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Influence of chemotherapy and endocrine treatment on fractures in postmenopausal women with breast cancer – a retrospective cohort study

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ABSTRACT

Due to a significant increase in the overall survival of women with breast cancer (BC), preventing the long-term consequences of BC treatments is of the utmost importance. Treatments such as aromatase inhibitors (AI), chemotherapy (CHT), and tamoxifen (TAM) may lead to accelerated bone loss and increased fracture risk. The aim of this retrospective cohort study was to evaluate the treatment-induced fracture risk in a large cohort of postmenopausal women with or without BC. It included 4,115 women with BC and 4,115 healthy women from the Disease Analyzer database (IQVIA). Women with breast cancer were matched 1:1 to women without BC with regard to age, index year, and physician. Within 5 years of the index date, 25.3% of women with BC and 14.6% of healthy women sustained fractures. In this study, aromatase inhibitor therapy was significantly associated with a higher incidence of fractures compared to healthy women who had not undergone such therapy (HR: 3.36, $p < 0.001$).

In conclusion, postmenopausal women with BC who receive AI treatment exhibited an increased incidence of fractures when compared to the healthy cohort, while treatment with TAM or CHT showed no such association.

1. Introduction

Breast cancer (BC) is the most frequent malignant disease in women, affecting one in every 9-10 women [1, 2]. Despite improvements in early diagnosis and treatment options, a breast cancer diagnosis is still substantially associated with morbidity and mortality [2]. As breast cancer survival has continuously increased over the past decades, there has been increasing interest in studying the long-term side effects of cancer treatments, including bone loss and fractures [3-6]. One key regulator of the bone turnover is estrogen [7, 8]. Postmenopausal status, which is associated with a very low level of estrogen, leads to significantly increased bone resorption and the constant decrease of bone mineral density, ultimately leading to a higher risk of fractures. BC and its treatment may significantly add to this already increasing fracture risk by directly affecting the bone structure and gonadal steroid hormone production or by inhibiting the peripheral aromatization of androgens into estrogen, thereby leading to cancer treatment-induced bone loss (CTIBL) [9, 10].

In the past, tamoxifen, a selective estrogen receptor modulator (SERM), was the first-line treatment for endocrine-responsive, postmenopausal breast cancer. However, depending on the target organ, tamoxifen may have agonistic or antagonistic effects. It increases fracture incidence in premenopausal women, while it is neutral or may even decrease fracture incidence in postmenopausal women with breast cancer [11]. Today, aromatase inhibitors (AIs) alone or in combination with tamoxifen are the first-line adjuvant treatment for hormone-responsive breast cancer in postmenopausal women [12]. As AIs further reduce the peripheral conversion of androgen to estrogen beyond the levels of physiological menopause, a significant increase of fracture risk with AIs has been reported, leading to an increasing number of hospitalizations and higher morbidity [13].

So far, the influence of chemotherapy on fracture risk has not been well investigated. A few studies have reported an increased fracture risk after chemotherapy, but they did not distinguish between the effect of endocrine treatment and that of CHT [14-16]

The aim of the present study was to investigate fracture incidence in women with breast cancer compared to a matched healthy cohort and to further distinguish the effects of aromatase inhibitors, tamoxifen, and chemotherapy in a large cohort of postmenopausal women.

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2. Methods

2.1. Database

This study was based on data from the Disease Analyzer database (IQVIA), which compiles drug prescriptions, diagnoses, and basic medical and demographic data obtained directly and in anonymous format from computer systems used in the practices of general practitioners and specialists. Diagnoses (International Classification of Diseases, 10th revision [ICD-10]), prescriptions (Anatomical Therapeutic Chemical [ATC] Classification system), and the quality of reported data are monitored by IQVIA based on a number of criteria (e.g., completeness of documentation and linkage between diagnoses and prescriptions). In the UK, the sampling methods used to select physicians' practices were appropriate for obtaining a representative database of outpatients [17]. The sampling method for the Disease Analyzer database is based on statistics pertaining to all doctors in the UK. These statistics are used to determine the panel composition according to the following strata: region, community size category, and physician age.

2.2. Study population

The current study sample included patients who had received a BC diagnosis (ICD-10: C50) for the first time in one of 205 general practices in the UK between January 2005 and December 2015 (index date). Inclusion criteria were as follows: a follow-up time of at least 12 months after the index date; age ≥60 years at the index date; and no diagnosis of osteoporosis (ICD-10: M80, M81) or fracture (S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12), or osteoporosis therapy (ATC: M05B) prior to or at the index date. After applying similar inclusion criteria, patients without a cancer diagnosis were matched 1:1 to patients with BC based on age, index year, and physician. The index date for participants without cancer was a randomly selected visit date between January 2005 and December 2015 (Fig. 1).

2.3. Study outcome

The main outcome of the study was the incidence of any fracture as a function of BC within five years of the index date. Furthermore, we investigated fracture incidence as a function of breast cancer therapy within five years of the index date. Three therapy groups were selected: tamoxifen (TAM), aromatase inhibitors (AI), and no endocrine therapy. Women who had not received endocrine treatment were presumed to represent patients treated with chemotherapy. However, a proportion of these women, especially those over 70 years of age, may not have received chemotherapy. In women treated with TAM or AI, the day of the first TAM or AI prescription was considered the index date in this analysis. As most of the women received TAM or AI for up to five years, the cumulative incidence of fractures was estimated for this five-year period.

2.4. Statistical analyses

Differences between the sample characteristics of women with BC and those without cancer, as well as between different therapy groups, were tested using chi-squared tests for categorical variables and Wilcoxon tests for continuous variables. We calculated the cumulative incidence of fractures in the BC and no-cancer groups for up to five years and in the different therapy groups for up to five years after the index date using Kaplan-Meier curves. In the analyses of breast cancer versus no cancer, patients were censored at the time of their first fracture diagnosis or loss to follow-up, whichever occurred first. In the analysis of therapy groups, women were followed until the first fracture diagnosis or the time of TAM or AI therapy discontinuation, whichever occurred first.

Since mortality data are not available in the Disease Analyzer database, dead participants were considered as lost to follow-up. We used multivariate Cox regression models to study the association between BC and fractures in the overall sample. In a second step, regression analyses were conducted separately in women with BC who had received TAM therapy, AI therapy, chemotherapy, and women without a cancer diagnosis. Women receiving sequential treatment with tamoxifen and aromatase inhibitors were excluded from the analysis, irrespective of the sequence used. A p-value of <0.05 was considered statistically significant, and statistical analyses were performed using SAS 9.4.

3. Results

The present study included 4,115 women with BC and 4,115 healthy women without breast cancer (Fig. 1). Postmenopausal women with breast cancer were subdivided into women treated with an aromatase inhibitor, with no distinction regarding which specific AI was used, women treated with tamoxifen, and women receiving chemotherapy. In accordance with current guidelines, women in the latter group were considered to be estrogen receptor-negative and consequently many would have received chemotherapy. The mean age of the total population was 68.6 years (SD = 9.4 years). We observed no significant difference in the proportions of women who currently smoked (16.7% versus 17.0%), but we did find small differences between ex-smokers and never-smokers. Both cohorts differed slightly but significantly with regard to BMI. No statistical differences between the groups were found for diabetes incidence, disorders of bone mineral density and structure, or visual disturbances (Table 1).

The differences between women with breast cancer treated with TAM, AI, or chemotherapy were only significant with regard to age, proportions of ex- and never-smokers, BMI, and co-morbidities, but the absolute differences were relatively small (Table 2).

Within 10 years of the index date, 25.3% of women with breast cancer and 14.6% of those without breast cancer sustained a first fracture (log-rank p-value <0.001; Fig. 2). When the treatment groups were analyzed in more detail, only women treated with AI exhibited an increased fracture incidence (21.2%) compared to women receiving tamoxifen, chemotherapy, and healthy women, who had fracture incidences of 7%- 9% (Fig. 3). In women treated with AI, 9% received at least one prescription of bone-modifying drug during observation period (prior to the fracture date). The proportion was under 1% in the TAM, chemotherapy, and healthy cohorts.

Furthermore, multivariate Cox regression analyses were performed. We observed a positive association between breast cancer and fractures (adjusted hazard ratio [HR] = 2.44, $p<0.001$) (Table 2). Next, we separately analyzed the different treatment groups. After adjusting for covariables (BMI, smoking behavior, comorbidities, and corticosteroid therapy), the HR was 3.36 ($p<0.001$) for women with breast cancer receiving AI therapy versus the healthy cohort, but we observed no significant associations between TAM and fracture risk (HR = 0.63, $p=0.145$) or the use of chemotherapy versus the healthy cohort (HR = 0.88, $p=0.496$) (Table 3).

Forearm fractures were the most frequent fracture type diagnosed in the total cohort. Fractures of the shoulder and upper arm as well as the wrist, foot, and toe were more common and fractures of the femur were less common in women treated with tamoxifen compared to the healthy cohort (Fig. 4).

4. Discussion

The results of our retrospective cohort study indicate that women with breast cancer have a significantly higher fracture risk compared to healthy women. This increased fracture risk was seen mainly in women treated with AI, who exhibited an overall fracture incidence of 21%. This corresponds to the findings of several recent studies, which showed that AI-associated bone loss is 2-6 times higher compared to

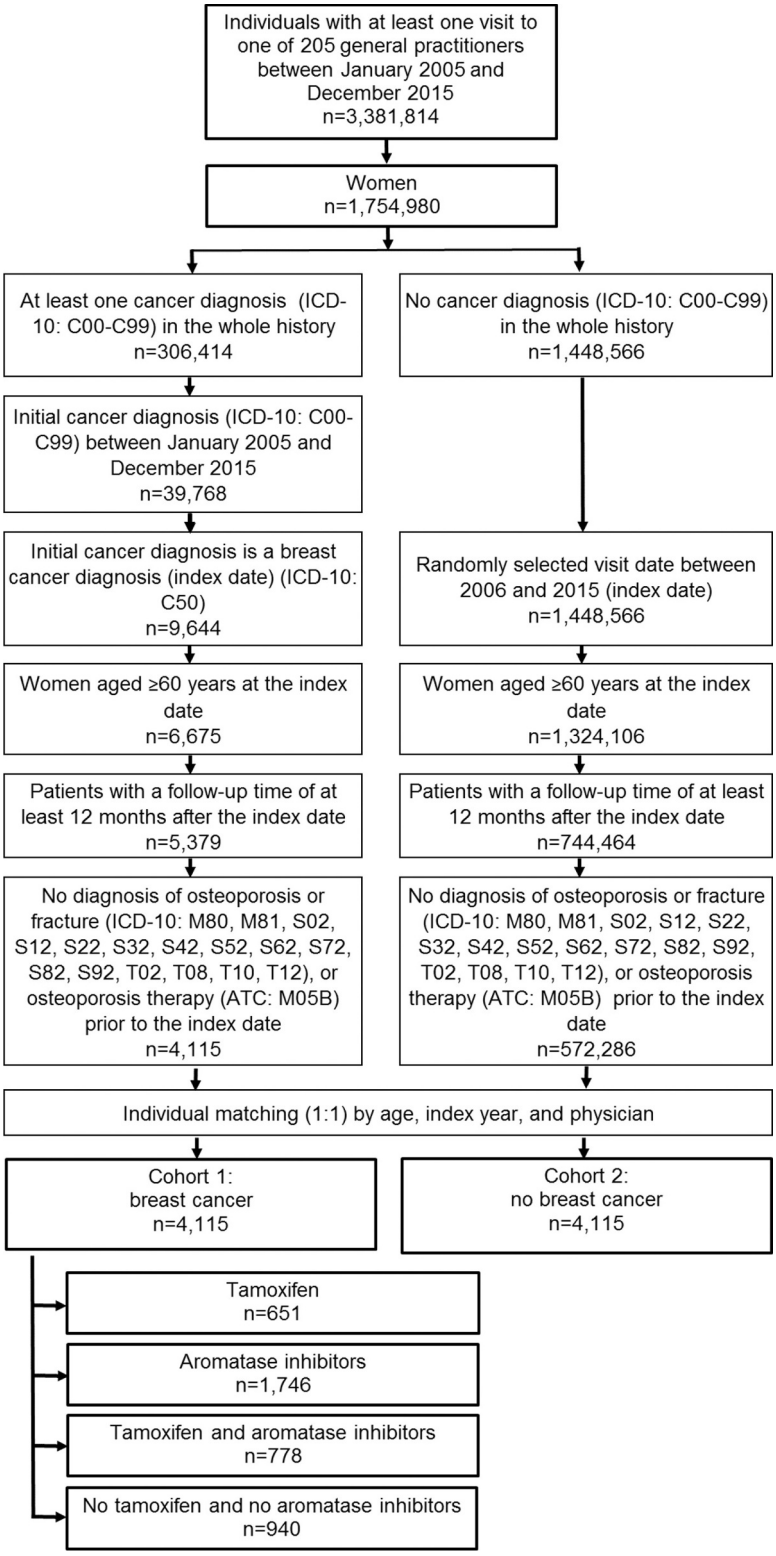

Fig. 1. Selection of study patients

physiological postmenopausal bone loss [18-21]. RCTs in postmenopausal women with breast cancer receiving adjuvant AI treatment versus tamoxifen have reported an absolute fracture incidence of around 10% [22-24]. This translates into a ratio of one in ten women who will sustain a fracture during the course of a five-year AI treatment. Study populations in RCTs are subject to strict inclusion and exclusion criteria and represent a highly selected population. The results are not adequately transferable to the unselected population in clinical practice. Therefore, real-world fracture data needs to be evaluated in observational trials to report a more realistic fracture incidence. Most of these studies examined real-world clinical fracture incidence only in the form of small-scale single-center studies [24-26]. As a result, postmenopausal women with breast cancer treated with AI exhibited a significantly higher incidence of fractures (around 18%-

Table 1
Baseline characteristics of women with or without breast cancer after (1:1) matching.

Variable	Breast cancer (%)	Healthy cohort (%)	p-value
N	4,115	4,115	
Age at baseline (Mean, SD)	68.6 (9.4)	68.6 (9.4)	1.000
Smoking behavior			
Current smoker	16.7	17.0	0.773
Ex-smoker	32.7	29.6	0.019
Never-smoker	48.2	51.9	0.009
Body mass index			
≤ 19.0	2.9	3.6	<0.001
>19.1 - 24.9	32.8	36.1	
>25.0 - 29.9	33.2	34.4	
≥ 30.0	31.1	25.9	
Diagnosis within 12 months prior to the index date			
Diabetes mellitus (E10-E14)	10.5	9.4	0.122
Disorders of bone density and structure (M82-M85)*	1.8	1.9	0.685
Visual disturbances (H53, H54)	6.7	6.9	0.727
Prescriptions within 12 months prior to the index date			
Systemic corticosteroids (ATC: H02)	6.4	7.4	0.075

* disorders of bone density and structure include adult osteomalacia, malunion of fracture, fibrous dysplasia, skeletal fluorosis, hyperostosis of skull, and osteitis condensans

20%) after a 5-year follow-up period [27-29]. Since current international recommendations have expanded the use of AI from five to up to ten years, fracture incidence is expected to further increase [24, 30].

Tamoxifen is a selective estrogen receptor modulator with well-documented bone protective effects in postmenopausal [31], but not in premenopausal, women with breast cancer [11, 15]. Several studies have indicated that risk of fracture was reduced or remained stable in postmenopausal tamoxifen users versus non-users, while premenopausal women with breast cancer taking tamoxifen have a two-fold increased risk of fracture compared to healthy women [32].

The influence of chemotherapy on fracture incidence in postmenopausal women with breast cancer has not yet been studied. To the best of our knowledge, our study is the first to investigate this correlation. To date, only preclinical studies have shown the negative effects of chemotherapy on osteoblasts and osteoclasts in the form of direct toxic effects, as well as indirectly by damaging gonadal function and consequently reducing sex steroid levels, which may even be emphasized by the use of aromatase inhibitors [16]. In addition to these effects on the mineralized matrix, chemotherapy might interfere with the unmineralized matrix, leading to an increased fracture risk that is not mirrored in BMD changes.

4.1. Effects on specific fracture type

Tamoxifen in postmenopausal women with breast cancer has a certain bone-protective effect, which could explain the lower proportion of proximal femoral fractures in women taking tamoxifen (1.0%) versus healthy women (1.2%). This is of the utmost clinical importance, as femur fractures lead to significantly increased mortality. Conversely, shoulder and proximal humerus fractures showed a reverse distribution, with 0.9% (lowest) in healthy controls, 1.6% in women on tamoxifen, and 2.0% (highest) in women treated with an AI.

Proximal humeral fractures account for 5% of all adult fractures and indicate existing osteoporosis [33-35]. Preliminary work has analyzed specific differences in local bone quality of the proximal humerus in relation to patients' age, bone mineral density (BMD), trabecular bone volume fraction (Tb.BV/TV), cortical thickness (Ct.Th), and cortical porosity (Ct.Po) [32, 33]. Helfen et al. underlined the cortical bone loss of the proximal humerus in elderly patients. Patients above the age of 65 years showed a loss in Ct.Th of about -34% and Tb.BV/TV of -40% and an increase in Ct.Po of about +93% compared to middle-aged and young patients (18-44 years).

Cortical bone loss in the elderly may explain a reduction in mechanical strength and stiffness and thus an increasing risk of consecutive fractures of the proximal humerus following low-energy trauma [36]. In our study, the mean age was 68 years. According to Helfen et al., this age group has the highest relative risk for proximal humerus fractures due to a reduction of mechanical strength [36]. Age-related reduction of local bone quality may mask the bone-protective and local bone quality-stabilizing effect of tamoxifen, specifically at the proximal humerus.

In postmenopausal osteoporosis, distal radius fractures are considered indicator fractures for osteoporosis. The high incidence and distribution of forearm fractures in all subgroups supports this supports the hypothesis of distal radius fractures as an indication of reduced bone mineral density and a decrease in cortical porosity [37, 38].

We observed different incidences of defined fracture sites compared to postmenopausal osteoporosis. We found an unexpectedly high incidence of non-weight-bearing upper extremity fractures compared to the typical full weight-bearing lower extremity fractures. Furthermore, spine and pelvis fractures, which are frequent in osteoporosis patients,

Table 2
Baseline characteristics of women receiving tamoxifen treatment, aromatase inhibitor treatment, or chemotherapy and a matched healthy cohort.

Variable	Tamoxifen	Aromatase inhibitors	Chemo-therapy	Healthy cohort (%)	p-value
N	651	1,746	940	4,115	
Age at baseline (Mean, SD)	68.1 (9.2)	70.1 (9.6)	66.5 (8.9)	68.6 (9.4)	<0.001
Smoking					
Current smoker	15.0	17.1	17.6	17.0	0.731
Ex-smoker	32.5	31.2	37.0	29.6	0.006
Never-smoker	49.9	49.1	42.9	51.9	0.001
Body mass index					
≤ 19.0	3.4	3.0	3.1	3.6	<0.001
>19.1 - 24.9	33.6	29.3	37.1	36.1	
>25.0 - 29.9	34.5	34.2	30.4	34.4	
≥ 30.0	28.6	33.6	29.5	25.9	
Diagnosis within 12 months prior to the index date					
Diabetes mellitus (E10-E14)	9.8	12.7	9.9	9.4	0.002
Disorders of bone density and structure (M82-M85)*	1.8	3.1	1.7	1.9	0.026
Visual disturbances (H53, H54)	6.9	8.0	5.0	6.9	0.040
Prescriptions within 12 months prior to the index date					
Systemic corticosteroids (ATC: H02)	8.8	7.5	5.7	7.4	0.137

* disorders of bone density and structure include adult osteomalacia, malunion of fracture, fibrous dysplasia, skeletal fluorosis, hyperostosis of skull, and osteitis condensans

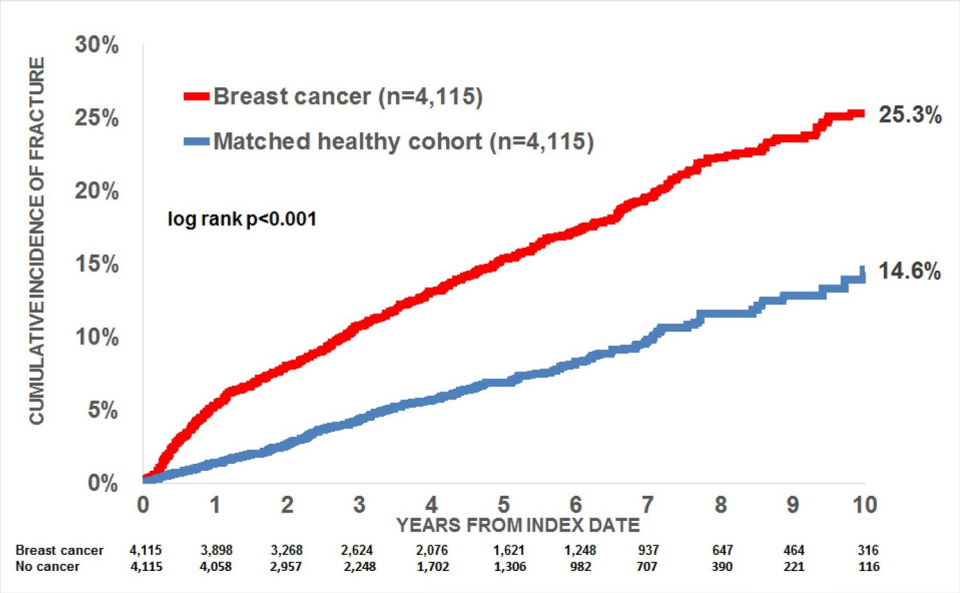

Fig. 2. Cumulative incidence of fracture in women aged ≥60 with breast cancer and a matched healthy cohort.

were rarely found in women in the overall breast cancer group, suggesting that cancer treatment-induced bone loss (CTIBL) is distinct from postmenopausal osteoporosis [18]. This underreporting of certain fractures, especially vertebral fractures, has been shown in several European countries.

5. Limitations

The present study has several limitations. The incidence of fractures relies on the documentation of ICD codes by general practitioners and thus has the potential for miscoding. Additionally, no differentiation between traumatic vs. atraumatic fractures could be performed in our dataset. However, even if miscoding had occurred, we believe that it would most probably be equally distributed between the groups.

We examined five groups of patients in our retrospective analysis: postmenopausal women with or without breast cancer, women with breast cancer receiving AI treatment, women with breast cancer receiving tamoxifen, and women with breast cancer receiving chemotherapy. Our database does not contain information about specific cancer treatments or chemotherapy in these women, but as the vast majority of women with breast cancer in the UK are treated in accordance with NICE guidelines, we assumed these women predominantly received standard chemotherapy. Bone mineral density was not recorded in our database, so we were unable to correlate fractures with BMD. Furthermore, no data on hospitalization, or life-style factors, including physical activity, alcohol use, smoking, nutrition, etc. were available in our database. However, because of the large sample size and the high number of fractures, we believe that it would most probably be equally distributed between the groups. Mortality data are not available in the Disease Analyzer database. Consequently, dead participants were considered as lost to follow-up, which may lead to bias. However, as women with BC and healthy controls were matched, we believe that the influence on the overall results is rather small. Furthermore, a proportion of women with AI therapy, may have

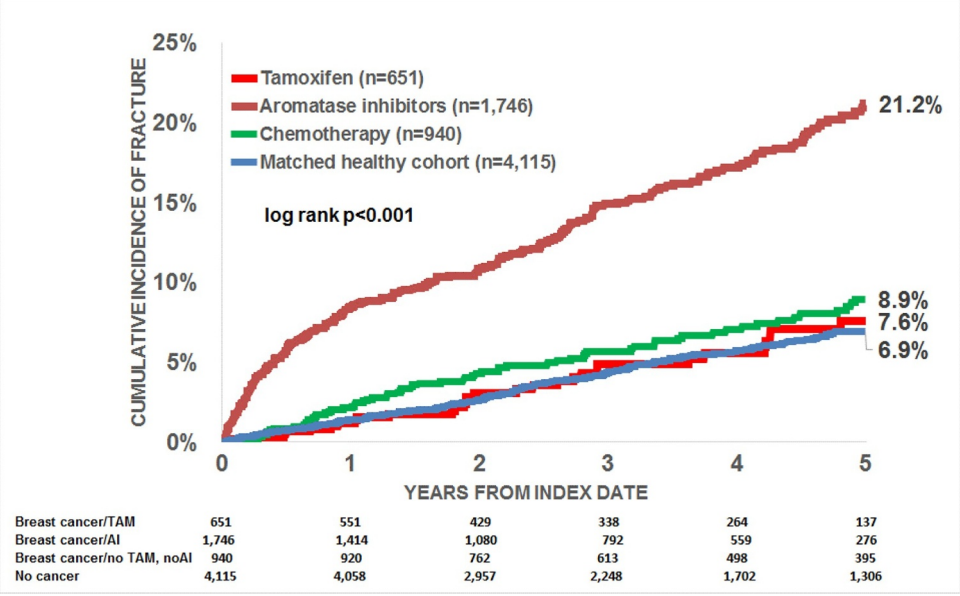

Fig. 3. Cumulative incidence of fracture in women aged ≥60 with breast cancer as a function of the specific treatment and a matched healthy cohort.

Table 3
Association between breast cancer, its treatments, and fracture incidence (multivariate Cox regression models).

	OR (95% CI)*	p-value
Breast cancer vs. matched healthy cohort	2.44 (1.99-2.98)	<0.001
Breast cancer and tamoxifen vs. matched healthy cohort	0.63 (0.34-1.17)	0.145
Breast cancer and aromatase inhibitors vs. matched healthy cohort	3.36 (2.65-4.26)	<0.001
Breast cancer and chemotherapy vs. matched healthy cohort	0.88 (0.60-1.28)	0.496

* multivariable Cox regression adjusted for BMI, smoking behavior, comorbidities, and corticosteroid therapy

received bone-modifying drug prescriptions during the follow-up period, and the cumulative incidence of fractures may be underestimated in these women. Finally, in this study, women who had not received endocrine treatment were presumed to represent patients treated with chemotherapy. However, a part of these women, especially those over 70 years, may not have received chemotherapy.

In conclusion, our study underlines the significantly increased risk of fracture in postmenopausal women with breast cancer. Neither tamoxifen nor chemotherapy use contributed to this increased fracture risk. The increased risk only appeared in women receiving AI treatment. Further prospective studies investigating the long-term side effects of cancer treatments on osteoporosis and fractures are warranted.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest with regard to this article.

Author statement

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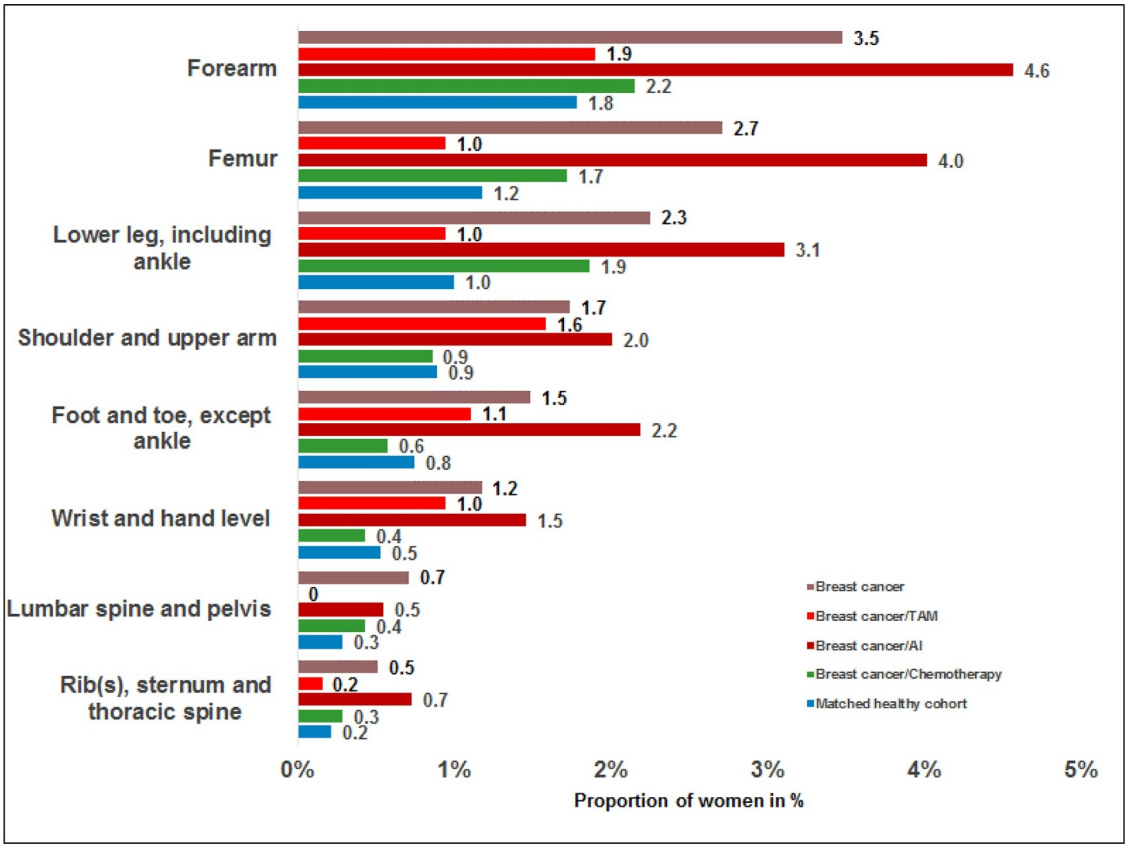

Fig. 4. Cumulative incidence of different fractures in women aged ≥60 with breast cancer as a function of the specific treatment and a matched healthy cohort.

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