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

3 **Short title: Risk of bone fractures in breast cancer patients**

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30 **Abstract**

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

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

37 Results: For breast cancer patients, the five-year risk of bone fracture hospitalization was
38 4.8% and the 30-day risk of death following a bone fracture hospitalisation was 2.0%.
39 Compared with general population, breast cancer patients had incidence rate ratios of 1.25
40 (95% CI: 1.23, 1.28) and 1.18 (95% CI: 1.14, 1.22) for hospitalization due to any bone
41 fracture and hip fracture respectively. These ratios remained significantly increased for ten
42 years. Comorbidities (Charlson comorbidity index \geq 1) were associated with the risk of being
43 hospitalized with bone fracture. Women taking aromatase inhibitors were at increased risk as
44 compared with women taking tamoxifen (HR=1.48; 95% CI: 0.98-2.22). Breast cancer
45 patients hospitalized for a bone fracture showed a higher risk of death (HR=1.83; 95% CI:
46 1.50, 2.22), compared to those without bone fracture.

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

49

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

51 **Introduction**

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

57 Breast cancer treatment influences risk of bone fracture through different mechanisms.
58 Adjuvant treatment in particular may affect calcium and bone metabolism possibly leading to
59 an increased risk (Becker 2012). Hormonal therapy with aromatase inhibitors has in fact been
60 found to be associated with risk of bone fracture in contrast to tamoxifen that has shown a
61 protective effect (Breast Cancer Trials Committee 1987, Fisher 1989, Rutqvist 2007, Cooke
62 2008, Amir 2011, Edwards 2011). Other types of oncologic adjuvant treatment may also
63 have potential negative effects on the skeleton independent of sex hormones (Pfeilschifter
64 2000, Arnold 2013). Additionally, increasing evidence is suggesting that bone marrow
65 microenvironment is involved in the metastatic process (Semesiuk 2013, Benoy 2006).
66 Finally, it was shown that bone-targeted drugs, like bisphosphonates, may reduce skeletal
67 metastasis and improve survival (Coleman 2014, Wong 2012). For all these reasons,
68 bisphosphonates are currently administered to some patients in parallel to the adjuvant
69 treatment in order to reduce the risk of bone metastasis and to strengthen the bone tissue
70 (Rizzoli 2012, Van Poznak 2011).

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

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

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

81

82 **Materials and Methods**

83 Study cohorts

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

85 The first, national cohort, comprised data extracted from a national database. Individuals
86 from the Swedish Total Population Register were linked by personal identification numbers
87 to the National Cancer Register (Mattsson 1984, Barlow 2009), the National Cause of Death
88 Register (Rutqvist 1985), and the Inpatient Register (Ludvigsson 2011). The National Cancer
89 Register reports all records for each cancer diagnosis made in Sweden coded through the 7th
90 version of International Classification of Diseases (ICD-7) since 1958. The National Cause of
91 Death Register collects all causes of death in Sweden that are mandatorily reported since
92 1952. The Inpatient Register reports hospitalizations in all Sweden since 1987, coded through
93 the 9th and 10th versions of International Classification of Diseases (ICD-9 and ICD-10), and
94 has nationwide coverage. This national cohort was restricted to women aged 45 years and
95 over for the calendar period 1990-2010.

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

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

110 In an additional linkage based on the same registries as the regional cohort, women diagnosed
111 with breast cancer between 2005 and 2008, were further linked to the Swedish Prescribed
112 Drug Register in order to investigate the potential effect of type of adjuvant hormone
113 treatment on future fractures. The Swedish Prescribed Drug Register contains information on
114 all prescribed medicines dispensed by Swedish pharmacies since July 1, 2005, including
115 dates of prescription and dispense, number of defined daily doses, and classification of drugs
116 according to the Anatomical Therapeutic Chemical (ATC) Classification System. This
117 register is reported to be nationwide complete, with <0.3% of data entries with missing
118 Personal Identification Numbers (Wettermark 2007). Through this linkage, we identified
119 2551 patients diagnosed with breast cancer between 2005 and 2008 who initiated adjuvant
120 hormone therapy with at least one prescription of tamoxifen (ATC codes L02BA01) or
121 aromatase inhibitors (ATC codes L02BG) and were followed until end of 2012.

122 ICD codes and Events

123 Breast cancer diagnoses were based on ICD-7 code 170. The hospitalization events were
124 defined as: hospitalization after breast cancer diagnosis due to bone fracture, excluding
125 fractures of the skull and of the neck (ICD-9 codes 805-829, 733.0, 733.93-98 and ICD-10
126 codes S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12, T14.2, M80); and
127 hospitalization after breast cancer diagnosis due to hip fracture (ICD-9 codes 820, and ICD-
128 10 codes S72.0, S72.1, S72.2). All hospitalization events were defined based on the main
129 diagnosis of hospitalization. The death events were categorized using the underlying cause of
130 death.

131 Ethics

132 The study was entirely based on data from Swedish health and population registers and was
133 approved by the Ethical Review Board at Karolinska Institutet, Stockholm, Sweden (Dnr
134 2011/1898 32; Dnr 2007/821-31/3; Dnr 2012/217-32/2; Dnr 2014/1401-32). No contact was
135 made with the study participants, data were analyzed anonymously and thus informed
136 consent was not obtained. This exception from informed consent was confirmed by the
137 ethical committee.

138 Statistical analysis

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

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

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

172 causes of death. The analysis of the regional cohort was performed using the statistical
173 software package STATA 12.1. All tests were two-sided and the level of significance was
174 5%.

175

176 **Results**

177 Of all 10,866 hospitalizations due to bone fractures in the Swedish national cohort of women
178 diagnosed with breast cancer between 1990 and 2010 and aged less than 75 years at
179 diagnosis, 4,008 (36.9%) were hip fractures. Hip fractures increased over age and
180 consequently over time since diagnosis, while other lower limb fractures decreased, and
181 upper limb fractures remained stable (Supplementary Table 1). In total, 3,895 (35.8%)
182 hospitalizations due to bone fractures occurred within 5 years since breast cancer diagnosis.
183 Most hospitalizations due to bone fractures occurred in women aged 61-74 years at breast
184 cancer diagnosis (n=7,364, 67.8%). For the breast cancer patients diagnosed during 2005-
185 2010, the one-year risk of bone fracture was 0.94% (95% CI: 0.83-1.05) and the five-year
186 risk was 4.82% (95% CI: 4.55-5.06). For the population excluding the breast cancer patients
187 during 2005-2010, the standardised one-year risk was 0.812% (95% CI: 0.806-0.817) and the
188 standardised five-year risk was 3.97% (95% CI: 3.94-3.99). When looking at risk of death
189 after bone fracture hospitalization, for breast cancer patients with a bone fracture
190 hospitalisation during 2005-2010, the 30-day risk of death was 1.95% (95% CI: 1.72-2.18)
191 and the one-year risk of death was 18.4% (95% CI: 17.2-19.5). For the population without
192 breast cancer patients with a bone fracture hospitalisation, the standardised 30-day risk of
193 death was 1.43% (95% CI: 1.41-1.46) and the standardised one-year risk of death was 16.1%
194 (95% CI: 15.8-16.3).

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

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

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

220 0.05-0.22) respectively, as compared with women 61-74 years at breast cancer diagnosis.
221 Calendar period at breast cancer diagnosis, tumor characteristics and adjuvant treatment
222 combinations were not significantly associated with the risk of hospitalization due to bone
223 fracture. Charlson comorbidity index scoring as low as one was significantly associated with
224 the risk of hospitalization due to any bone fracture (HR=1.63; 95%CI: 1.29-2.06) or due to
225 hip fracture alone (HR=2.31; 95%CI: 1.61-3.32).

226 We also performed an additional analysis using a regional cohort of women with information
227 on drug use based on The Swedish Prescribed Drug Register (Figure 3). The 5-year
228 cumulative incidence of bone fracture for those patients treated with tamoxifen, aromatase
229 inhibitors, or chemotherapy without hormone therapy were 3.0% (95% CI: 2.3%-4.0%), 5.9%
230 (95% CI: 4.6%-7.6%), and 4.1% (95% CI: 2.5%-6.7%), respectively. As compared with the
231 general population, the corresponding standardized incidence ratios for bone fractures were
232 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),
233 respectively. Furthermore, we found that women taking aromatase inhibitors were at higher
234 risk of being hospitalized with a bone fracture as compared with women taking tamoxifen
235 (HR=1.52; 95% CI: 1.03-2.22) in postmenopausal women. Similar results were found when
236 further adjusting for age, tumor size and lymph node status (HR=1.48; 95% CI: 0.98-2.22).

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

243

244 **Discussion**

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

251 It has previously been shown that breast cancer adjuvant treatment, in particular hormonal
252 treatment, may affect bone metabolism and bone mineral density, thus potentially influencing
253 the risk of fractures in breast cancer patients (Becker 2012, Breast Cancer Trials Committee
254 1987, Fisher 1989, Rutqvist 2007, Cooke 2008, Amir 2011, Edwards 2011, Santen 2011).
255 Still, some previous observational studies were unable to show a significantly increased risk
256 of bone fracture in women with a previous breast cancer (Melton 2012, Pawloski 2013). An
257 increased risk of bone fractures as compared with the general population was nonetheless
258 found in other hormone-dependent tumors (Melton 2011, Thorstenson 2012). In our study we
259 found a significant long-term increase (up to 10 years) of the risk of hospitalization due to
260 bone fracture in women with a previous breast cancer diagnosis, independent of age. This risk
261 gradually decreased during the follow-up, suggesting a potential association with treatment.
262 The magnitude of this risk increase is however not particularly pronounced (20-25%) and
263 may not be considered of primary clinical relevance in a breast cancer patient; however it is
264 still an important risk estimation, and its potential impact on quality of life of women
265 surviving with a previous breast cancer diagnosis should not be underestimated.

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

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

273 Aromatase inhibitors, in combination with menopause and older age, can lead to bone loss
274 and to a higher risk of fractures (Becker 2012, Santen 2011, Chen 2009). On the other hand,
275 tamoxifen was shown to be protective against the risk of osteoporosis and subsequent bone
276 fractures in postmenopausal patients (Cooke 2008, Santen 2011). Increased risk of bone
277 fractures in breast cancer patients treated with aromatase inhibitors as compared to patients
278 treated with tamoxifen was seen in large clinical trials (Cuzick 2010, Van Poznak 2010,
279 Crivellari 2008). In our analysis, which is based on an observational study design, we also
280 found an increased risk of bone fracture in patients treated with aromatase inhibitors as
281 compared to tamoxifen treated patients (Figure 3). Bisphosphonates, a class of drugs
282 commonly administered to prevent bone loss and treat osteoporosis, have been widely used to
283 prevent disease recurrence and mortality in breast cancer metastatic patients (Wong 2012,
284 van Poznak 2011, Hillner 2003). Recently, a growing body of evidence is also supporting
285 their use in women with early breast cancer to improve prognosis (Coleman 2013, He 2013,
286 Gnant 2009, EBCTCG 2015). Also, the use of adjuvant denosumab has been found to reduce
287 the risk of bone fractures in postmenopausal women treated with aromatase inhibitors (Gnant
288 2015).

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

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

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

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

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

330 **Competing interests section**

331 The authors declare that they have no competing interests.

332

333 **Authors' contributions**

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

341

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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 $\alpha=0.05$

§ 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 $\alpha=0.05$

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 comorbidity 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[#].

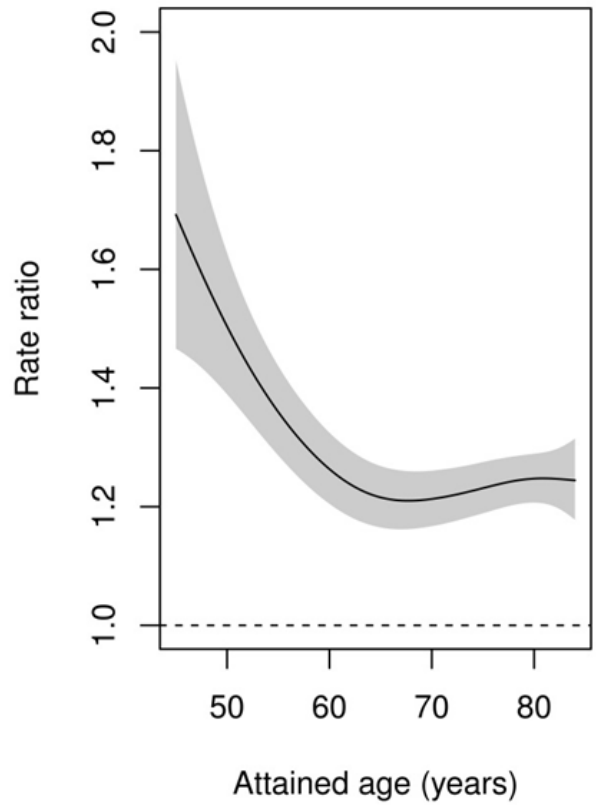
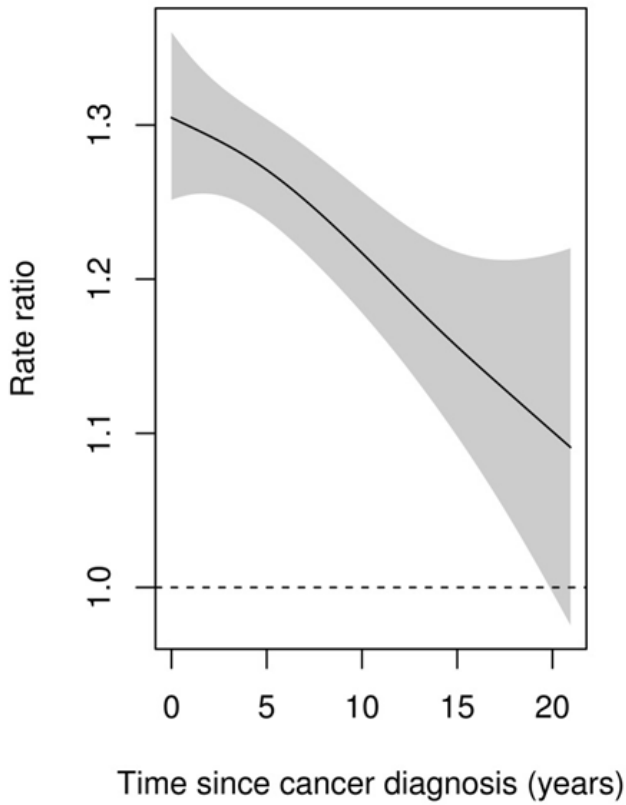
Footnote: # Premenopausal women, women diagnosed with distant metastases, women aged >75 years at diagnosis, and women with a bone fracture history before breast cancer diagnosis were excluded from this analysis.

Additional files

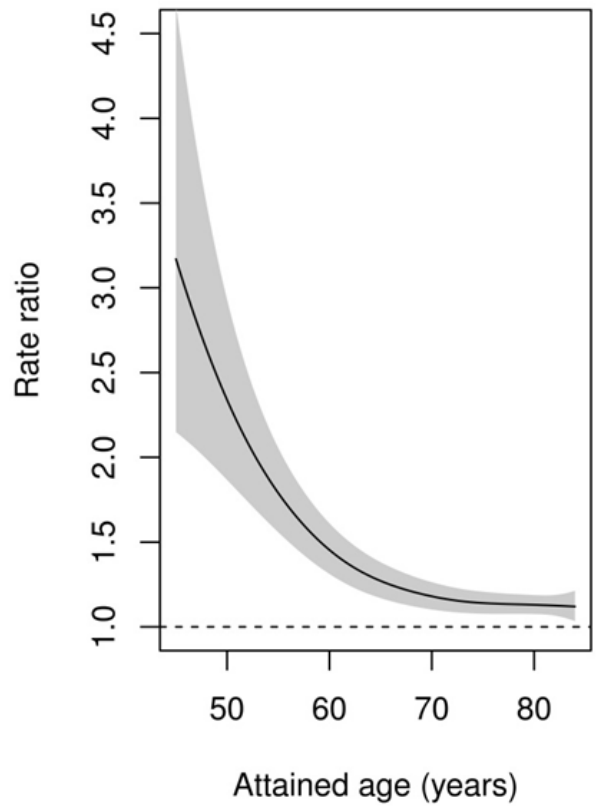
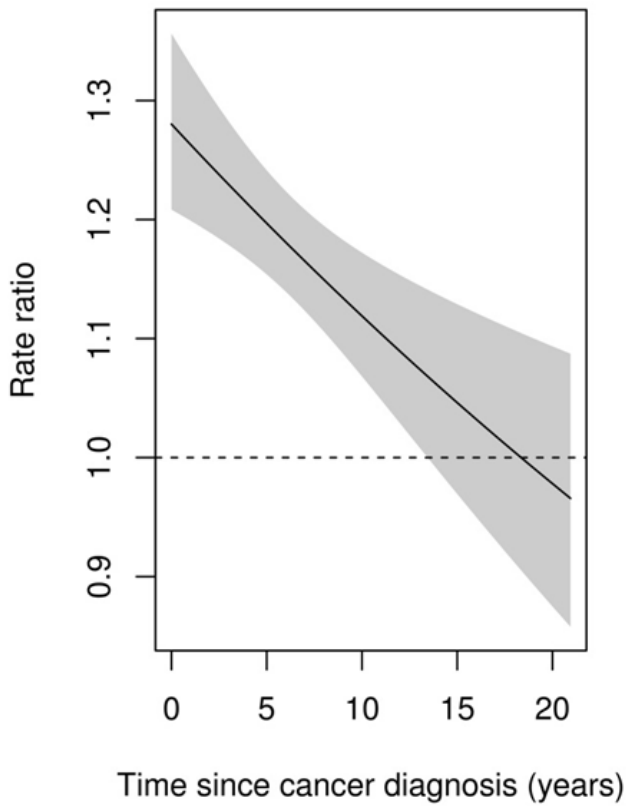
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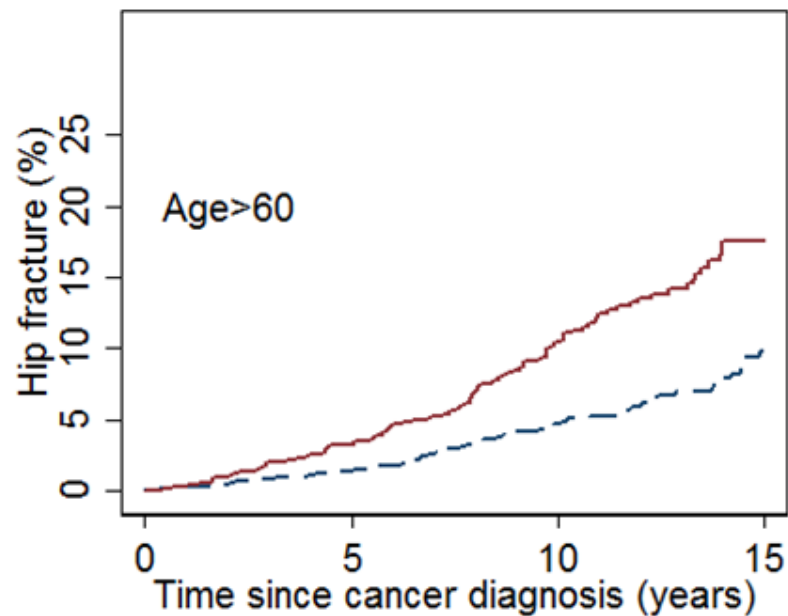
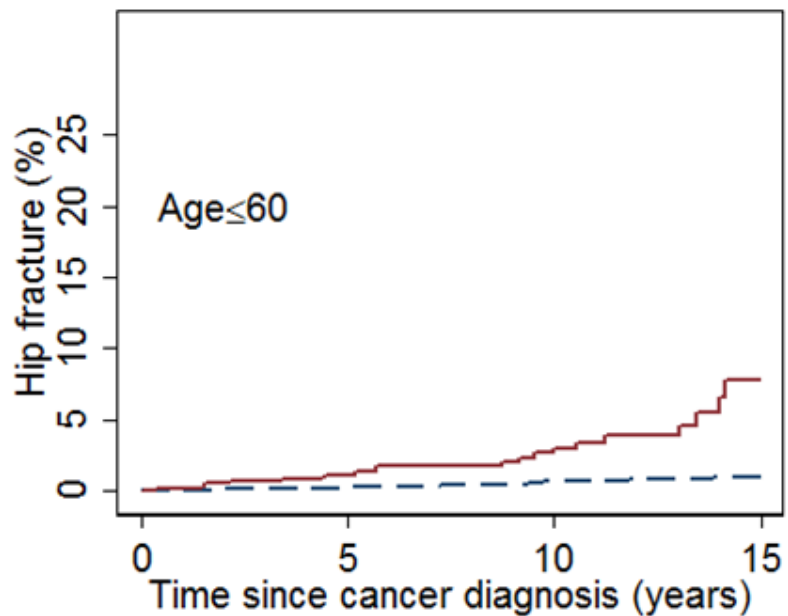
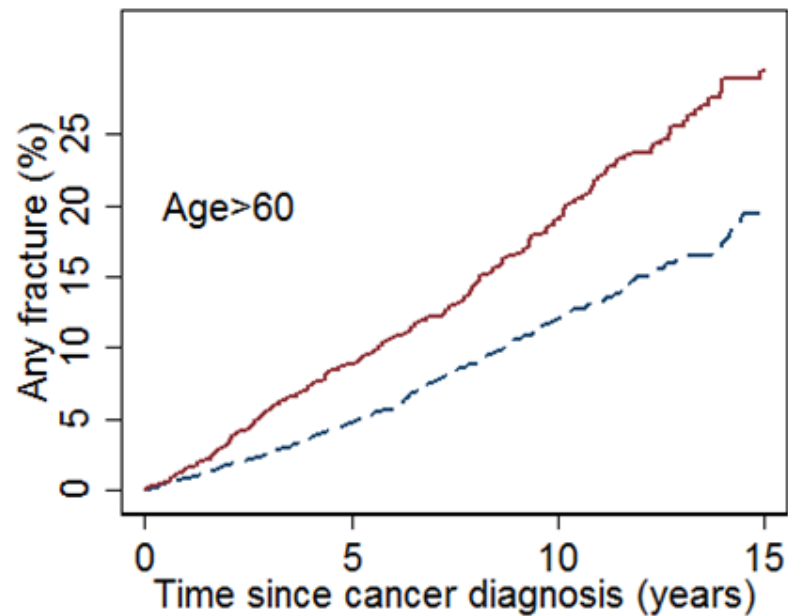
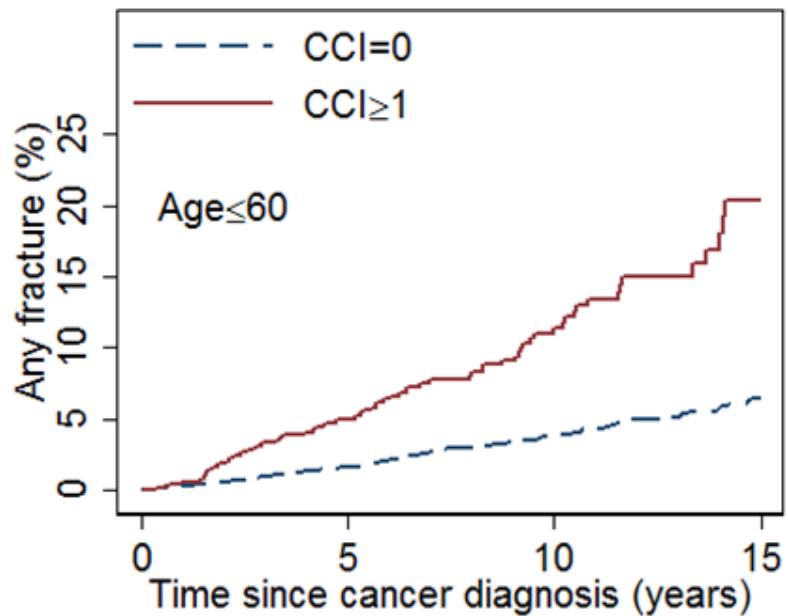
Title: Table 1 supplementary - Description of data: Site distribution of first hospitalizations due to bone fracture since breast cancer diagnosis, according to age and time since diagnosis, Swedish national cohort, 1990-2010.

Any bone fracture hospitalization



Hip fracture hospitalization





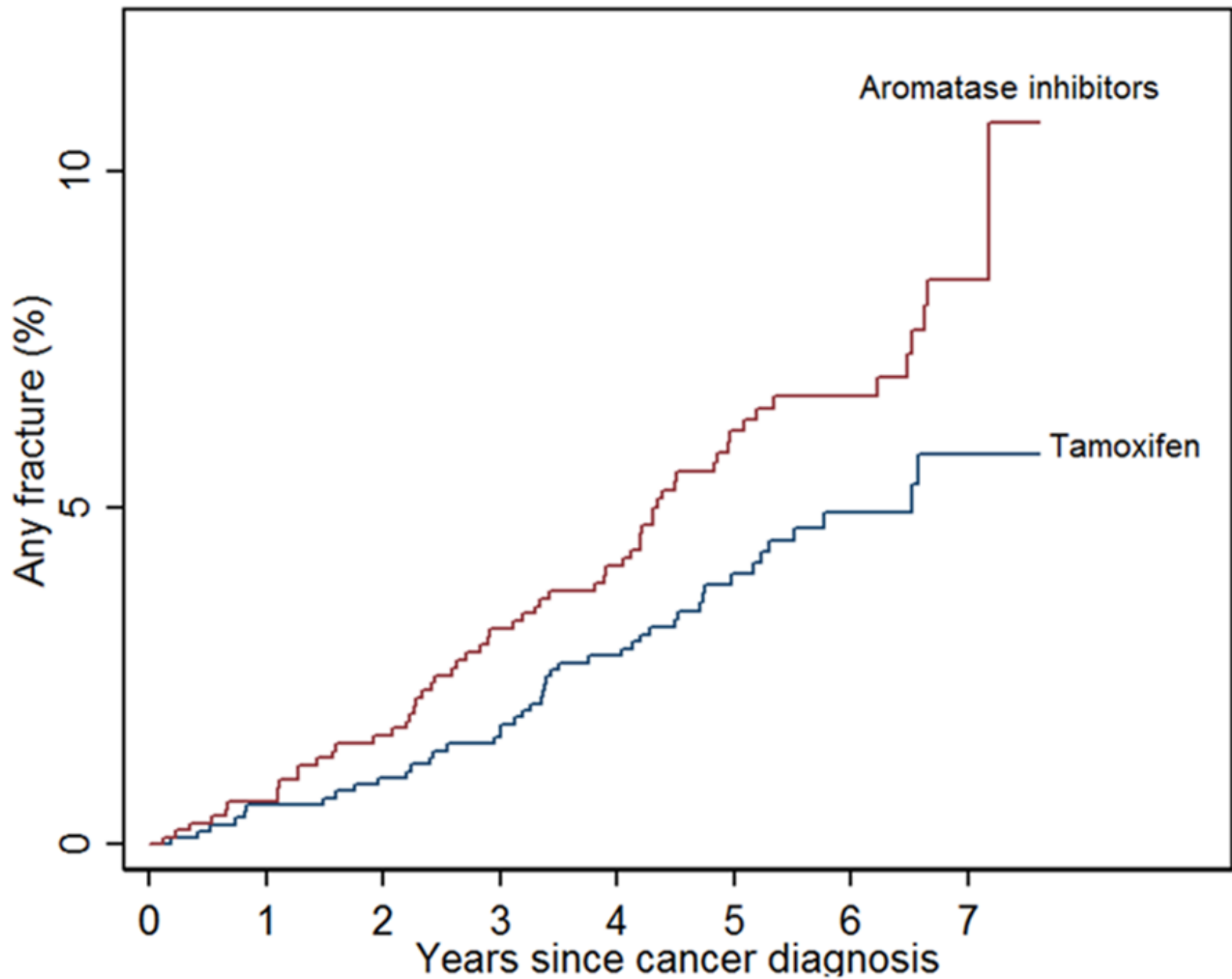


Table 1 supplementary. Site distribution of first hospitalizations due to bone fracture since breast cancer diagnosis, according to age and time since diagnosis, Swedish national cohort, 1990-2010.

Site of bone fracture	Total		Diagnosed with breast cancer (aged <75 years at diagnosis)						Not diagnosed with breast cancer Age 45-84 years at hospitalisation							
			Age at diagnosis (years)			Time since diagnosis (years)										
	N	(%)	<=50	51-60	61-74	0-2	2-5	5+	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)