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Risk of hospitalization and death due to bone fractures after breast cancer: a registry-based cohort study

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Title: **Risk of hospitalization and death due to bone fractures after breast cancer: a registry-based cohort study**

Short title: Risk of bone fractures in breast cancer patients

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Abstract

Background: Bone fractures may have an impact on prognosis of breast cancer. The long-term risk of bone fracture in breast cancer patients have not been thoroughly studied.

Methods: Poisson regression was used to investigate the incidence of hospitalization due to bone fracture comparing women with and without breast cancer based on Swedish National registers. Cox regression was used to investigate the risk of being hospitalized with bone fracture, and subsequent risk of death, in a regional cohort of breast cancer patients.

Results: For breast cancer patients, the five-year risk of bone fracture hospitalization was 4.8% and the 30-day risk of death following a bone fracture hospitalisation was 2.0%. Compared with general population, breast cancer patients had incidence rate ratios of 1.25 (95% CI: 1.23, 1.28) and 1.18 (95% CI: 1.14, 1.22) for hospitalization due to any bone fracture and hip fracture respectively. These ratios remained significantly increased for ten years. Comorbidities (Charlson comorbity index≥1) were associated with the risk of being hospitalized with bone fracture. Women taking aromatase inhibitors were at increased risk as compared with women taking tamoxifen (HR=1.48; 95% CI: 0.98-2.22). Breast cancer patients hospitalized for a bone fracture showed a higher risk of death (HR=1.83; 95% CI: 1.50, 2.22), compared to those without bone fracture.

Conclusions: Women with a previous breast cancer diagnosis are at increased risk of hospitalization due to a bone fracture, particularly if they have other comorbidities.

Key words: breast cancer, bone fracture, hospitalization, comorbidity, survival, death

Introduction

The improved survival over the last few decades has increased awareness about other health outcomes in women diagnosed with breast cancer. Bone fractures, in particular hip fractures, have a potential impact on morbidity, quality of life and prognosis of breast cancer patients. To study risk of bone fracture after a breast cancer diagnosis is of particular clinical relevance given that osteoporosis is common in postmenopausal women (Bliuc 2009).

Breast cancer treatment influences risk of bone fracture through different mechanisms. Adjuvant treatment in particular may affect calcium and bone metabolism possibly leading to an increased risk (Becker 2012). Hormonal therapy with aromatase inhibitors has in fact been found to be associated with risk of bone fracture in contrast to tamoxifen that has shown a protective effect (Breast Cancer Trials Committee 1987, Fisher 1989, Rutqvist 2007, Cooke 2008, Amir 2011, Edwards 2011). Other types of oncologic adjuvant treatment may also have potential negative effects on the skeleton independent of sex hormones (Pfeilschifter 2000, Arnold 2013). Additionally, increasing evidence is suggesting that bone marrow microenvironment is involved in the metastatic process (Semesiuk 2013, Benoy 2006). Finally, it was shown that bone-targeted drugs, like bisphosphonates, may reduce skeletal metastasis and improve survival (Coleman 2014, Wong 2012). For all these reasons, bisphosphonates are currently administered to some patients in parallel to the adjuvant treatment in order to reduce the risk of bone metastasis and to strengthen the bone tissue (Rizzoli 2012, Van Poznak 2011).

An increased risk of bone fractures in women diagnosed with breast cancer has been shown but the duration and the magnitude of this risk have not been clarified (Peppone 2014). It is also not clear whether there is an increased risk of fractures among women with breast cancer independent of treatment and whether tumor characteristics and comorbidities influence the

risk. It is also of outmost clinical importance to assess the risk of dying after being hospitalized with bone fracture in women with a previous breast cancer diagnosis.

The aim of this study is to investigate, in women with a breast cancer diagnosis, the risk of being hospitalized with a bone fracture and possible effects of patient and tumor characteristics at breast cancer diagnosis as well as treatment. In addition, we study the risk of dying following a hospitalization due to a bone fracture.

Materials and Methods

Study cohorts

Two different cohorts of Swedish women were used to address the research questions.

The first, national cohort, comprised data extracted from a national database. Individuals from the Swedish Total Population Register were linked by personal identification numbers to the National Cancer Register (Mattsson 1984, Barlow 2009), the National Cause of Death Register (Rutqvist 1985), and the Inpatient Register (Ludvigsson 2011). The National Cancer Register reports all records for each cancer diagnosis made in Sweden coded through the 7th version of International Classification of Diseases (ICD-7) since 1958. The National Cause of Death Register collects all causes of death in Sweden that are mandatorily reported since 1952. The Inpatient Register reports hospitalizations in all Sweden since 1987, coded through the 9th and 10th versions of International Classification of Diseases (ICD-9 and ICD-10), and has nationwide coverage. This national cohort was restricted to women aged 45 years and over for the calendar period 1990-2010.

The second, regional cohort, included data extracted from the Stockholm Breast Cancer Register, a population-based register comprising all women diagnosed with invasive breast

cancer in the Swedish counties of Stockholm and Gotland from 1976, linked to other national registers as described for the first cohort. The register has about 99% completeness for women aged less than 75 years at diagnosis and provides good information about tumor characteristics at breast cancer diagnosis and treatment (Mattsson 1985). From this register we extracted all women with a first invasive breast cancer diagnosis in the period 1990-2006 and less than 75 years at diagnosis. Of the n=14,188 remaining observations we further excluded women with stage IV disease (n=264), with tumors smaller than 1 mm (n=52), who received neoadjuvant treatment (n=802), and who did not receive any breast cancer surgery (n=220). A total of n=12,850 women were left for the analysis. We also retrieved information on comorbid conditions prior to diagnosis through the Inpatient Register and summarized this into the Charlson Comorbidity Index (CCI) score, a widely used methodology for grouping comorbid conditions (Quan 2005, Charlson 1987).

In an additional linkage based on the same registries as the regional cohort, women diagnosed with breast cancer between 2005 and 2008, were further linked to the Swedish Prescribed Drug Register in order to investigate the potential effect of type of adjuvant hormone treatment on future fractures. The Swedish Prescribed Drug Register contains information on all prescribed medicines dispensed by Swedish pharmacies since July 1, 2005, including dates of prescription and dispense, number of defined daily doses, and classification of drugs according to the Anatomical Therapeutic Chemical (ATC) Classification System. This register is reported to be nationwide complete, with <0.3% of data entries with missing Personal Identification Numbers (Wettermark 2007). Through this linkage, we identified 2551 patients diagnosed with breast cancer between 2005 and 2008 who initiated adjuvant hormone therapy with at least one prescription of tamoxifen (ATC codes L02BA01) or aromatase inhibitors (ATC codes L02BG) and were followed until end of 2012.

ICD codes and Events

Breast cancer diagnoses were based on ICD-7 code 170. The hospitalization events were defined as: hospitalization after breast cancer diagnosis due to bone fracture, excluding fractures of the skull and of the neck (ICD-9 codes 805-829, 733.0, 733.93-98 and ICD-10 codes S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12, T14.2, M80); and hospitalization after breast cancer diagnosis due to hip fracture (ICD-9 codes 820, and ICD-10 codes S72.0, S72.1, S72.2). All hospitalization events were defined based on the main diagnosis of hospitalization. The death events were categorized using the underlying cause of death.

Ethics

The study was entirely based on data from Swedish health and population registers and was approved by the Ethical Review Board at Karolinska Institutet, Stockholm, Sweden (Dnr 2011/1898 32; Dnr 2007/821-31/3; Dnr 2012/217-32/2; Dnr 2014/1401-32). No contact was made with the study participants, data were analyzed anonymously and thus informed consent was not obtained. This exception from informed consent was confirmed by the ethical committee.

Statistical analysis

In the national cohort, we first compared the incidence of first recorded bone fracture-related hospitalizations in women with breast cancer with that in the general female population resident in Sweden between 1990 and 2010. For women with breast cancer not previously hospitalized for fracture, the person-time was split by attained age, attained calendar period and time since cancer diagnosis. For women without breast cancer not previously hospitalized for fracture, the person-time was split by attained age and attained calendar period. The follow-up time was calculated as the date of first recorded fracture (for an event), death, emigration or 31 December 2010, whichever came first. The cohort was analysed

using Poisson regression, modelling the hospitalization rate using attained age, attained calendar period and interaction between breast cancer status and time since breast cancer diagnosis. For flexible model specification, we used generalized additive models with thin plate splines for the smoothers. We adjusted for a two-dimensional thin plate spline for attained age and attained calendar period. To calculate the absolute risks in breast cancer patients, the one- and five-year risks of bone fracture hospitalization were calculated for cancer diagnoses during 2005-2010, and the 30-day and one-year risk of death following a bone fracture hospitalisation were calculated for hospitalisations during 2005-2010. For women from the national population excluding the breast cancer patients, the incidence were age-standardised to the person-time distribution for the breast cancer patients, and the mortality rates were age-standardised to the person-time distribution for the breast cancer patients hospitalised for a bone fracture. The data extraction was performed with SAS 9.4; the generalized additive models used mgcv package (version 1.7) in R 3.0.

In the regional cohort comprising only women with a previous breast cancer diagnosis, follow-up started at date of breast cancer diagnosis and was continued until date of first fracture event, death, first distant metastasis or 31 December 2006, whichever came first. Hazard ratios (HR) of fracture rates (or death rates depending on the analysis) were estimated using Cox regression with time since diagnosis as the underlying time scale. The proportional hazard assumption was tested using the Therneau and Grambsch test. Test for interaction between age and Charlson comorbidity index was carried out using likelihood ratio test. We also looked at the risk of dying after hospitalization due to a bone fracture considering three outcomes: death due to any cause, death due to breast cancer and death due to causes other than breast cancer. In the analysis of the risk of dying after being hospitalised for a fracture, person-time was divided by time before and after first recorded hospitalization due to a fracture. When looking at cause-specific death we also censored the analysis for the other

causes of death. The analysis of the regional cohort was performed using the statistical software package STATA 12.1. All tests were two-sided and the level of significance was 5%.

Results

Of all 10,866 hospitalizations due to bone fractures in the Swedish national cohort of women diagnosed with breast cancer between 1990 and 2010 and aged less than 75 years at diagnosis, 4,008 (36.9%) were hip fractures. Hip fractures increased over age and consequently over time since diagnosis, while other lower limb fractures decreased, and upper limb fractures remained stable (Supplementary Table 1). In total, 3,895 (35.8%) hospitalizations due to bone fractures occurred within 5 years since breast cancer diagnosis. Most hospitalizations due to bone fractures occurred in women aged 61-74 years at breast cancer diagnosis (n=7,364, 67.8%). For the breast cancer patients diagnosed during 2005-2010, the one-year risk of bone fracture was 0.94% (95% CI: 0.83-1.05) and the five-year risk was 4.82% (95% CI: 4.55-5.06). For the population excluding the breast cancer patients during 2005-2010, the standardised one-year risk was 0.812% (95% CI: 0.806-0.817) and the standardised five-year risk was 3.97% (95% CI: 3.94-3.99). When looking at risk of death after bone fracture hospitalization, for breast cancer patients with a bone fracture hospitalisation during 2005-2010, the 30-day risk of death was 1.95% (95% CI: 1.72-2.18) and the one-year risk of death was 18.4% (95% CI: 17.2-19.5). For the population without breast cancer patients with a bone fracture hospitalisation, the standardised 30-day risk of death was 1.43% (95% CI: 1.41-1.46) and the standardised one-year risk of death was 16.1% (95% CI: 15.8-16.3).

The overall rate ratios for hospitalization due to any bone fracture and for hospitalization due to hip fracture comparing breast cancer patients with the general population was 1.25 (95% CI: 1.23-1.28) and 1.18 (95% CI: 1.14-1.22) respectively, after adjusting for attained age and calendar period. These rate ratios gradually decreased over time, but remained significantly increased for 10 years since breast cancer diagnosis (Figure 1). The rate ratio of hospitalization due to any bone fracture after breast cancer was significantly increased in all ages and decreased with increasing age, from about 1.70 at the attained age of 40 years to about 1.20 at the age of 80 years. The rate ratio of hospitalization due to a hip fracture was also significantly increased in women of all ages, ranging from above 3.00 at the attained age of 40 years to about 1.20 at the age of 80 years.

Table 1 shows, in the regional cohort of women with breast cancer, the frequency distribution of breast cancer patients (n=12,850) with hospitalizations due to any bone fracture (n=600) and with hospitalizations due to hip fracture (n=209) after breast cancer diagnosis, across different characteristics. Hospitalizations due to bone fracture after breast cancer occurred more often in patients 61-74 years of age at breast cancer diagnosis (64.0% for any bone fracture, 79.4% for hip fracture). Of the total n=12,850 breast cancer patients included in the analysis, n=1,534 (12%) developed a first distant metastasis during the study period (mean follow-up time=5.8 years). All 1,534 (100%) had available information on date of first distant metastasis.

Table 2 shows the adjusted HRs of hospitalizations due to bone fracture after breast cancer diagnosis, comparing different subgroups of breast cancer patients from the regional cohort of breast cancer patients. After testing for proportional hazards, we could not find any evidence of time-dependent effects, therefore only a proportional hazards analysis was performed. The HR for being hospitalized with any bone fracture or with hip fracture for women ≤50 years at breast cancer diagnosis was 0.28 (95% CI: 0.20-0.38) and 0.10 (95% CI:

0.05-0.22) respectively, as compared with women 61-74 years at breast cancer diagnosis. Calendar period at breast cancer diagnosis, tumor characteristics and adjuvant treatment combinations were not significantly associated with the risk of hospitalization due to bone fracture. Charlson comorbidity index scoring as low as one was significantly associated with the risk of hospitalization due to any bone fracture (HR=1.63; 95%CI: 1.29-2.06) or due to hip fracture alone (HR=2.31; 95%CI: 1.61-3.32).

We also performed an additional analysis using a regional cohort of women with information on drug use based on The Swedish Prescribed Drug Register (Figure 3). The 5-year cumulative incidence of bone fracture for those patients treated with tamoxifen, aromatase inhibitors, or chemotherapy without hormone therapy were 3.0% (95% CI: 2.3%-4.0%), 5.9% (95% CI: 4.6%-7.6%), and 4.1% (95% CI: 2.5%-6.7%), respectively. As compared with the general population, the corresponding standardized incidence ratios for bone fractures were 0.94 (95% CI: 0.60-1.45), 1.32 (95% CI: 0.89-1.96), and 1.39 (95% CI: 0.66-2.91), respectively. Furthermore, we found that women taking aromatase inhibitors were at higher risk of being hospitalized with a bone fracture as compared with women taking tamoxifen (HR=1.52; 95% CI: 1.03-2.22) in postmenopausal women. Similar results were found when further adjusting for age, tumor size and lymph node status (HR=1.48; 95% CI: 0.98-2.22).

Table 3 shows the risk of dying comparing women with or without a bone fracture in the regional cohort of breast cancer patients. After being hospitalized with a bone fracture the HR of dying due to any cause was 1.83 (95% CI: 1.50-2.22) as compared with not being hospitalized with a bone fracture. This HR was most pronounced among women 61-74 years at breast cancer diagnosis (HR=2.16; 95% CI: 1.70-2.75) while it was not significant in women younger than 61 years at breast cancer diagnosis.

Discussion

Our major findings are that breast cancer patients were at increased risk of being hospitalized with a bone fracture for at least 10 years since breast cancer diagnosis, that the presence of at least one comorbidity was associated with an increased risk of being hospitalized with a bone fracture, that patients using aromatase inhibitors were at higher risk of having a fracture compared to tamoxifen users, and that being hospitalized with a bone fracture was significantly associated with overall mortality.

It has previously been shown that breast cancer adjuvant treatment, in particular hormonal treatment, may affect bone metabolism and bone mineral density, thus potentially influencing the risk of fractures in breast cancer patients (Becker 2012, Breast Cancer Trials Committee 1987, Fisher 1989, Rutqvist 2007, Cooke 2008, Amir 2011, Edwards 2011, Santen 2011). Still, some previous observational studies were unable to show a significantly increased risk of bone fracture in women with a previous breast cancer (Melton 2012, Pawloski 2013). An increased risk of bone fractures as compared with the general population was nonetheless found in other hormone-dependent tumors (Melton 2011, Thorstenson 2012). In our study we found a significant long-term increase (up to 10 years) of the risk of hospitalization due to bone fracture in women with a previous breast cancer diagnosis, independent of age. This risk gradually decreased during the follow-up, suggesting a potential association with treatment. The magnitude of this risk increase is however not particularly pronounced (20-25%) and may not be considered of primary clinical relevance in a breast cancer patient; however it is still an important risk estimation, and its potential impact on quality of life of women surviving with a previous breast cancer diagnosis should not be underestimated.

In our study, tumor characteristics were not associated with the risk of being hospitalized with a bone fracture after a breast cancer diagnosis. In our study comorbidities were

significantly associated with the risk of being hospitalized with a bone fracture at a Charlson comorbidity Index score of 1 (Table 2). In particular, women with at least one comorbidity and aged 60 years or less at breast cancer diagnosis showed a 10 years' cumulative incidence of bone fracture hospitalization similar to women aged more than 60 and without comorbidities (Figure 2).

Aromatase inhibitors, in combination with menopause and older age, can lead to bone loss and to a higher risk of fractures (Becker 2012, Santen 2011, Chen 2009). On the other hand, tamoxifen was shown to be protective against the risk of osteoporosis and subsequent bone fractures in postmenopausal patients (Cooke 2008, Santen 2011). Increased risk of bone fractures in breast cancer patients treated with aromatase inhibitors as compared to patients treated with tamoxifen was seen in large clinical trials (Cuzick 2010, Van Poznak 2010, Crivellari 2008). In our analysis, which is based on an observational study design, we also found an increased risk of bone fracture in patients treated with aromatase inhibitors as compared to tamoxifen treated patients (Figure 3). Bisphosphonates, a class of drugs commonly administered to prevent bone loss and treat osteoporosis, have been widely used to prevent disease recurrence and mortality in breast cancer metastatic patients (Wong 2012, van Poznak 2011, Hillner 2003). Recently, a growing body of evidence is also supporting their use in women with early breast cancer to improve prognosis (Coleman 2013, He 2013, Gnant 2009, EBCTCG 2015). Also, the use of adjuvant denosumab has been found to reduce the risk of bone fractures in postmenopausal women treated with aromatase inhibitors (Gnant 2015).

Bone fracture hospitalizations in individuals older than 60 years is associated with an approximately two-fold increased risk of death in the first 5 years that can remain significantly elevated up to 10 years depending on type of fracture (Bliuc 2009). Hip fractures in particular are also associated with potentially severe complications like deep vein

thrombosis, pressure ulcers and pulmonary embolism, while vertebral fractures can affect pulmonary function (Schlaich 1998, Margolis 2003, Nakase 2009, Anand 2007). Our findings showed an increased overall mortality in breast cancer patients following hospitalization with bone fracture, which was interestingly independent of other comorbidities and tumor characteristics (Table 3).

In this study we used large population data sources with long and complete periods of follow-up. It could be that some of the reported events were pathological fractures due to breast cancer metastasis, in case bone metastases were not correctly and timely reported to the register. However, in order to avoid this bias in the regional cohort analysis we censored at time of first distant metastasis; moreover, the lack of association between hospitalization due to bone fracture and risk of breast cancer-specific death argues against this bias being pronounced. We used specific and appropriate ICD codes to retrieve data on hospitalizations due to bone fracture from the Swedish Inpatients Register, yet we cannot rule out some degree of inaccuracy in the reporting into the register. Hip fractures usually require hospitalization, therefore we believe that our analysis captured most such cases; however there may be some underestimation in the number of other fractures associated with bone loss, like wrist or vertebral fractures, which can also be treated in an outpatients setting. We believe that many of the bone fractures in our study were related to bone loss given that the majority of the women were in postmenopausal age, and given that we could not find significant differences in the findings concerning hospitalization due to any-bone fracture and due to hip fracture, with the latter being often associated with bone loss. However, one cannot rule out the presence of a certain proportion of bone fractures in absence of bone loss (e.g., frailty that was not captured by the Charlson comorbidity index). Attribution of specific causes of death can sometimes be inaccurate, therefore the lack association we found, between hospitalization due to bone fracture and death due to breast cancer, should be taken

with caution. Finally, in this observational study, because of the study design, we could not account for other risk factors of bone fracture, such as bone mineral density at breast cancer diagnosis, use of certain medications (e.g., corticosteroids), life-style, and frailty resulting from cancer and/or treatment, and for bone preserving treatment (though bisphosphonates were gradually introduced in Sweden late into the study period) (Van Hemelrijck 2013, Søgaard 2013, Kiderlen 2014), and this may have potentially biased some of our findings.

In conclusion, in our cohort women with breast cancer are at increased risk of developing bone fractures. This association is particularly pronounced in fragile patients, defined as those with one or more comorbidity, including patients ≤60 years at diagnosis. In this observational study, aromatase inhibitors-treated patients were at increased risk of being hospitalized with a bone fracture compared with tamoxifen-treated patients. Finally, hospitalization due to a bone fracture was associated with an increased risk of death.

Competing interests section

The authors declare that they have no competing interests.

Authors' contributions

EC participated in the study designing and data collection, performed the statistical analysis and drafted the manuscript. MC and AJ participated in the data collection and contributed to the statistical analysis. WH and JB participated in the study design, contributed to the statistical analysis and revised the manuscript for important intellectual content. AL, JA, PH and TF conceived the study, participated in its design and revised the manuscript for important intellectual content. KC conceived, designed and coordinated the study and helped in drafting the manuscript. All authors read, reviewed and approved the final manuscript.

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Table 1. First hospitalization due to bone fracture within 10 years after breast cancer diagnosis in women from the Stockholm Breast Cancer Register's regional cohort, Stockholm-Gotland counties, 1990-2006.					
	Any bone fracture[#] (%)	**No bone fracture (%)**	**Hip fracture[¤] (%)**	**No hip fracture (%)**	**Total (%)**
Age					
≤ 50 years	77 (12.8)	3701 (30.2)	12 (5.7)	3766 (29.8)	3778 (29.4)
51-60 years	139 (23.2)	4052 (33.1)	31 (14.8)	4160 (32.9)	4191 (32.6)
61-74 years	384 (64.0)	4497 (36.7)	166 (79.4)	4715 (37.3)	4881 (38.00)
Period					
1990-1994	260 (43.3)	3136 (25.6)	102 (48.8)	3294 (26.1)	3396 (26.4)
1995-1999	222 (37.0)	3381 (27.6)	75 (35.9)	3528 (27.9)	3603 (28.0)
2000-2006	118 (19.7)	5733 (46.8)	32 (15.3)	5819 (46.0)	5851 (45.5)
Tumor size					
More than 20mm	171 (28.50)	3427 (27.98)	62 (29.7)	3536 (28.0)	3598 (28.0)
Less than 20mm	413 (68.83)	8631 (70.46)	140 (67.0)	8904 (70.4)	9044 (70.4)
Missing	16 (2.67)	192 (1.57)	7 (3.4)	201 (1.6)	208 (1.6)
Lymph node status					
Positive nodes	176 (29.3)	4045 (33.0)	63 (30.1)	4158 (32.9)	4221 (32.9)
Negative nodes	389 (64.8)	7558 (61.7)	129 (61.7)	7818 (61.9)	7947 (61.8)
Missing	35 (5.8)	647 (5.3)	17 (8.1)	665 (5.3)	682 (5.3)
ER-status					
ER-positive	392 (65.3)	8082 (66.0)	150 (71.8)	8324 (65.9)	8474 (66.0)
ER-negative	82 (13.7)	1790 (14.6)	25 (12.0)	1847 (14.6)	1872 (14.6)
Missing	126 (21.0)	2378 (19.4)	34 (16.3)	2470 (19.5)	2504 (19.5)
Charlson Comorbidity Index					
0	372 (62.0)	10,264 (83.8)	106 (50.7)	10,530 (83.3)	10,636 (82.8)
1	145 (24.2)	1,467 (12.0)	65 (31.1)	1,547 (12.2)	1,612 (12.5)
2 or more	83 (13.8)	484 (4.0)	38 (18.2)	529 (4.2)	567 (4.4)
Missing	0 (0.0)	35 (0.3)	0 (0.0)	35 (0.3)	35 (0.0)
Adjuvant treatment[§]					
CT any without HT	35 (5.8)	1369 (11.2)	5 (2.4)	1399 (11.1)	1404 (10.9)
HT any without CT	403 (67.2)	6943 (56.7)	151 (72.3)	7195 (56.9)	7346 (57.2)
HT+CT any	51 (8.5)	2224 (18.2)	11 (5.3)	2264 (17.9)	2275 (17.7)
Other	111 (18.5)	1714 (14.0)	42 (20.1)	1783 (14.1)	1825 (14.2)
Type of surgery					
Total mastectomy	292 (48.7)	4820 (39.4)	113 (54.1)	4999 (40.0)	5112 (39.8)
Partial mastectomy	298 (49.7)	7246 (59.2)	95 (45.5)	7449 (58.9)	7544 (58.7)
Other	10 (1.7)	174 (1.4)	1 (0.5)	183 (1.5)	184 (1.4)
Missing	0 (0.0)	10 (0.1)	0 (0.0)	10 (0.1)	10 (0.1)
Total	600 (100.0)	12250 (100.0)	209 (100.0)	12641 (100.0)	12850 (100.0)

First hospitalization due to any bone fracture after breast cancer diagnosis

¤ First hospitalization due to hip fracture after breast cancer diagnosis (hospitalizations for other bone fractures may have occurred earlier)

§ Adjuvant treatment combinations - CT any without HT: any combination with or without radiation therapy including chemotherapy and not including hormone therapy; HT any without CT: any combination with or without radiation therapy including hormone therapy and not including chemotherapy; HT+CT any: any combination with or without radiation therapy including both chemotherapy and hormone therapy; other: any combination with or without radiation therapy not including chemotherapy or hormone therapy

Table 2. Adjusted hazard ratios# for first hospitalization due to bone fracture within 10 years since breast cancer diagnosis in women from the Stockholm Breast Cancer Register's regional cohort, Stockholm-Gotland counties, 1990-2006.

	Any bone fracture HR (95% CI)	Hip fracture HR (95% CI)
Age		
<50 years	0.28 (0.20-0.38)*	0.10 (0.05-0.22)*
51-60 years	0.42 (0.33-0.53)*	0.24 (0.15-0.39)*
61-74 years	1.0 (ref.)	1.0 (ref.)
Calendar period		
1990-1994	0.91 (0.73-1.13)	1.03 (0.72-1.47)
1995-1999	1.0 (ref.)	1.0 (ref.)
2000-2006	0.91 (0.69-1.21)	0.96 (0.57-1.61)
Tumor characteristics		
Tumor size larger than 20mm	1.21 (0.98-1.50)	1.26 (0.89-1.78)
Tumor size smaller than 20mm	1.0 (ref.)	1.0 (ref.)
Positive lymph nodes	1.00 (0.80-1.25)	1.26 (0.89-1.79)
Negative lymph nodes	1.0 (ref.)	1.0 (ref.)
ER-positive	1.0 (ref.)	1.0 (ref.)
ER-negative	1.14 (0.85-1.53)	0.90 (0.54-1.51)
Charlson Comorbidity Index		
0	1.0	1.0
1	1.63 (1.29-2.06)*	2.31 (1.61-3.32)*
2 or more	2.44 (1.85-3.24)*	3.01 (1.95-4.64)*
Adjuvant treatment combination§		
CT any combination without HT	0.98 (0.68-1.40)	0.41 (0.12-1.37)
HT any combination without CT	1.0 (ref.)	1.0 (ref.)
HT and CT any combination	0.98 (0.63-1.50)	0.97 (0.47-1.97)
Other	1.04 (0.70-1.54)	1.01 (0.65-1.57)
Surgery		
Total mastectomy	1.0 (ref.)	1.0 (ref.)
Partial mastectomy	0.80 (0.65-0.98)*	0.65 (0.46-0.92)*

All estimates are adjusted for all variables shown in the table

* Statistically significant at alfa=0.05

§ Adjuvant treatment combinations - CT any without HT: any combination with or without radiation therapy including chemotherapy and not including hormone therapy; HT any without CT: any combination with or without radiation therapy including hormone therapy and not including chemotherapy; HT+CT any: any combination with or without radiation therapy including both chemotherapy and hormone therapy; other: any combination with or without radiation therapy not including chemotherapy or hormone therapy

Table 3. Adjusted§ hazard ratios (95%CI) for all-cause, breast cancer and other-cause of death comparing breast cancer patients with and without a hospitalization due to a bone fracture, Stockholm Breast Cancer Register's regional cohort, Stockholm-Gotland counties, 1990-2006.

Causes of death	HR (95% CI)
Overall death	1.83 (1.50-2.22)*
Breast cancer-specific death	0.96 (0.66-1.40)
Other cause of death	2.78 (2.11-3.67)*

§ Model adjusted for age at diagnosis, calendar period, lymph node positivity, ER-status, tumor size, Charlson comorbidity Index, adjuvant treatment combination and type of surgery

*Statistically significant at alfa=0.05

Figure legends

Figure 1. Rate ratios for hospitalization due to bone fracture after breast cancer diagnosis by time since diagnosis and by attained age, Swedish national cohort, 1990-2010.

Figure 2. Risk of first hospitalization due to bone fracture after breast cancer diagnosis by age and Charlson comorbity index (CCI) in women from the SBCR regional cohort, Stockholm-Gotland counties, 1990-2006.

Figure 3. Risk of first hospitalization due to bone fracture by tamoxifen/aromatase inhibitors after breast cancer diagnosis in women from the SBCR regional cohort, Stockholm-Gotland counties, 2005-2008, with additional merge to the Swedish Prescribed Drug Register and follow-up until 2013[#].

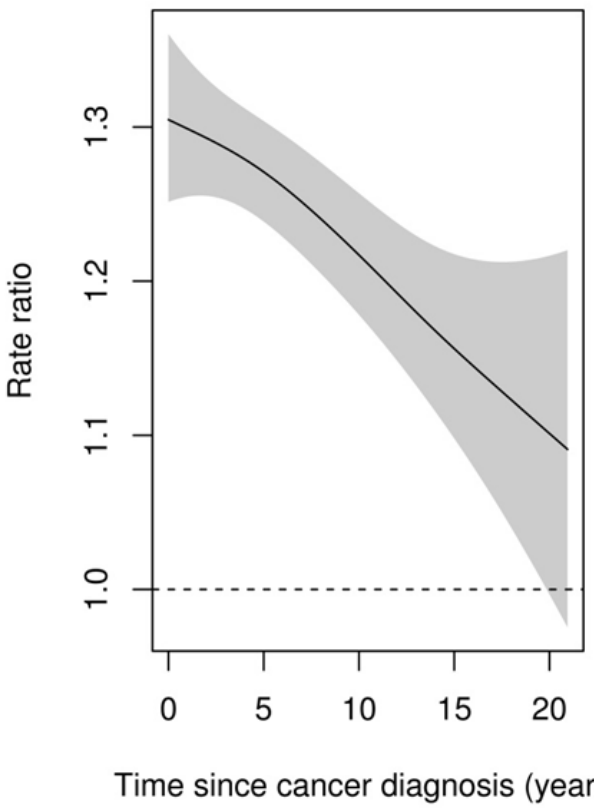
Footnote: # Premenopausal women, women diagnosed with distant metastases, women aged>75 years at diagnosis, and women with a bone fracture history before breast cancer diagnosis were excluded from this analysis.

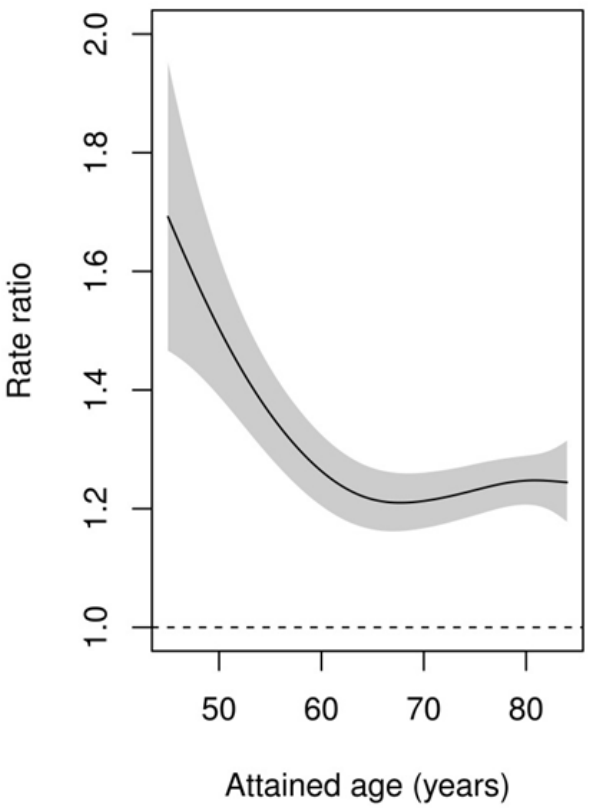
Additional files

File name: Additional file 1

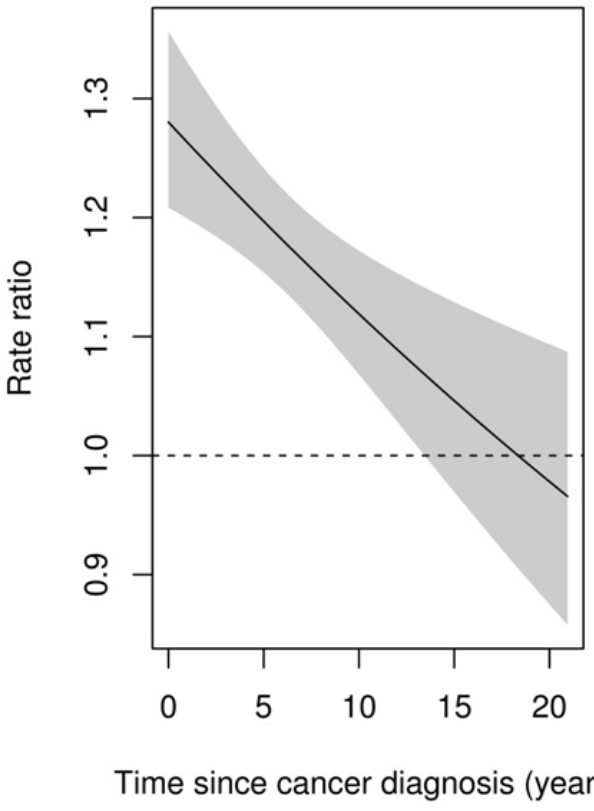
Title: Table 1 supplementary - Description of data: Site distribution of first hospitalizations due to bone fracture since breast cancer diagnosis, according to age and time since diagnosis, Swedish national cohort, 1990-2010.

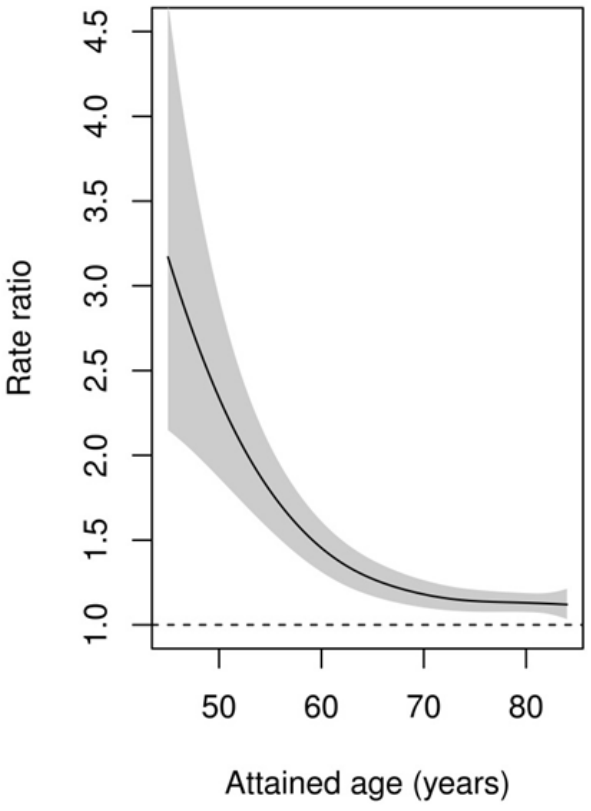
Any bone fracture hospitalization

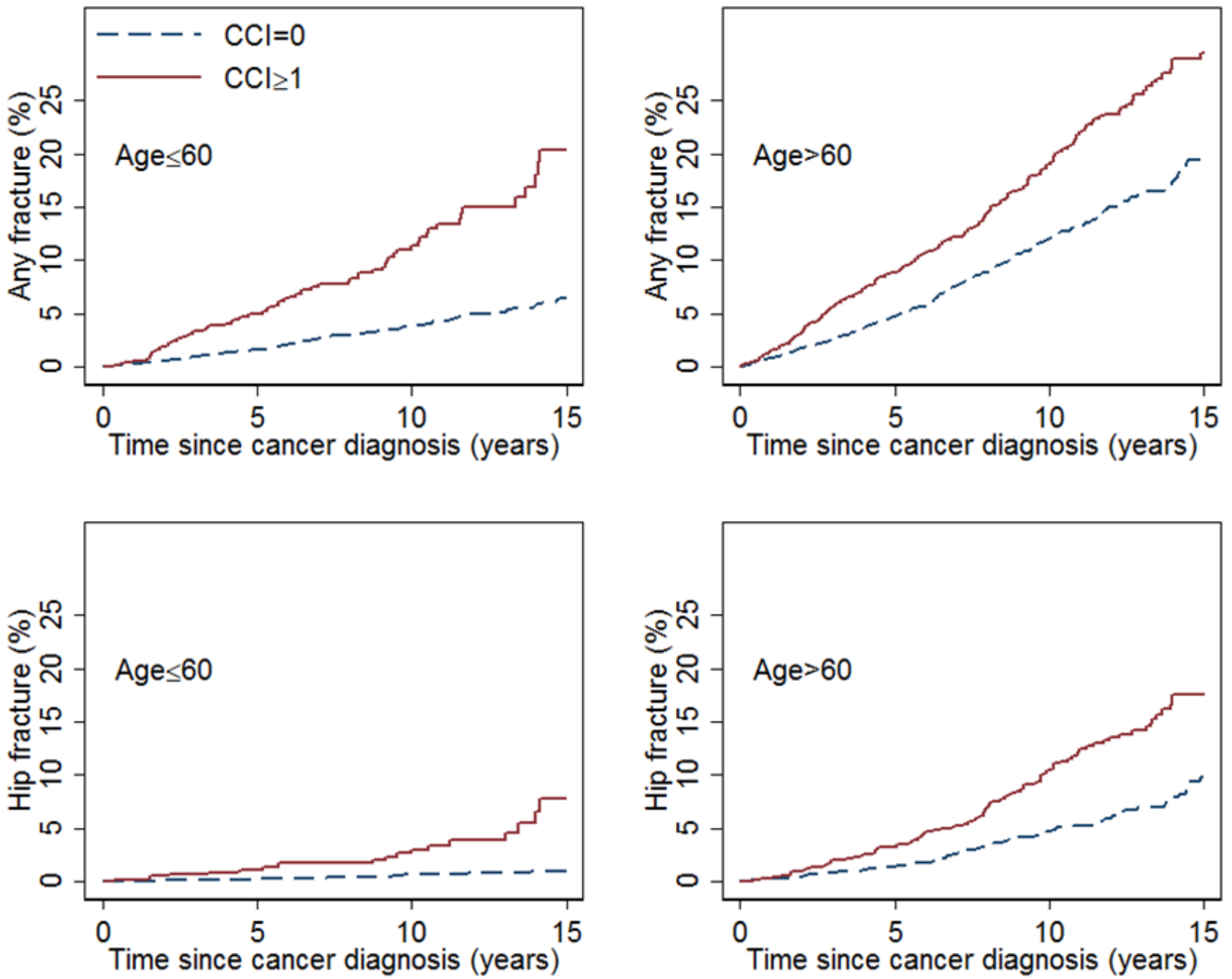




Hip fracture hospitalization






CCI=0
CCI≥1
Age≤60
Age>60
Any fracture (%)
Hip fracture (%)
0
5
10
15
20
25
Time since cancer diagnosis (years)

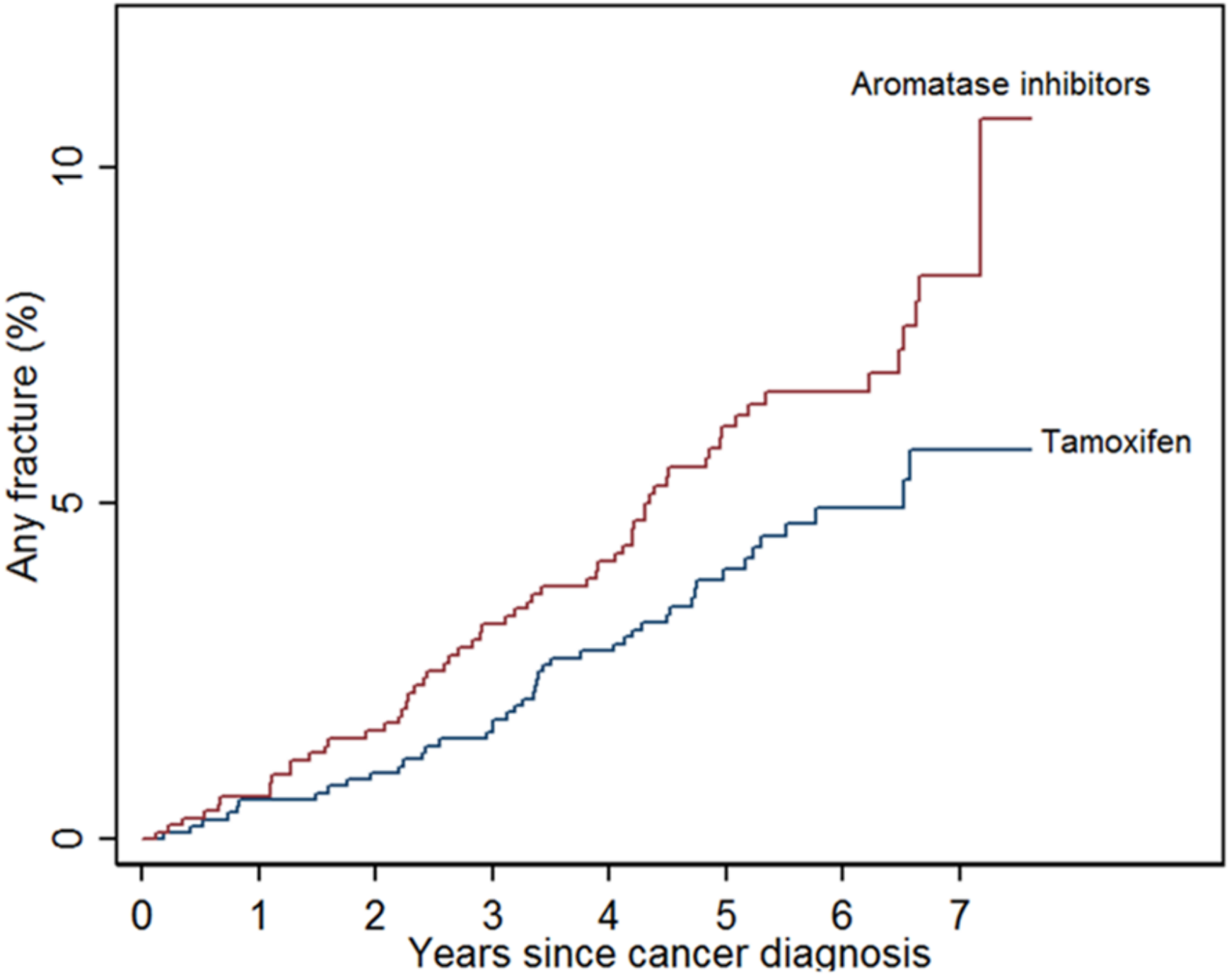

Aromatase inhibitors
Tamoxifen
Any fracture (%)
0
5
10
0
1
2
3
4
5
6
7
Years since cancer diagnosis

Table 1 supplementary. Site distribution of first hospitalizations due to bone fracture since breast cancer diagnosis, according to age and time since diagnosis, Swedish national cohort, 1990-2010.

Site of bone fracture	Diagnosed with breast cancer (aged<75 years at diagnosis)														Not diagnosed with breast cancer	
	Total		Age at diagnosis (years)						Time since diagnosis (years)						Age 45-84 years at hospitalisation	
			<=50		51-60		61-74		0-2		2-5		5+			
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Column	612	(5.6)	68	(5.5)	112	(4.9)	432	(5.9)	96	(6.4)	133	(5.6)	383	(5.5)	46,363	(5.9)
Chest	304	(2.8)	42	(3.4)	72	(3.2)	190	(2.6)	42	(2.8)	64	(2.7)	198	(2.8)	20,448	(2.6)
Pelvis	652	(6.0)	40	(3.3)	102	(4.5)	510	(6.9)	57	(3.8)	120	(5.0)	475	(6.8)	49,637	(6.3)
Upper limb	2,475	(22.8)	330	(26.9)	631	(27.7)	1,514	(20.6)	365	(24.3)	574	(24.0)	1,536	(22.0)	160,634	(20.4)
Hip	4,008	(36.9)	187	(15.2)	600	(26.4)	3,221	(43.7)	446	(29.7)	754	(31.5)	2,808	(40.3)	325,745	(41.4)
Lower limb (excluding hip)	2,556	(23.5)	551	(44.9)	713	(31.4)	1,292	(17.5)	473	(31.4)	702	(29.4)	1,381	(19.8)	166,954	(21.2)
Multiple, other or unspecified	259	(2.4)	10	(0.8)	44	(1.9)	205	(2.8)	25	(1.7)	44	(1.8)	190	(2.7)	17,092	(2.2)
All	10,866	(100.0)	1,228	(100.0)	2,274	(100.0)	7,364	(100.0)	1,504	(100.0)	2,391	(100.0)	6,971	(100.0)	786,873	(100.0)