Reduced risk of metastatic breast cancer recurrence after bone fractures

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Abstract

Recent experimental studies indicate that bone fractures result in the release of cytokines and cells that promote metastasis. Obtaining observational data on bone fractures after breast cancer diagnosis related to distant breast cancer recurrence risk could help determine whether fall prevention strategies can contribute to reduce breast cancer mortality. We used data from the largest German statutory health insurance fund (Techniker Krankenkasse) in a population-based cohort study of breast cancer patients diagnosed between January 2015 and November 2019. ICD-10 codes were documented monthly to quarterly. Fractures diagnosed simultaneous or after the initial breast cancer and metastases diagnosed initially from half a year later on served as exposure and outcome, respectively. The risk of regional, distant non-bone or bone metastasis related to a fracture was modelled by adjusted conditional logistic regression analysis. Of 154,000 breast cancer patients, 82,039 had a follow-up time of more than half a year. During follow-up, fractures were diagnosed in 11,900 (14.5%) patients and regional or distant metastases occurred in 7,011 (8.5%). The risk for a metastasis was reduced in patients, who had a fracture (OR 0.57, 95% CI 0.53, 0.62) compared to patients without, particularly for lymph node metastasis and moderately less pronounced in bone-metastasis (OR 0.69, 95% CI 0.61, 0.79). In view of the positive effects of sports on health of cancer survivors, the present results will decrease the anxiety of breast cancer patients that risking bone fractures might have a negative impact on their disease-specific outcome.

Introduction

Breast cancer is the most commonly diagnosed cancer in women (2.1 million new cases in 2018) and the leading cause of cancer death in women globally (627,000 deaths in 2018) ¹. Metastasis - spread of tumor cells to distant sites and outgrowth into secondary lesions - is the main cause of cancer-related death in breast cancer and most cancer-related deaths (83% in estrogen receptor (ER)-positive and 87% in ER-negative tumors) happen after distant metastasis formation ². Recurrence can occur years after diagnosis and surgical resection of the primary tumor and affects the regional lymph nodes and/or distant organs such as bone, liver, lungs or brain. In this regard, ER-negative tumors relapse frequently early after diagnosis but the relapse frequency progressively declines over time ². In contrast, ER-positive breast cancer recurrences are initially low but continue to occur steadily throughout 20 years after initial diagnosis ^{2,3}. Accumulating evidence suggests that tumor intrinsic genomic alterations are most relevant for determining the risk of tumor recurrence and metastatic relapse ^{2,4}; on the other hand, external events affecting recurrence and metastatic outgrowth in cancer patients are largely unknown.

The idea that tumor growth and recurrence are evoked by trauma and proximate inflammation or healing processes exists for more than a century ⁵⁻⁷. This hypothesis is supported by experimental models suggesting a true impact of inflammation ⁸ and possibly tissue repair ⁹. However, these models are hampered by the fact that mice have only a short life span and most tumor models mimic a situation where recurrence occurs within weeks. Thus, although experimental studies provide novel mechanistic

insights, they need to be cross validated by adequate clinical data. To our best knowledge, there is a lack of observational data analyzing whether bone fractures will accelerate or slow down the development of breast cancer recurrence.

In the present study, we therefore tested the hypothesis that bone fractures occurring after initial breast cancer diagnosis might have an impact on the risk of distant breast cancer recurrence. We performed a cohort analysis on 82,000 breast cancer patients using claims data of a statutory health insurance sample in Germany allowing a follow-up of 5 years.

Methods

Study design and data sources

A retrospective register- and population-based cohort study of breast cancer was performed using administrative data for claims purpose of the largest German statutory health insurance fund (Techniker Krankenkasse, TK). The TK has on average 10 million insurants. Diagnostic codes (WHO ICD-10) from ambulant and hospital care were documented quarterly or monthly respectively. Treatment prescriptions were coded according to international classification for pharmaceutical substances (ATC). Sources of diagnoses were flagged as either ambulant or hospital based, and certainty of ambulant diagnoses had the “status assured” or “status post”. Date variables refer to the year, end of the quarter of ambulant diagnoses, end of the month for the day of discharge from a hospital, and month of having filled a prescription, respectively. Clinical data on tumor subtype, stage and menopausal status were not available.

Data protection and ethical considerations

Based on a legal regulation for use of administrative claims data in public health research (§ 75 SGB X), extracted TK data were anonymized, and included a non-speaking identifier, subject’s birth year and few other variables (see above), so that backtracking of a person is impossible. Therefore, an informed consent was not necessary (see also EU-General data protection regulation, recital 26). This research was conducted according to the principles of the Declaration of Helsinki.

Study population

The cohort consisted of 154,260 individuals that have been diagnosed with malignant neoplasm of breast (ICD-10: C50) between 1st January 2015 and 30th November 2019 selected from TK data base. The follow-up period is up to 4 years and 11 months (median 4.0, IQR 2.49-4.25). We aimed only to consider the sequential arrangement of the initial events of interest. (i) breast cancer diagnosis (BCa), (ii) bone fracture, (iii) metastasis diagnosis. Thus, we excluded those patients whose ICD-codes for breast cancer, fractures and metastasis diagnosis have been tagged with the German ICD-modification “status post”¹⁰ or were diagnosed for metastasis prior or simultaneously to the initial BCa diagnosis (Figure 1). Furthermore, patients with a BCa diagnosis in only a singular quarter were excluded due to a potentially

false BCa diagnosis. To exclude possible prevalent BCa recurrent and metastatic patients, we furthermore excluded all patients with a short follow-up time of up to two quarters in case of metastatic event or in case of censoring. Finally, we included 82,039 patients with BCa diagnosis in the analysis (Figure 1).

Statistical analysis

Exposure

The diagnosis of bone fracture (all ICD-codes S and T) simultaneous or subsequent to BCa diagnosis was the main exposure variable. In total 13,861 of patients with BCa diagnosis were diagnosed for a bone fracture. Of those, 1,961 patients had a diagnosis of fracture prior to the initial BCa diagnosis. To compare this occurrence of a fracture with fractures simultaneously ($n = 1,884$) or subsequent to BCa ($n = 10,016$), the variable was controlled in all models. Those who were diagnosed with metastasis before the diagnosis of bone fracture were included as having had no fracture. Finally, we included 11,900 cases with bone fractures showing the desired sequence of the events of interest.

Outcomes

The main outcome parameter was a diagnosis of metastasis, (i) overall metastases. We further stratified the outcome into three outcome subgroups. (ii) lymph node metastasis, ICD-10 C77, (iii) distant non-bone metastasis, C78, C79 without C79.5 and (iv) distant bone metastasis, C79.5. The subgroups were non-exclusive, i.e. a patient may have been diagnosed with a lymph node metastasis in 2016 and subsequently with a distant bone metastasis in 2017. This patient was then included in the analysis of lymph node and distant bone metastasis using the date of first occurrence, respectively.

Potential confounders

Apart from the outcome and exposure ICD codes, the TK dataset included information on potential confounders, such as birth year, source of BCa/fracture/metastasis diagnosis (outpatient care or hospital), year of diagnosis (2015-2019), ICD-codes for diagnosis of osteoporosis with current pathological fracture (M80) and of osteoporosis without current pathological fracture (ICD M81) as well as prescription of anti-estrogens (L02BA), aromatase inhibitors (L02BG), bisphosphonates (M05BA) and bisphosphonate combinations (M05BA). Any depletion of the peripheral estrogen concentration by anti-estrogen treatment, particularly AI, might be associated with a higher risk for osteoporosis¹¹, which in turn confers a higher risk of fractures. Bisphosphonates, on the other hand, are prescribed as treatment for osteoporosis and may reduce the risk of fractures as well as metastasis¹².

For a descriptive overview, follow-up time between the initial BCa diagnosis and last record in the TK database for those without metastasis, and time of diagnosis of first specified metastasis in those with an event was calculated. A waiting period of at least two quarters between diagnosis of BCa and metastasis was introduced to reduce the possibility of concomitant events (e.g. primary metastasized or

recurrence of the BCa) and increase the follow up time between initial breast cancer diagnosis and metastatic relapse.

We performed a conditional logistic regression analysis for each outcome of metastasis with control subjects not having a diagnosis of metastasis during observation time stratified by year of diagnosis. Patients with a bone fracture after BCa were compared to those without fractures. Those patients, who had a diagnosis of fracture prior to BCa were included as a quasi control group. Analyses were further adjusted for age at breast cancer diagnosis, source of BCa diagnosis, osteoporosis (yes/no), and pathological fracture due to osteoporosis (yes/no), prescriptions of anti-estrogen therapy (yes/no), aromatase inhibitors (yes/no) and bisphosphonates (yes/no) if at least one diagnosis or prescription was documented independent from time of BCa diagnosis.

In a sensitivity analysis, we refined our model by excluding all BCa cases that have been diagnosed in 2015 in order to minimize the potential for initially prevalent cases. Another sensitivity analysis was conducted to minimize the probability of prevalent metastasis in prolonging the waiting period from >0.5 to >1 year between initial breast cancer diagnosis and occurrence of metastasis or censoring. We repeated this analysis for those with a BCa diagnosis after 2015. Additionally, we restricted the analysis to patients with prescriptions of anti-estrogens and AI as an indicator for estrogen receptor positive tumors, which is in view of prognosis a more homogeneous group.

Results

Diagnosis of bone fractures and risk of metastasis

We included 82,039 patients with BCa diagnosis in the main analysis. 75,028 (91.5%) of those patients had no diagnosis of metastasis during observation time, whereas 7,011 (8.5%) patients were diagnosed with metastasis during the follow-up period (Table 1). The median follow-up time for non-metastatic patients was 4.25 years (range 0.58 - 4.91); in contrast, the median follow-up in metastatic patients was 1.75 years (range 0.58 - 4.83) (supplementary figure S1, Table 1), whereas fractures were diagnosed a median time of 1.5 years (range 0 – 4.91 years) after diagnosis. A majority of the patients was initially diagnosed in 2015 followed by less than ten percent in each respective year up to 2019. The median age of the patients was 61 years and similar across subgroups.

In BCa patients without diagnosis of metastasis, we observed in 11,143 (14.9%) cases a fracture after or concurrently with the BCa diagnosis and in 1,828 (2.4%) cases a fracture before the BCa diagnosis. In patients with diagnosis of metastasis, we observed in 757 (10.8%) cases a fracture after or concurrently with the BCa diagnosis and in 133 (1.9%) cases a fracture before the BCa diagnosis (Table 1).

The overall risk of a diagnosis of metastasis after the initial BCa was significantly lower in patients who were diagnosed with a bone fracture compared to those without a fracture (odds ratio (OR) 0.57, 95% confidence interval (95% CI 0.53, 0.62) (Table 2). The lowest risk of diagnosis of metastasis was seen in the subgroup of patients with subsequent lymph node metastasis (OR 0.57, 95% CI 0.51, 0.65), followed

by the group, with distant non-bone metastasis (OR 0.63, 95% CI 0.58, 0.69) and the group with distant bone metastasis (OR 0.69, 95% CI 0.61, 0.79) (Table 2). Interestingly, when the diagnosis of fracture was recorded before the diagnosis of BCa, the magnitude of association was lower, and statistically significant only in the overall metastasis group (OR 0.81, 95% CI 0.67, 0.97).

Sensitivity analysis

After excluding patients with an initial diagnosis of BCa in 2015, we still observed a reduced risk of metastasis in the group of patients diagnosed with a bone fracture during the follow-up period (OR 0.55, 95% CI 0.41, 0.74) (Table 3). As well, in the patient subgroup with the diagnosis of lymph node metastasis, we observed a significant reduced risk for diagnosis of lymph node metastasis (OR 0.47, 95% CI 0.32, 0.70) and of distant metastasis other than bone metastasis (OR 0.69, 95% CI 0.51, 0.93). The occurrence of fractures was non-significantly associated with bone metastasis (OR 0.78, 95% CI 0.50, 1.19). Compared to those without a fracture, patients with a diagnosis of bone fracture before the initial diagnosis of BCa showed no significant differences in the risk of a subsequent diagnosis of a metastasis.

When the waiting period was extended to more than one year, estimates for fractures on metastasis overall changed little (OR 0.61, 95% CI 0.56, 0.67 and OR 0.60, 95% CI 0.42, 0.87, respectively) or in subgroups, whether patients with BCa diagnosis in 2015 were included or excluded (Table 3).

The same pattern of associations was observed in the subgroup of patients with endocrine therapy as an indicator for ER-positive tumors (Table 4), i.e., the strongest reduction in risk of lymph node metastasis was observed in patients with fractures after the BCa diagnosis (OR 0.54, 95% CI 0.46, 0.63).

In summary, our analysis showed that patients diagnosed with a bone fracture after or concurrent with the diagnosis of breast cancer have a reduced risk to be diagnosed with metastasis at a later time point.

Discussion

The present study indicates that fractures occurring after patients were diagnosed with breast cancer reduces the risk to develop metastases. The observed effect was statistically stronger for regional lymph node metastases than metastases in distant organs. Among the distant organs, the influence of fractures was not restricted to bone metastases but also observed for metastases at other sites, suggesting a systemic mechanism of action.

Breast cancer cells are frequently present in lymph nodes and distant organs such as bone marrow of early stage breast cancer patients without any clinical or radiological signs of overt metastasis (TNM-stage M0) ¹³⁻¹⁵. Although these DTCs pose an increased risk for breast cancer recurrence, approximately 50% of DTC-positive patients do not develop metastasis within 10 years after diagnosis ^{15,16}. DTCs can survive adjuvant therapy and reside in the bone marrow (and probably other organs) for many years in a stage of “dormancy” ¹⁷⁻²⁰.

Although the presented epidemiologic data cannot prove any causal relationships, it is tempting to speculate how bone fractures may affect dormant DTCs present in lymph nodes and distant organs. Tissue repair after bone fractures is followed by changes in the immune system (and systemic release of cytokines)²¹ that could explain a systemic effect on DTCs located even far away from the fracture site^{21,22}. Immune-mediated processes²³ and other systemic effects of fractures and concomitant use of anti-inflammatory drugs^{24,25} may also block the growth of DTCs into overt metastases.

Despite the large data base and the strong statistical association found between fractures and metastatic relapse, using a database of a statutory health insurance sample has obvious limitations. In Germany, data need to be deleted after 5 years of storage due to data protection regulations. Our database provides, therefore, no information on late relapses which are more frequent in hormone receptor-positive patients than HER2-positive or triple negative patients³. It is possible that the present sample included patients with an aggressive disease (e.g., ER-negative patients) over proportional compared to the average population because of the short observation time and the higher need to visit physicians for treatment demands. However, an analysis restricted to patients treated with endocrine therapy as a surrogate for estrogen receptor positivity yielded the same pattern of results as within the total sample. Hence, despite the lack of pathological information, the data do not indicate a major difference according to hormone receptor status. However, we cannot exclude that the observed correlations are due to unknown confounding factors.

Health insurance data have been sporadically used for studies of health (care) conditions; some of which performed time-to event analyses^{26,27} or annual incidence/mortality calculations^{28,29}. A general concern with the use of German claims data for epidemiological purposes is that prevalent and incident diagnoses are not distinguishable, leading to an overestimation of the latter, as has been demonstrated for colorectal cancer¹⁰. We have reduced prevalent breast cancer cases by excluding all diagnoses flagged as “status post” as well as introduced a disease-free interval of one year by only including initial C50 diagnoses between 2016 and 2019 with consistent results. Apart from uncertainty in the date of primary diagnosis, the end of observation time depended on the last date of prescription of treatments or diagnoses of breast cancer, fracture, osteoporosis or metastasis, therefore a time-to-event analysis would have been somewhat biased. Nevertheless, we cannot rule out that the observed association is caused by uncertainty of the sequence of events. Therefore, well designed prospective studies with longer follow-up and the integration of data on bone fractures in epidemiologic data bases on breast cancer are warranted.

In conclusion, the results of our current analysis provide no evidence that fractures may pose an increased risk to develop metastasis. In view of the positive effects of sports on health in cancer survivors, the present result will decrease the anxiety derived that fractures might have a negative influence of outcome. A better understanding of the mechanisms behind a potential protective effect of bone fractures on early metastatic progression might lead to new therapeutic strategies to block or slow down metastatic relapse in breast cancer patients.

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Tables

Table 1: Distribution of patient characteristics according to state of metastasis.

N=82039	No Metastasis (%)	Overall metastasis (%)	Lymph node metastasis (%)	Distant non-bone metastasis (%)	Distant bone metastasis (%)
N (%)	75068 (100)	7011 (100) ^a	3505 (100)	5460 (100)	2604 (100)
Source of BCa diagnosis					
Hospital care	12996 (17.3)	1244 (17.7)	740 (21.1)	960 (17.6)	466 (17.9)
Ambulant care	62032 (82.7)	5767 (82.3)	2765 (78.9)	4500 (82.4)	2138 (82.1)
Year of BCa diagnosis (C50.-)					
2015	54946 (73.2)	5725 (81.7)	2688 (76.7)	4561 (83.5)	2198 (84.4)
2016	7447 (9.9)	575 (8.2)	332 (9.5)	458 (8.4)	213 (8.2)
2017	6507 (8.7)	416 (5.9)	275 (7.9)	286 (5.2)	140 (5.4)
2018	5804 (7.7)	246 (3.5)	170 (4.9)	138 (2.5)	52 (2.0)
2019	324 (0.4)	49 (0.7)	40 (1.1)	17 (0.3)	1 (0.04)
Follow-up-time					
Median (IQR)	4.25 (2.83, 4.25)	1.75 (1.00, 2.84)	1.66 (0.92, 2.75)	2.00 (1.25, 3.00)	2.17 (1.25, 3.25)
Source of metastasis diagnosis					
Hospital care	-	3497 (49.9)	2012 (57.4)	2768 (51.0)	1465 (56.3)
Ambulant care	-	3514 (50.1)	1493 (42.6)	2674 (49.0)	1139 (43.7)
Age (years)					
Median (IQR)	61 (52, 71)	62 (52, 72)	59 (50, 70)	62 (52, 73)	61 (51, 72)
Fractures					
None	62057 (82.7)	5487 (86.0)	3094 (88.3)	4722 (86.5)	2231 (85.7)
At/after BCa diagnosis	11143 (14.9)	757 (10.8)	336 (9.6)	644 (11.8)	320 (12.6)
Before Bca	1828 (2.4)	133 (1.9)	75 (2.1)	94 (1.7)	45 (1.7)

diagnosis					
Osteoporosis without pathological fracture					
Yes	17332 (23.1)	11953 (27.9)	880 (25.1)	1442 (26.4)	697 (26.8)
No	57696 (76.9)	5058 (72.1)	2625 (74.9)	4018 (73.6)	1907 (73.2)
Osteoporosis with pathological fracture					
Yes	3342 (4.5)	428 (6.1)	167 (4.8)	309 (5.7)	157 (6.0)
No	71686 (95.5)	6583 (93.9)	3338 (95.2)	5151 (94.3)	2447 (94.0)
Bisphosphonates					
Yes	5852 (7.8)	1140 (19.1)	632 (18.0)	1126 (20.6)	925 (35.5)
No	69176 (92.2)	5671 (80.9)	2873 (82.0)	4334 (79.4)	1679 (64.5)
Anti-estrogens					
Yes	22495 (30.0)	2737 (39.0)	1388 (39.6)	2186 (40.0)	1253 (48.1)
No	52533 (70.0)	4274 (61.0)	2117 (60.4)	3274 (60.0)	1351 (51.9)
Aromatase-inhibitors					
Yes	17179 (22.9)	3115 (44.4)	1578 (45.0)	2446 (44.8)	1496 (57.4)
No	57849 (77.1)	3896 (55.6)	1927 (55.0)	3014 (55.2)	1108 (42.6)

^a The total number of single metastases do not add up to 100% since some patients were affected in more than one location.

Table 2: Associations between fractures and different subgroups of metastasis in breast cancer (adjusted logistic regression analysis*)

	Overall metastasis (%)	Lymph node metastasis (%)	Distant non-bone metastasis (%)	Distant bone metastasis (%)
	Odds Ratio (95%-KI)	Odds Ratio (95%-KI)	Odds Ratio (95%-KI)	Odds Ratio (95%-KI)
Fractures (Reference: none)				
At/after BCa diagnosis	0.57 (0.53, 0.62)	0.57 (0.51, 0.65)	0.63 (0.58, 0.69)	0.69 (0.61, 0.79)
Before Bca diagnosis	0.81 (0.67, 0.97)	0.87 (0.68, 1.11)	0.82 (0.66, 1.03)	0.93 (0.68, 1.27)
Osteoporosis without pathological fracture				
	0.86 (0.81, 0.92)	0.82 (0.75, 0.90)	0.74 (0.68, 0.79)	0.50 (0.45, 0.56)
Osteoporosis with pathological fracture				
	1.15 (1.02, 1.29)	0.85 (0.71, 1.21)	1.00 (0.87, 1.14)	0.89 (0.72, 1.05)
Bisphosphonates				
	2.52 (2.34, 2.72)	2.66 (2.39, 2.95)	3.02 (2.78, 3.29)	7.52 (6.76, 8.35)
Anti-estrogens				
	1.44 (1.36, 1.52)	1.33 (1.23, 1.43)	1.50 (1.41, 1.59)	1.88 (1.72, 2.04)
Aromatase-inhibitors				
	2.43 (2.30, 2.56)	2.60 (2.42, 2.79)	2.41 (2.27, 2.56)	3.55 (3.26, 3.87)
Source of BCa diagnosis (Reference: hospital)				
Ambulant	0.98 (0.91, 1.06)	0.92 (0.84, 1.01)	0.94 (0.87, 1.02)	1.07 (0.95, 1.20)
Age (years)				
	1.002 (0.999, 1.004)	0.99 (0.98, 0.99)	1.004 (1.001, 1.007)	0.99 (0.99, 1.00)

*Models were stratified by year of diagnosis and adjusted for the covariates presented

Abbreviations: BCa, breast cancer

Table 3: Sensitivity analyses of associations between fractures and different subgroups of metastasis after excluding breast cancer diagnoses in 2015 and extending the waiting period to metastasis to more than one year.

	Overall metastasis	Lymph node metastasis	Distant non-bone metastasis	Distant bone metastasis
	Odds Ratio (95%-CI)	Odds Ratio (95%-CI)	Odds Ratio (95%-CI)	Odds Ratio (95%-CI)
Exclusion of BCa diagnosis in 2015 (N = 20,082)				
	N=1,286	N=817	N=899	N=406
Fractures (Reference: none)				
With/after BCa diagnosis	0.55 (0.41, 0.74)	0.47 (0.32, 0.70)	0.69 (0.51, 0.93)	0.78 (0.50, 1.19)
Before Bca diagnosis	0.94 (0.75, 1.19)	1.02 (0.76, 1.36)	0.95 (0.71, 1.30)	1.08 (0.72, 1.63)
Extended waiting period >1 year, BCa diagnosis in 2015 included (N = 76,407)				
	N=5,459	N=2,578	N=4,572	N=2228
Fractures (Reference: none)				
With/after BCa diagnosis	0.61 (0.56, 0.67)	0.61 (0.54, 0.69)	0.67 (0.61, 0.73)	0.73 (0.64, 0.84)
Before Bca diagnosis	0.70 (0.54, 0.91)	0.87 (0.62, 1.23)	0.72 (0.55, 0.95)	0.92 (0.64, 1.31)
Extended waiting period >1 year, BCa diagnosis in 2015 excluded (N = 16,885)				
	N=581	N=311	N=560	N=288
Fractures (Reference: none)				
With/after BCa diagnosis	0.60 (0.42, 0.87)	0.55 (0.32, 0.93)	0.74 (0.52, 1.06)	0.71 (0.43, 1.17)
Before Bca diagnosis	0.74 (0.50, 1.09)	1.10 (0.69, 1.73)	0.79 (0.53, 1.18)	1.02 (0.62, 1.66)

Table 4: Sensitivity analysis of the subgroup of patients who received endocrine therapy as an indicator for ER positive breast cancer

	Overall metastasis	Lymph node metastasis	Distant non-bone metastasis	Distant bone metastasis
	Odds Ratio (95%-CI)	Odds Ratio (95%-CI)	Odds Ratio (95%-CI)	Odds Ratio (95%-CI)
Inclusion of BCa diagnosis in 2015 (N = 37,959)				
	N=4,354	N=2,212	N=3,326	N=1,881
Fractures (Reference: none)				
With/after BCa diagnosis	0.57 (0.51, 0.63)	0.54 (0.46, 0.63)	0.68 (0.60, 0.76)	0.69 (0.60, 0.81)
Before Bca diagnosis	0.90 (0.70, 1.14)	0.92 (0.67, 1.26)	0.95 (0.72, 1.27)	0.85 (0.57, 1.28)
BCa diagnosis in 2015 excluded (N = 12,967)				
	N=798	N=499	N=515	N=264
Fractures (Reference: none)				
With/after BCa diagnosis	0.48 (0.33, 0.71)	0.40 (0.23, 0.69)	0.74 (0.50, 1.09)	0.91 (0.55, 1.49)
Before Bca diagnosis	0.98 (0.72, 1.32)	1.07 (0.74, 1.55)	1.01 (0.70, 1.46)	0.84 (0.47, 1.47)

Figures

Figure 1

Inclusion and exclusion criteria for test subjects, exposure and outcomes

Figure 1

Inclusion and exclusion criteria for test subjects, exposure and outcomes

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