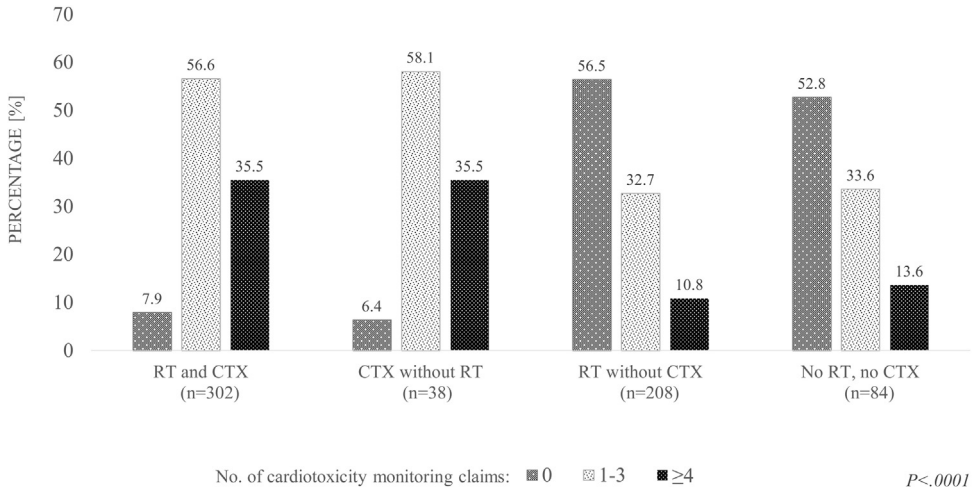

Fig. 3. Cardiotoxicity monitoring claims during follow-up, by adjuvant therapy. CTX, chemotherapy; RT, radiotherapy.

currently possible mechanism is fibrosis and associated factors such as ischemia, oxidative stress, and inflammation [44], which are cofactors in the causal pathway between radiotherapy and heart disease [7]. It is equally plausible that psychosocial stress mixed with negative emotions of anxiety and depression that come with job loss elevate the risk of CVD [45,46]. Irrespective of the mechanism involved, our results underscore the importance of augmenting the direct effect of radiotherapy on CVD with the indirect effect that goes beyond the myocardial volume in the field to include perturbations in modifiable lifestyle behavior, a phenomenon that Jones and colleagues coined 'the multiple-hit hypothesis' [14], if true effect is to be revealed.

Within the limitations of this study is the lack of a national cardiovascular registry, which hampered the estimation of cardiovascular excess incidence relative to the general population. As increasing age is a prognostic determinant of CVD among the general population, comparison to reference rates is essential to disclose associations potentially attributed to BC treatment [47]. Future national register-based research comparing breast cancer patients and non-breast cancer cohorts is, therefore, highly recommendable. We could not also stratify analyses by age because this determinant was set as the time-scale. However, using age as the time-scale achieves a more effective control of this factor than standard statistical procedures, such as adjustment or stratification, and is a more appropriate approach to handling risk analyses of the elderly population than the elapsed time from entry into the study [48]. Even though a straightforward effect of age cannot be estimated in our study, the sensitivity findings indirectly reinforce the contributory role of increasing age with the attenuation of risk estimates after restriction to patients younger than 80 years. Additionally, we could not establish a significant association with chemotherapy. The allocation to chemotherapy that was driven in part by cardiac risk, compounded with the close monitoring for early chemotherapy-induced CVD complications, could have facilitated timely preventive measures, possibly lowering CVD risk in chemotherapy-treated patients. Nonetheless, the likelihood of this selection bias to affect the validity of the radiotherapy results is abated given the unattenuated risk estimates after exclusion of women who received chemotherapy. Moreover, whilst LHS is reflective of real-world community

Table 5
Sensitivity analysis for the association between primary adjuvant treatment and incidence of cardiovascular diseases.

	Model 1[a]		Model 2[b]		Model 3[c]		Model 4[d]	
	Weighted adjusted HR (95% CI)	*p*	Weighted adjusted HR (95% CI)	*p*	Weighted adjusted HR (95% CI)	*p*	Weighted adjusted HR (95% CI)	*p*
Primary adjuvant treatment								
RT without CTX	2.36 (1.03–5.43)	.043	2.38 (1.14–4.96)	.020	2.72 (1.04–7.14)	.042	5.40 (1.83–15.90)	.002
CTX without RT	2.34 (0.70–7.86)	.168	2.43 (0.93–6.37)	.070	2.64 (0.72–9.61)	.142	–	
RT and CTX	2.09 (0.86–5.10)	.106	1.91 (0.88–4.13)	.101	2.21 (0.88–5.56)	.093	–	
No RT, no CTX	1.00 [reference]		1.00 [reference]		1.00 [reference]		1.00 [reference]	

HR, hazard ratio; CI, confidence interval; RT, radiotherapy; CTX, chemotherapy. Models 1–4 were stratified by angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.
[a] Model 1: Propensity score model; sampling weight 1730/338 = 5.118. Adjusted for propensity score that embeds pre-treatment predictive variables (age at diagnosis, parity, menopausal status at breast cancer diagnosis, breast cancer clinical stage and laterality, lymph node involvement, family history of CVD, comorbid conditions of hypertension, hyperlipidemia, diabetes, depression), ethnicity, cohabitation status, residence, immigration status, education, surgery, hormone therapy, breast cancer diagnosis procedure, year of breast cancer, outpatient visits, use of dexrazoxane, statins, and antidiabetic drugs, cardiac monitoring claims, employment status before diagnosis, and transition in employment.
[b] Model 2: Multiple imputations; sampling weight: 2165/421 = 5.143. Adjusted for all variables listed in Table 3.
[c] Model 3: Restriction to survivors aged 80 or less at breast cancer diagnosis; sampling weight 1699/332 = 5.117. Adjusted for all variables listed in Table 3.
[d] Model 4: Restriction to survivors who received RT without CTX and those who did not receive RT or CTX; sampling weight 772/140 = 5.514. Adjusted for all variables listed in Table 3.

practice wherein radiotherapy-treated patients of all ages and backgrounds are not subjected to routine cardiovascular monitoring [49], LHS is only one of four healthcare funds in Israel, limiting the generalizability of our results. However, by virtue of the National Health Insurance that allows all citizens to be registered with and move between any of these four healthcare funds at their discretion, the potential for selection bias is reduced. We were also limited by lack of adequate statistical power to detect risk for subcategories of CVD. Further research in this area with a larger sample is, therefore, warranted. However, the credibility of our primary results related to composite CVD should be unaffected as they remained robust in a wide range of sensitivity models. Notwithstanding comprehensive information was collected, uncontrolled confounders, such as lifestyle behavior, the timing of cardioprotective therapy relative to the event, or radiotherapy technical details, could potentially bias the results. While lifestyle factors were available at the time of the survey, however, to avoid potential reverse causality, they were not accounted for in risk analyses. Although we required at least three dispensed prescriptions of cardioprotective therapy within a 6-month interval during follow-up as a surrogate for extended periods of drug intake, we could not guarantee medication adherence. Therefore, the timing of cardioprotective therapy relative to the event and the subsequent impact on CVD remain unknown. Despite the widespread use of individualized 3D-CT planning in our cohort that minimizes the dose and heart volume irradiated, lack of data on radiation doses hindered assessment of a dose–response relationship. However, if anything, this bias is likely nondifferential given the lack of excess risk between left- and right-sided BC. Lastly, the self-report of employment may be subject to recall bias. Despite this potential source of bias cannot be excluded, we believe it is unlikely inasmuch cancer and its impact on BCS career trajectory are major events engraved in memories of women [50]. We also ordered the work questions chronologically, so that women could more easily establish a sequence of events, a method known to aid recall [51].

Conclusions

Taken together, evidence reviewed in this investigation suggests that radiotherapy elevates the risk of CVD. Management of CVD is clearly insufficient as evident in the unhealthy lifestyle led by CVD cases. Strategies, therefore, should be targeted to prevention of CVD in potentially vulnerable patients. Withholding radiation treatment is not justified given the long-term benefit it imparts on overall survival. Focus should be directed to surveillance for radiotherapy-related CVD dysfunction, lifestyle modification, and implementation of occupational rehabilitation programs at the policy level to minimize the risk of developing CVD and reassure that victory on cancer is long-term.

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Conflicts of interest

The authors declare that there is no conflict of interest.

Authorship

Data access: RH, HH, IM.
Study concept and design: RH, HH, LKB.
Acquisition, analysis or interpretation of data: RH, HH, IM, LKB.
Manuscript drafting: RH.
Critical revision of the manuscript: RH, HH, IM, LKB.
Statistical analysis: RH.
Supervision and approval of manuscript: RH, HH, IM, LKB.
All authors take responsibility for the integrity of the data and the accuracy of the data analysis, have read and approved the final manuscript.
This work has been done in partial fulfillment of the requirements for a PhD degree of RH (supervised by LKB) in the School of Public Health at the University of Haifa.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Appendix 1. Detailed statistical methods

Cumulative incidence function was used to estimate the crude incidence of CVD outcomes among the parent CVD population in the presence of death as a competing risk [19]. The oversampling of cases typical of the case-cohort design was accounted for in the analyses by weighting according to Miettinen [20], with weights of 1 and inverse subcohort sampling probability given to cases and the subcohort, correspondingly.

Differences in distribution of characteristics between CVD cases and subcohort noncases were summarized using the SAS survey procedures that incorporate the sample design into the analyses and compared using the weighted Cox proportional hazards analyses that incorporated the subcohort and all the cases with age set as the time scale and left truncation at study entry. To quantify the effect of ATx on CVD risk, multiple weighted Cox proportional hazards analyses were constructed with incremental adjustments to estimate the extent of CVD risk that could be explained by variations in factors. Analyses were performed by use of a SAS macro adapted from the MORGAM project [21], which computes the weighted estimates together with a robust standard error. Deviation from the proportional hazards assumption was detected by both inspecting Schoenfeld-type scaled residuals of each covariate included in the model, and testing correlation of these residuals with event time [22]. The assumption of proportionality was not violated with the exposure (constant ATx effect over time) or other covariates, except for use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB); therefore, all analyses were stratified by this variable, unless otherwise specified. Impact measures of attributable risk fraction (ARF), and population attributable fraction (PAF) using Miettinen's formula [23] for adjusted estimates were assessed.

Multiple sensitivity analyses were performed to address potential limitations in observational administrative and reported information, including a propensity score analysis to assess the possibility of bias resulting from confounding by indication, since older patients suffering from preexisting comorbidities may be less likely to receive chemotherapy than other patients [5,10,24]. The probability of receiving ATx was calculated using a multinomial logistic regression model that incorporated patients' age and clinical profile. A propensity score was then assigned to each patient according to the probability of receiving ATx. The relationship with CVD was estimated, after substituting the actual covariates in the multivariable model with the composite propensity score as a continuous covariate and compared with corresponding results using the individual covariates with standard modeling. Furthermore, to address the potential introduction of survival bias, as those who died were excluded from analyses, missing values on questionnaire confounders were imputed by means of the SAS multiple imputations procedure. The monotone pattern was used, and the sample size used for analysis was 809 subcohort and cases. The self-reported variables with missing information were: ethnicity, cohabitation status, education, menopausal status at breast cancer diagnosis, breast cancer diagnosis procedure, employment before breast cancer treatment, and employment transition. The variables included in the imputation procedure in the order specified in the variable list were: elapsed time since breast cancer diagnosis, attained age, age at breast cancer diagnosis, year of breast cancer, income, outpatient visits, immigration status, district, cohabitation status (LHS data source), ethnicity (LHS data source), comorbidity at time of breast cancer diagnosis (diabetes, hypertension, hyperlipidemia), CVD, clinical stage, estrogen receptor status, surgery, axillary lymph node dissection, radiotherapy, chemotherapy, ATx, hormone therapy, hormone agents, consumption of cardioprotective drugs (ACEI/ARB, statins, dexrazoxane, thiazide diuretics, anti-diabetic medications), cohabitation status (questionnaire data source), ethnicity (questionnaire data source), education, parity, family history of CVD, menopausal status, breast cancer diagnosis procedure, employment before breast cancer diagnosis, and employment transition. Weighted Cox proportional hazards models were applied on five imputed datasets. Results were combined by the MIANALYZE procedure, then exponentiated to yield correspondent hazard ratios (HR) and 95% CIs and contrasted to parallel model with missing data. To contend with a possible sampling bias resulting from the inclusion of patients $\geq$80 years, who may manifest elevated cardiovascular risk profile regardless of treatment received, we reran analysis restricted to patients younger than 80 years [10]. Lastly, to appraise the effect of radiotherapy alone, women who received chemotherapy were excluded from analysis.

Statistical significance was defined as a two-tailed $p < .05$. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

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