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Risk of cardiovascular adverse events from trastuzumab (Herceptin®) in elderly persons with breast cancer: a population-based study

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Abstract

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Randomized controlled trials have reported a 4–5 times increased risk of heart failure (HF) in breast cancer patients receiving trastuzumab (Herceptin®) compared to patients who do not receive trastuzumab. However, data regarding the cardiac effects of trastuzumab on elderly patients treated in general practice remain very limited. Using the US surveillance, epidemiology, and end results (SEER)-Medicare database, we conducted a retrospective cohort study on the cardiac effects of trastuzumab use in all incident breast cancer patients diagnosed from 1998 to 2007 who were 66 years and older, had no prior recent claims for cardiomyopathy (CM) or HF, and were followed through 2009. We defined our outcome as the first CM/HF event after diagnosis. We performed Cox-proportional hazard models with propensity score adjustment to estimate CM/HF risk associated with trastuzumab use. A total of 6,829 out of 68,536 breast cancer patients (median age: 75) had an incident CM/HF event. Patients who received trastuzumab tended to be younger, non-white, diagnosed more recently, and had a stage IV diagnosis. Trastuzumab use was associated with an increased risk of CM/HF (HR = 2.08, 95 % CI 1.77–2.44, $p < 0.001$). The trastuzumab-associated CM/HF risk was stronger in patients who were younger (HR = 2.52 for 66–75 years and HR = 1.44 for 76 years and older, $p < 0.001$) and diagnosed in recent years (HR = 2.58 for 2006–2007 vs. 1.86 for 1998–2005, $p = 0.01$). The twofold risk of CM/HF associated with trastuzumab remained regardless of patients' diagnosis stage, presence of hypertension, cardiovascular comorbidities, or receipt of anthracyclines, taxanes, or radiation. Trastuzumab may double CM/HF risk among elderly breast cancer patients. Our findings reinforce the need to prevent and manage cardiac risk among elderly breast cancer patients receiving trastuzumab.

Keywords

Trastuzumab; Cardiomyopathy; Heart failure; Breast cancer; Risk; Adverse event

Introduction

Treatment-related cardiotoxicity has been a significant issue in the care of breast cancer (BCa) patients, with cardiotoxic effects reported for anthracyclines [1] and for trastuzumab (Herceptin®), a humanized monoclonal antibody binding to the extracellular domain of the HER2 protein. Trastuzumab was first approved in 1998 for treatment of metastatic HER2 positive patients when clinical trials showed that trastuzumab prolonged overall survival (median: 31.2 vs. 22.7 months) in metastatic disease [2]. In 2006, trastuzumab was approved as adjuvant therapy in patients with early-stage HER2 positive disease. The Herceptin Adjuvant (HERA) trial found that adjuvant trastuzumab significantly extended 4-year disease-free survival (78.8 vs. 72.2 %, HR = 0.76, 95 % CI 0.66–0.86, $p < 0.0001$), and that heart failure (HF) events occurred in less than 1.0 % of patients [3]. Data from the NSABP B-31 trial found a higher (4.0 %) risk of HF in trastuzumab-treated patients at 7-year follow-up [4]. Additionally, a recently published population-based study found trastuzumab use to be associated with a 12.1 % 5-year risk of cardiomyopathy (CM)/HF when used alone, and a 20.1 % risk when used with an anthracycline [5].

Knowledge regarding trastuzumab-induced cardiotoxicity in elderly BCa patients is very limited. It remains unclear whether such risk occurs widely and consistently across patients

with different characteristics. Results from clinical trials are limited, as subgroups often have relatively small sample sizes. Additionally, most clinical trials exclude patients with advanced age and pre-existing heart disease, which hinders generalizability of study findings. To fill these data gaps, we conducted this large population-based study to investigate the cardiovascular risk of trastuzumab use in elderly patients diagnosed at all stages of BCa.

Patients and methods

Design and data source

We conducted a retrospective cohort study using data linked among the US surveillance, epidemiology, and end results (SEER) cancer registries and Medicare claims. Details about the SEER-Medicare linked database are described in an earlier study [6]. Briefly, the SEER registries are population-based cancer registries that collect cancer incidence data from defined geographic areas that include approximately 26 % of the US population, and Medicare is the primary health insurer for people aged 65 years or older in the United States.

Patient population

Our cohort comprised women aged 66 years and older who were newly diagnosed with BCa as their first cancer during 1998–2007 and who had no history of CM or HF in the 2 years before their BCa diagnosis. Patients meeting any of the following criteria were excluded: (1) women enrolled in health maintenance organizations (HMOs) and patients without continuous Part B medicare coverage, as their claims were insufficient for accurate classification of their treatment and outcomes (n = 135,261); (2) patients with data limitations, including those who had claims with a service date later than 90 days after death (n = 1,037) or no medicare claims following BCa diagnosis (n = 1,434); and (3) women likely to have undetected CM/HF comorbidity, defined as CM/HF diagnosis within 30 days after BCa diagnosis (and before trastuzumab or anthracyclines usage if received) (n = 430).

Outcomes assessment

Our outcome of interest, the incidence of CM/HF event after diagnosis, was defined as when a patient met any of the following criteria: (1) had CM/HF as their primary inpatient discharge diagnosis; (2) had two outpatient records of CM/HF diagnosis; or (3) had one record of CM/HF as their secondary discharge diagnosis and one record of CM/HF diagnosis in their outpatient data. Requiring more than one claim for an outpatient or secondary inpatient diagnosis balanced the sensitivity and specificity of CM/HF ascertainment. The follow-up time began with BCa diagnosis and ended with the occurrence of CM/HF event or censoring due to death or end of the study period (December 31, 2009).

We also assessed the effect of trastuzumab on the risk of non-CM/HF cardiovascular events, including acute myocardial infarction, angina, arrhythmias, hypertensive heart disease, cardiac arrest, cardiac conduction disorder, occlusion of cerebral arteries, and valvular disease. Because our study population included women with a history of non-CM/HF cardiovascular disease, we ascertained non-CM/HF cardiovascular events using the primary inpatient diagnosis on the hospital claim to insure that we captured serious non-CM/HF

cardiovascular events, instead of diagnoses reported during routine outpatient visits. Disease codes are summarized in Supplemental Table 1.

Treatment characteristics

We identified trastuzumab use by searching for code J9355 in all Medicare claims starting from cancer diagnosis to the end of follow-up. We captured the initiation dates of trastuzumab and other systematic therapy for BCa (taxanes and anthracyclines and their analogues) and of dexrazoxane, a cardioprotective agent, to adjust for potential confounding effects of other therapeutic agents. We followed recommended methods to measure surgery and radiation therapy using a union of the SEER registry data and the Medicare claims starting 30 days before the BCa diagnosis date to the end of the study period [6]. Codes for capturing treatment characteristics are summarized in Supplemental Tables 1 and 2, respectively.

Measurement of covariates

From the SEER registries, we obtained patients' cancer stage at diagnosis according to American Joint Committee on Cancer (AJCC) definitions. We also captured socioeconomic status using median household income at the census tract level. For the 8.4 % of patients who were missing stage information, we assessed this variable by performing single imputations using all variables, status of estrogen and progesterone receptors, and tumor size. We used ICD-9 codes to identify patients' comorbidities existing within 2 years before BCa diagnosis, with the exception of patients aged 66 years at diagnosis, who had only one prior year of claims. A comorbid condition was determined by at least one inpatient record or at least two outpatient records separated by 30 days to minimize the possibility of ''rule-out'' diagnoses. To measure overall health, we calculated modified Charlson comorbidity scores that incorporated both inpatient and physician records [7] to ascertain non-cardiovascular conditions.

Statistical analysis

We first calculated the number of CM/HF events per 100 person-years of follow-up (incidence rate) in our study population. We used person-years to measure the time-at-risk of developing a CM/HF event. Therefore, the estimated incidence rate reflects the absolute risk of a CM/HF event in our study population. We then assessed patient characteristics associated with trastuzumab use using single and multiple logistic regressions. Finally, we performed Cox-proportional hazard models to estimate the risk, presented as a hazard ratio (HR), of CM/HF associated with trastuzumab use. We modeled the use of trastuzumab and other therapeutic regimens as time-dependent variables and adjusted for patient characteristics to account for potential confounding effects.

We performed subgroup analyses to assess whether any patient characteristics modified the trastuzumab-related risk of CM/HF. The stratified factors we assessed included age at diagnosis (66–75 vs. 76 years and older), stage at diagnosis (IV vs. I–III), presence of hypertension, non-CM/HF cardiac history, diagnosis year (2006–2007 vs. 1998–2005), and receipt of radiation, anthracylines, and taxanes.

We also performed propensity score (PS) analysis using the standard-mortality-ratio (SMR) weight approach to assess the robustness of our conventional analysis results. [8] The PS was computed using a multiple logistic regression model with trastuzumab use as the dependent variable and patient characteristics as independent variables. We checked the performance of the PS approach in balancing out differences between the trastuzumab and non-trastuzumab groups by using the conventional criteria of 10 % or less difference on SMR-weighted proportions (for binary variables) or means (for continuous variables). [9] We also trimmed patients who had a PS outside the range of their contrast group (n = 1,966) in outcome models.

Results

Population characteristics and trastuzumab use

Our cohort included 68,536 incident BCa patients (median age: 75 years). Most patients were white (89 %), had stage I–III disease (86 %), and had at least one major cardiovascular comorbidity (50 %) (Table 1). A total of 2,138 patients (3 %) received trastuzumab and their median duration of use was 350 days. The median ages of patients in the trastuzumab and non-trastuzumab groups were aged 72 and 75 years, respectively. The median follow-up was 3.1 and 4.5 years for the trastuzumab and non-trastuzumab groups, respectively. Compared to the non-trastuzumab group, women receiving trastuzumab tended to be younger, non-White, diagnosed with stage IV disease, and with fewer comorbidities (adjusted odds ratios in Table 2). The differences in all patient characteristics between the trastuzumab and non-trastuzumab groups were balanced after we adjusted for PS weights (data not shown).

Risk of CM/HF and non-CM/HF cardiovascular events

A total of 6,829 incident CM/HF events occurred during a follow-up of 331,439 person-years in our cohort, which translated to an incidence rate of 2.1 per 100 person-years. The incidence rate of developing CM/HF among patients receiving and not receiving trastuzumab was 3.8 and 2.0 events per 100 person-years of follow-up, respectively. We found trastuzumab use to be an independent risk factor for developing CM/HF events after adjusting for patients' age, comorbidities, and receipt of other cancer-related treatments (Table 3). Other significant risk factors for CM/HF events included older age, presence of hypertension and cardiac history, more cardiovascular comorbidity, and a stage IV diagnosis. We did not detect an association between trastuzumab use and risk of other non-CM/HF cardiovascular events (Table 3).

We did not find trastuzumab-related CM/HF risk to differ substantially according to patients' stage at diagnosis, diagnosis year, presence of hypertension history or non-CM/HF CVD comorbidities, and receipt of anthracyclines, taxanes, or radiation therapy in our subgroup analyses (Table 4). Trastuzumab-related CM/HF risk was larger among patients diagnosed at age 66–75 years than those diagnosed at age 76 and older (HR = 2.52 vs. 1.44).

We obtained similar results in our sensitivity analysis using PS SMR-weight analysis. These results are reported in Supplemental Tables 3 and 4.

Discussion

In this population-based cohort study of 68,536 BCa patients aged 66 years and older, we confirmed that trastuzumab use is associated with doubled risk of CM/HF events. Our findings are consistent with clinical trials reporting that trastuzumab caused CM/HF in BCa patients and that trastuzumab-related CM/HF risk occurred in both early- and late-stage patients. A meta-analysis of 10 randomized controlled trials (RCTs) with a total of 11,882 patients reported an increased relative risk of HF associated with trastuzumab use; the elevated risk was similar in patients with early stage (RR = 4.05, 95 % CI 2.49–6.58) and metastatic (RR = 4.75, 95 % CI 1.93–11.71) disease [10]. We found a lower trastuzumab-related relative risk of CM/HF than the RCTs; this may be partly due to differences in patient populations. Our population (median age = 75 years) is much older than typical RCT populations (median age <57 years) [10, 11], which would result in more competing events, such as death. Additionally, we included patients with pre-existing non-CM/HF cardiac conditions while most trials excluded these patients [10], which resulted in a higher absolute but lower relative risk of CM/HF in our study population than in RCTs.

Although it is not completely understood how trastuzumab induces cardiotoxicity [12, 13], interference with the HER2 signaling pathway has been suspected to play a central role [13]. Cardiomyocyte-specific disruption of the HER2 signaling pathway in mice leads to dilated cardiomyopathy and increased susceptibility to stressors such as ischemia, pressure overload, or cardiotoxic medications like anthracycline [14, 15]. Use of trastuzumab may block HER2 receptors, [16] thereby inhibiting the growth, repair, and survival of cardiomyocytes after damage by cardiotoxic chemotherapy agents. [12, 13, 16] However, early clinical results with lapatinib, another HER2 inhibitor, found minimal cardiotoxicity [17] suggesting that the disruption of the HER2 signaling pathway may not fully explain trastuzumab-induced cardiotoxicity. Another possible explanation is that trastuzumab, an immunoglobulin G1 (IgG1), may stimulate antibody-dependent cell-mediated cardiotoxicity [18]. However, pertuzumab, another IgG1 agent, showed only minimal cardiac dysfunction, highlighting the complexity of the biological mechanisms of trastuzumab-induced cardiotoxicity.

In a sub-group analysis, we found trastuzumab-related CM/HF risk to be higher in patients aged 66–75 years than in those older than 75 years. The difference could be partly due to a lower baseline incidence rate of CM/HF for non-trastuzumab patients aged 66–75 years than in those older than 75 years (1.51 vs. 2.76 per 100 person year, Table 4). The reduced trastuzumab-related CM/HF risk in patients aged 76 years and older also may be explained by physicians' selection of healthier patients among the oldest for trastuzumab use as demonstrated in Table 2 where trastuzumab use decreased with age, after adjusting for all other patients' factors. Additionally, we found a larger association between trastuzumab use and CM/HF event for patients diagnosed during 2006–2007 than those diagnosed during 1998–2005 (HR = 2.58 vs. 1.86; Table 4), which may be explained by the approval of trastuzumab in 2006 for treatment of early stage disease. The inclusion of early stage patients after 2006 resulted in healthier trastuzumab-indicated patients than in previous years when trastuzumab was only approved for metastatic patients.

Unlike previous studies, we did not find trastuzumab-related risk of CM/HF to differ in those receiving versus not receiving anthracyclines ($p = 0.89$; Table 4) [5, 10]. Chen's meta-analysis found that trastuzumab significantly raised the risk of HF in patients receiving anthracycline-containing chemotherapy (RR = 4.27, 95 % CI 2.75–6.61) but not in patients with other regimens (RR = 2.42, 95 % CI 0.36–16.19). [10] Bowles' retrospective study of 12,500 women aged 22–99 years also reported a higher risk of CM/HF in patients receiving trastuzumab plus anthracycline (HR = 7.19, 95 % CI 5.00–10.35) compared to patients receiving trastuzumab alone (HR = 4.12, 95 % CI 2.30–7.42) [5]. This discrepancy in results could partly be due to more careful selection of elderly BCa patients less susceptible to cardiac events (e.g., with fewer early clinical signs or risk factors) for anthracycline use in our study because of increasing awareness of anthracycline-induced cardiotoxicity in general oncologic practice [19]. Further support for this contention is our observation of a slightly elevated CM/HF risk with anthracycline use (Table 3). Another possible explanation for our lower risk of CM/HF is that the standard practice of cardiac monitoring and imaging in patients receiving HER2-targeted therapy detects patients who present with asymptomatic decreases in left ventricular ejection function (LVEF) following pretreatment with anthracycline. Early recognition and treatment of an asymptomatic LVEF decline prevents later CM/HF events in these patients. A study reported that 41 % of trastuzumab-induced CM/HF events occur in the first 3 months of therapy, particularly among older patients pretreated with doxorubicin (an anthracycline) [16].

Our study fills several research gaps. First, very little data are available regarding cardiac risk due to trastuzumab use in older patients, a group that comprises a sizable percent of all BCa patients. Second, existing trials are limited by sample sizes in detecting less common serious adverse events in patient subgroups. Our subgroup analysis has provided new information regarding the safety of trastuzumab use among various sub-groups of BCa patients. Third, because the SEER-Medicare linked database captures a broad national population, our findings are more generalizable to patients in general clinical practice than are RCT results. Highlights of our research methods include the data analyses, which were conducted using time-dependent adjustment of cancer-directed treatment to more accurately calculate exposure time from each treatment, and the PS approach to assess the robustness of our findings compared to alternative analytical methods.

Some limitations should be noted. First, we were unable to restrict the study population to only HER2 positive patients due to lack of HER2 status reported by cancer registries. Second, ascertainment of HF using ICD-9 codes in claims data has high specificity (>96 %) but only moderate sensitivity (76 %) [20], potentially resulting in under-diagnosis of patients with CM/HF disease. The misclassification partly results from the complexity of HF diagnosis that often appears as a CM diagnosis. We incorporated CM with HF to minimize potential reporting errors. Third, our study is observational and cannot eliminate residual confounding due to unmeasured risk factors of CM/HF, such as smoking history or physical activity level. Finally, restricting our study population to patients without prior history of other cancers may limit the generalizability of our findings. However, this exclusion enhanced the internal validity of our risk estimates of trastuzumab use by reducing survival bias from patients who tolerated chemotherapy used to treat prior cancers.

Conclusion

In this large population-based cohort study of elderly BCa patients, we found that trastuzumab is associated with a nearly doubled risk of incident CM/HF events. The elevated risk is consistent across different subgroups defined by stage at diagnosis, comorbidities, and use of other cancer treatments. Our findings re-affirm the need to consider cardiac complications when initiating trastuzumab use in elderly BCa patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Distribution of population characteristics among breast cancer patients aged 66 years and older diagnosed from 1998–2007 (n = 68,536)

Population characteristics	Number	Percentage
Age at diagnosis	8	7
66–70	18,601	27
71–75	17,694	26
76–80	15,832	23
81+	16,409	24
Race		
White	61,004	89
Black	4,006	6
Other	3,526	5
Initial stage at diagnosis		
I–III	59,015	86
IV	3,714	6
Missing	5,807	8
Comorbidity index[a]		
None	45,432	66
1	16,117	24
2+	6,987	10
Diagnosis year		
1998–2005	53,392	78
2006–2007	15,144	22
History of medical conditions		
Cardiovascular conditions[b]	33,997	50
Diabetes	19,700	29
Hyperlipidemia	48,738	71
Hypertension	52,441	77

[a] Charlson's index with exclusion of cardiovascular conditions

[b] Cardiovascular conditions included acute myocardial infarction, angina, arrhythmia, cerebral artery occlusion, cardiac conduction disorder, cardiac arrest, transient cerebral ischemia, and valvular disease

Table 2

Patient characteristics associated with trastuzumab use among breast cancer patients aged 66 years and older diagnosed from 1998 to 2007 (n = 68,536)

Patient characteristics	Trastuzumab	No trastuzumab	Unadjusted	Adjusted
Age at diagnosis	% (n = 2,138)	% (n = 66,398)	Odds ratio	Odds ratio
66–70	40	27	1.00	1.00
71–75	30	26	0.78 (0.69–0.85)**	0.79 (0.71–0.88)**
76–80	18	23	0.53 (0.47–0.60)**	0.55 (0.48–0.62)**
81+	12	24	0.32 (0.28–0.37)**	0.31 (0.27–0.36)**
Race				
White	85	89	1.00	1.00
Black	8	6	1.35 (1.14–1.59)**	1.18 (1.00–1.40)
Other	7	5	1.47 (1.24–1.74)**	1.43 (1.20–1.69)**
Initial stage at diagnosis				
I–III	83	94	1.00	1.00
IV	17	6	3.27 (2.91–3.68)**	3.58 (3.17–4.05)**
Comorbidity index[a]				
None	70	66	1.00	1.00
1	21	24	0.85 (0.76–0.94)*	0.89 (0.79–1.00)
2+	9	10	0.79 (0.67–0.92)*	0.81 (0.68–0.97)*
Diagnosis year				
1998–2005	60	78	1.00	1.00
2006–2007	40	22	2.38 (2.18–2.60)**	2.40 (2.19–2.62)**
History of medical conditions (with versus without each individual condition)				
Cardiovascular conditions[b]	44	50	0.77 (0.71–0.85)**	0.92 (0.84–1.01)
Diabetes	27	29	0.91 (0.83–1.01)	0.95 (0.85–1.07)
Hyperlipidemia	71	71	0.99 (0.90–1.09)	1.05 (0.94–1.16)
Hypertension*	74	77	0.88 (0.80–0.97)*	1.04 (0.93–1.16)

[a] Charlson's Index with exclusion of cardiovascular conditions

[b] Cardiovascular conditions included acute myocardial infarction, angina, arrhythmia, cerebral artery occlusion, cardiac conduction disorder, cardiac arrest, transient cerebral ischemia, and valvular disease

*, ** indicate a p value smaller than 0.05 and 0.001, respectively

Table 3

Risk of cardiomyopathy (CM) or heart failure (HF) event and other non-CM/HF cardiovascular events with trastuzumab use among breast cancer patients aged 66 years and older diagnosed from 1998 to 2007 without history of CM and HF (n = 68,536)

	CM/HF	Non-CM/HF CVD
Treatment factors (Received vs. not)	HR (95 % CI)[a]	HR (95 % CI)[a]
Trastuzumab	2.08 (1.77–2.44)**	1.05 (0.87–1.27)
Anthracyclines	1.16 (1.06–1.27)*	1.09 (1.00–1.20)*
Dexrazoxane	1.44 (0.77–2.68)	1.46 (0.78–2.72)
Taxanes	1.05 (0.94–1.18)	1.10 (0.98–1.22)
Breast-conserving surgery	0.91 (0.86–0.97)*	0.93 (0.88–0.98)*
Radiation	0.85 (0.80–0.90)**	0.86 (0.82–0.91)**
Other covariates		
Age at diagnosis (>75 vs. 66–75 years)	1.57 (1.50–1.66)**	1.68 (1.60–1.76)**
Race (non-white vs. white)	1.05 (0.98–1.14)	0.94 (0.87–1.02)
Household income (below vs. above median)	1.14 (1.09–1.20)**	1.02 (0.98–1.07)
History of hypertension	1.47 (1.38–1.58)**	1.43 (1.34–1.52)**
CVD history (presence vs. absence)	1.33 (1.26–1.39)**	1.51 (1.44–1.58)**
Diagnosis year (2006–2007 vs. 1998–2005)	0.51 (0.46–0.55)**	1.08 (1.00–1.16)*
Charlson index excl. CVD (1+ vs. 0)	1.62 (1.54–1.70)**	1.42 (1.35–1.48)**
Stage (IV vs. I–III)	1.23 (1.07–1.40)*	1.57 (1.34–1.52)**

[a] We modeled effects of trastuzumab, anthracycline, taxanes, and dexrazoxane as time-dependent covariates

*,** indicate p-value smaller than 0.05 and 0.001, respectively

Table 4

Stratified risk of cardiomyopathy (CM) and heart failure (HF) event with trastuzumab use among breast cancer patients aged 66 years and older, diagnosed during 1998–2007, and without history of CM and HF (n = 68,536)

Patient subgroups	Event number	Event rate (per 100 person-year)	HR (95 % CI)[a]	p value
Age at diagnosis				<0.001
Below median (66–75 years)				
T users	137	3.85	2.52 (2.08–3.05)**	
T non-users	2,860	1.51	1.00	
Above median (>75 years)				
T users	49	3.59	1.44 (1.07–1.96)*	
T non-users	3,783	2.76	1.00	
Anthracyclines				0.89
Anthracycline users				
T users	93	3.76	2.06 (1.65–2.58)**	
T non-users	927	2.03	1.00	
Anthracycline non-users				
T users	93	3.79	2.11 (1.66–2.68)**	
T non-users	5,716	2.09	1.00	
Hypertension history				0.15
Hypertension history				
T users	146	4.06	2.07 (1.73–2.49)**	
T non-users	5,604	2.33	1.00	
No hypertension history				
T users	40	2.69	2.11 (1.49–2.98)**	
T non-users	1,039	1.22	1.00	
Baseline CVD history				0.15
CVD history				
T users	90	4.39	2.09 (1.66–2.63)**	
T non-users	3,928	2.58	1.00	
No CVD history				
T users	96	3.34	1.07 (1.66–2.60)**	
T non-users	2,715	1.56	1.00	
Taxanes				0.16
Taxane users				
T users	151	3.98	2.17 (1.80–2.63)**	
T non-users	642	2.04	1.00	
Taxane non-users				
T users	35	3.10	1.71 (1.22–2.38)*	
T non-users	6,001	2.03	1.00	

Patient subgroups	Event number	Event rate (per 100 person-year)	HR (95 % CI)[a]	*p* value
Radiation receipt				0.20
Radiation				
T users	131	3.75	2.15 (1.78–2.60)**	
T non-users	3,591	1.76	1.00	
No radiation				
T users	55	3.84	2.04 (1.52–2.75)**	
T non-users	3,052	2.48	1.00	
Charlson score				0.80
Score of 0				
T users	108	3.02	1.98 (1.60–2.44)**	
T non-users	3,709	1.61	1.00	
Score of 1+				
T users	78	5.77	2.22 (1.73, 2.85)**	
T non-users	2,934	3.05	1.00	
Stage				0.97
I–III				
T users	154	3.61	2.10 (1.77–2.50)**	
T non-users	6,437	2.02	1.00	
IV				
T users	32	4.82	1.82 (1.20–2.77)*	
T non-users	206	2.76	1.00	
Diagnosis year				0.01
2006–2007				
T users	64	3.56	2.58 (1.91–3.50)**	
T non-users	513	1.33	1.00	
1998–2005				
T users	122	3.90	1.86 (1.53–2.26)**	
T non-users	6,130	2.13	1.00	

[a] Cox-proportional hazard models estimating *HR* hazard ratio, adjusted for the effects of radiation, surgery as part of initial treatment, age at breast cancer diagnosis, history of hypertension, other cardiovascular comorbidity and stage at diagnosis. We also adjusted for use of anthracycline, taxanes, and dexrazoxane (cardioprotective agent) as time-dependent covariates

*,** indicate a hazard ratio estimate had a *p* value smaller than 0.05 and 0.001, respectively