Osteoporosis International (2018) 29:2557–2564
https://doi.org/10.1007/s00198-018-4642-2

ORIGINAL ARTICLE

The tamoxifen paradox—influence of adjuvant tamoxifen on fracture risk in pre- and postmenopausal women with breast cancer

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Received: 29 April 2018 / Accepted: 11 July 2018 / Published online: 21 July 2018

Abstract

Summary Our data demonstrate that tamoxifen does not reduce fracture risk. Close surveillance is necessary to prevent bone loss in premenopausal women with breast cancer upon treatment initiation.

Introduction Endocrine treatment of breast cancer may interfere with bone turnover and influence fracture risk.

Methods Out of a cohort of almost 5 million patients in total, we identified 5520 women between 18 and 90 years of age with breast cancer receiving tamoxifen, matched them with 5520 healthy controls using the Disease Analyzer Database, and investigated the fracture risk.

Results We found a cumulative incidence of fractures of 6.3% in patients aged between 18 and 50 years ($n = 3634$) treated with tamoxifen versus a cumulative incidence of 3.6% in the control group ($p < 0.001$). As such, the risk of fracture was 75% higher for patients receiving tamoxifen than that for healthy controls (HR 1.75; 95% CI 1.25–2.48). With regard to patients aged between 55 and 90 years ($n = 7406$), the cumulative incidence of fractures in patients treated with tamoxifen was 10.1% compared to 9.3% in the control group ($p = 0.740$), i.e., there was no significant difference between the two groups (HR 0.97; 95% CI 0.81–1.16).

Conclusions Compared to healthy controls, premenopausal women with breast cancer treated with tamoxifen showed an increased risk of fracture, while postmenopausal women on tamoxifen did not show any risk reduction.

Keywords Breast cancer · Fracture risk · Menopause · Osteoporosis · Tamoxifen

Introduction

Breast cancer (BC) is the most common malignancy in women, accounting for over 40,000 deaths every year in the USA, while one in eight women worldwide will develop BC in her lifetime [1]. Increasing knowledge about the underlying pathophysiological mechanisms of BC has led to the introduction of endocrine treatment of subtypes positive for hormone receptor expression. Tamoxifen is a selective estrogen receptor modulator (SERM) indicated for hormone receptor-positive BC. With regard to its mechanism of action, it has partial agonistic and antagonistic characteristics. Depending on the menopausal status, tamoxifen may have positive or negative skeletal effects [2–6].

In contrast to premenopausal women, treatment with tamoxifen in postmenopausal women with BC is known to stabilize or even increase bone mineral density (BMD) [3, 7]. A randomized placebo-controlled trial by Love et al. [3] showed an increase in BMD in women receiving tamoxifen compared to an annual decrease of almost 1% in the control group, while a significant decrease in the incidence of fractures was observed [8]. Apart from this, the study also revealed a significant improvement in bone structure analysis results [5]. However, the question of whether the antagonistic properties of tamoxifen have differential effects on bone depending on

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the menopausal status [9] remains unanswered. A population-based study by Melton et al. [10] showed that the fracture risk appeared to be greater among women undergoing specific BC treatments, especially those who were premenopausal at diagnosis. Accordingly, fracture risk was higher among premenopausal women exposed to chemotherapy (HR 5.2; 95% CI 2.1 to 13) and tamoxifen (HR 2.5; 95% CI 1.1 to 5.6). Notably, these findings appeared to be accounted for mainly by the strong association between these risk factors and pathologic fractures, which were more common among premenopausal women. Similarly, the Women's Health Initiative Observational Study presented an increased risk of symptomatic vertebral fractures in women whose BC was diagnosed before the age of 55 [11].

Since the majority of the data is conflicting, especially with regard to premenopausal patients, we sought to investigate the long-term effect of tamoxifen on fracture risk separately for pre- and postmenopausal women with BC. These data are of the utmost importance since, for the first time, we investigated the effects of tamoxifen on fracture risk in the largest case-control study to date rather than simply counting the patients with fractures who had received tamoxifen [10–12]. Considering that the vast majority of women with BC are long-term survivors, data on fracture risk is relevant for the optimization of treatment approaches aimed at combating cancer treatment-induced bone loss (CTIBL).

Methods

Database

This retrospective study is based on data from the IMS Disease Analyzer® database (IQVIA), which provides information on diagnoses, prescribed treatments, laboratory values, and demographic data obtained directly and in anonymous format from the computer systems used daily in the offices of participating physicians. The quality of the data is monitored by means of various quality criteria to ensure that the database provides valuable information on diagnoses (ICD-10), prescriptions (Anatomical Therapeutic Chemical (ATC) classification system), and other medical records. Reviews include checks for the latest coding behavior, gapless documentation, and linkage between diagnoses and prescriptions. The selection of physicians in the DA database complies with the requirements for representativeness [13]. Finally, this database has already been used in several studies focusing on fractures [14–17].

Study population

We identified all women with an initial breast cancer diagnosis (ICD-10: C50) documented by 196 physicians' offices between January 1995 and December 2015 in the UK Disease Analyzer database. From this collective, we included women who received their first tamoxifen prescription between 1995 and 2015 (index date), had not been treated with aromatase inhibitors prior to the index date, had a follow-up time of at least 365 days after the index date, and had no diagnoses of fractures or osteoporosis (ICD-10: S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12, T142, M80, M81) or bone active drugs such as bisphosphonates, denosumab, teriparatide, calcitriol, raloxifene, and glucocorticoids prior to index date. Treatment with heparin before recruitment was not an exclusion criterion. Finally, only women in the age groups 18–50 and 55–90 were included so as to classify women into pre- and postmenopausal groups, since no information was available about menopausal status.

After individual 1:1 matching based on age, index year, and body mass index (BMI) for each patient, a healthy control case was matched to each case with a diagnosis of breast cancer. Once this process was complete, 5520 patients with breast cancer who were receiving tamoxifen and 5520 control patients were included in the analysis (Fig. 1).

Outcomes and variables

The risk of bone fracture was evaluated with respect to the use or non-use of tamoxifen. In addition to this division, the two age groups (18–50 and 55–90) were also taken into account.

Descriptive and clinical variables were investigated for the purpose of comparing the groups. Demographic variables included the age at event and clinical variables included the following diagnoses: diabetes (ICD-10: E10, E11, E14), disorders of bone density (ICD-10: M82-M85), dementia/Alzheimer's disease (ICD-10: F01, F03, G30), and visual disturbances (ICD-10: H53, H54).

Statistical analysis

The statistical measures for the matched case and control groups consisted of descriptive analyses for demographic and clinical variables. Mean and standard deviation (SD) values were calculated for age, while shares were calculated for the other variables. The site of fractures was indicated for women with breast cancer treated with tamoxifen and non-cancer controls in both age groups. The risk of fracture was evaluated using a Cox regression model based on patient characteristics using hazard ratios (HR) and confidence intervals (CI) of 95%. P values < 0.05 were considered statistically significant. Data were analyzed using version 9.4 of the SAS statistical software.

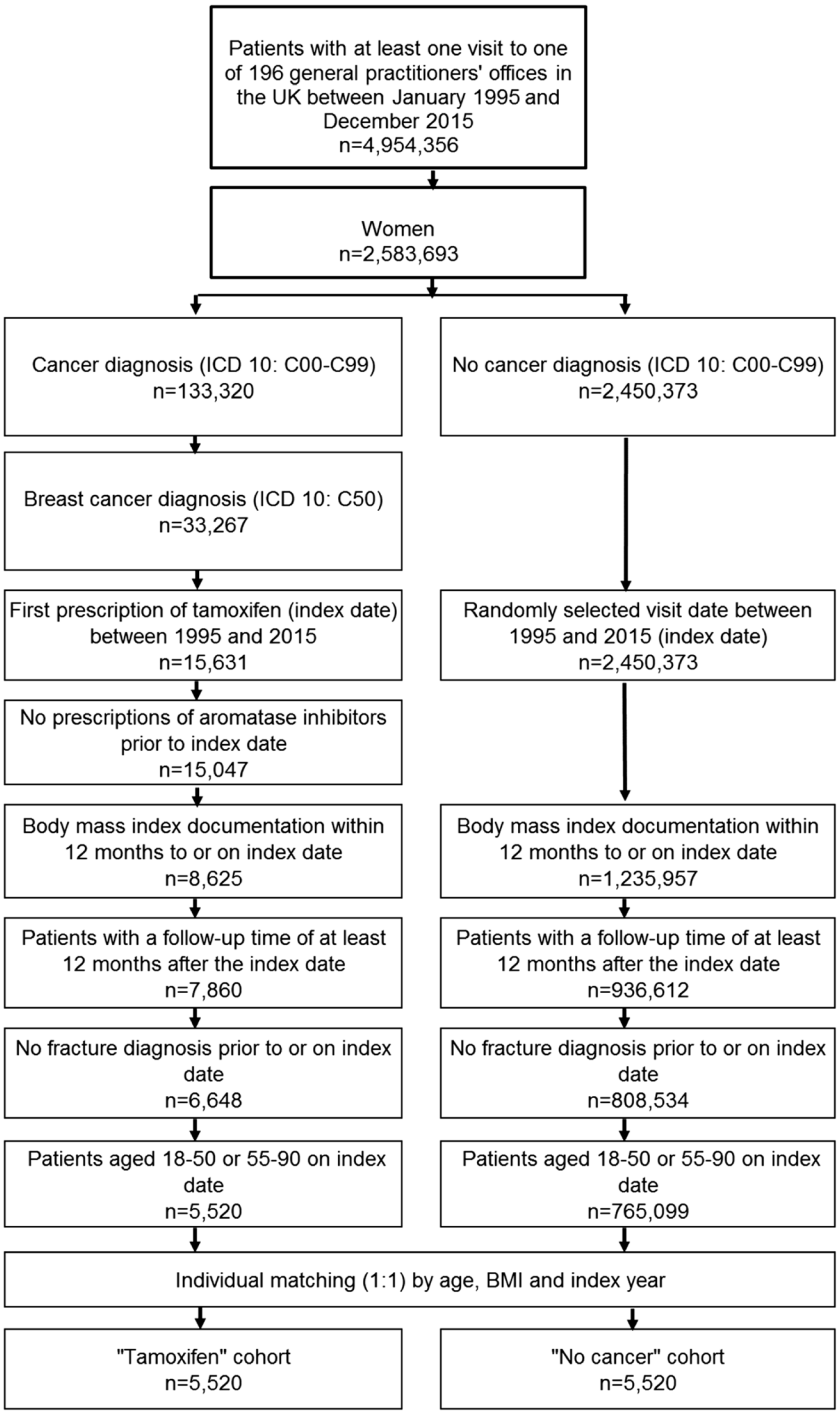

Fig. 1 Selection of study patients

Results

In total, 5520 BC patients receiving tamoxifen treatment and 5520 matched controls documented between January 1995 and December 2015 were identified. The consort diagram is depicted in Fig. 1. Out of a patient collective of almost 5 million patients with at least one visit to 1 of the 196 general practitioners' offices in the UK between 1995 and 2015, we extracted women with BC treated with tamoxifen ($n = 5520$) and compared them with healthy controls without any cancer diagnosis ($n = 5520$). Patients with fracture diagnosis or a follow-up time of less than 12 months were already excluded from these cohorts. Table 1 shows the baseline characteristics of women with BC treated with tamoxifen and non-cancer controls after matching for age, BMI, and index year. In order to perform sensitivity analyses based on age, we divided the

Table 1 Baseline characteristics of women with breast cancer treated with tamoxifen and non-cancer controls after (1:1) matching

Variable	Age 18–50		Age 55–90	
	Tamoxifen (%)	No cancer (%)	Tamoxifen (%)	No cancer (%)
N	1817	1817	3703	3703
Age at baseline (mean, SD)	44.1 (5.2)	44.1 (5.2)	68.1 (8.9)	68.1 (8.9)
Age 18–30	2.0	2.0		
Age 31–40	20.4	20.4		
Age 41–50	77.6	77.6		
Age 55–60			24.2	24.2
Age 61–70			39.6	39.6
Age 71–80			26.7	26.7
Age 81–90			10.5	10.5
Diagnosis within 12 months prior to the index date				
Diabetes mellitus (E10-14)	2.0	2.9	9.8	11.1
Dementia (F01, F03, G30)	0.0	0.0	0.7	0.9
Disorders of bone density and structure (M82-M85)	0.1	0.2	0.7	0.9
Visual disturbances (H53, H54)	1.9	2.5	7.5*	11.1*

*$p < 0.05$

patients into two cohorts. Patients aged between 18 and 50 were included in the premenopausal cohort while patients aged between 55 and 90 were included in the postmenopausal cohort. The mean age (SD) at diagnosis in the 18–50 and 55–90 cohorts was 44.1 (5.2) years and 68.1 (8.9) years respectively.

Among patients aged between 18 and 50 years ($n = 3634$), we found a cumulative incidence of fractures of 6.3% in patients treated with tamoxifen versus a cumulative incidence of fractures of 3.6% in the control group ($p < 0.001$). As such, the risk of fracture was 75% higher in patients receiving tamoxifen than that in healthy controls (HR 1.75; 95% CI 1.25–2.48) (Fig. 2).

With regard to patients aged between 55 and 90 years ($n = 7406$), the cumulative incidence of fractures in patients treated with tamoxifen was 10.1% compared to 9.3% in the control group ($p = 0.740$), i.e., there was no significant difference between the two groups (HR 0.97; 95% CI 0.81–1.16) (Fig. 3).

A series of sensitivity analyses was conducted. With regard to diagnoses within 12 months prior to the index date, there were no differences between patients receiving tamoxifen and healthy controls. In particular, the prevalence of disorders of bone density and structure did not differ between the two study groups. Notably, patients with fractures prior to the index date were excluded before matching. Interestingly, the only difference observed in the age group of 55–90 years

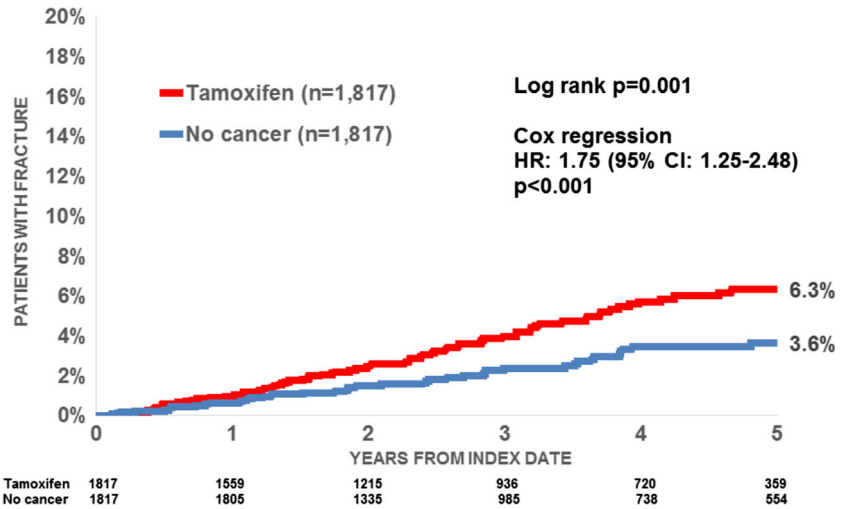

Fig. 2 Cumulative incidence of fractures in women aged 18–50 with breast cancer treated with tamoxifen and non-cancer controls

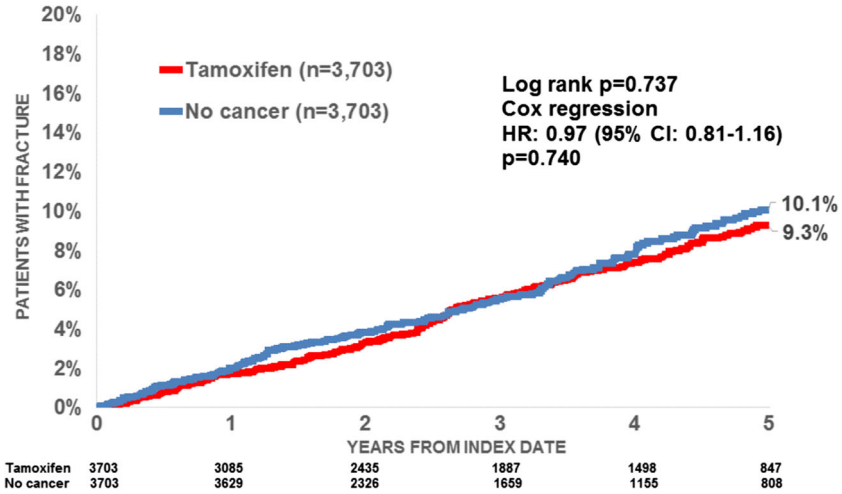

Fig. 3 Cumulative incidence of fractures in women aged 55–90 with breast cancer treated with tamoxifen and non-cancer controls

was in the variable regarding visual disturbances, with patients treated with tamoxifen presenting with a lower prevalence of fractures at 7.5% versus 11.1% in the control group ($p < 0.05$) (Table 1). Figures 4 and 5 show the types of clinically diagnosed fractures. As indicated, the highest prevalence of fractures in premenopausal women with BC treated with tamoxifen was observed in the feet (21%) and the lowest in the legs (17%), while the highest prevalence of fractures in postmenopausal women treated with tamoxifen was recorded in the forearm (25%) and the femur (19%).

Discussion

The present large-scale population-based case-control study confirms the negative impact of tamoxifen treatment on bone density and especially fracture risk in premenopausal women with BC. We found a 75% higher fracture risk in premenopausal patients receiving tamoxifen compared to healthy controls. With regard to postmenopausal patients receiving tamoxifen, there was no significant association with fracture risk. Interestingly, however, the incidence of fracture also did not decline below that of the control groups. In premenopausal women treated with tamoxifen, the highest prevalence of fractures was confined to the appendicular skeleton, especially the lower extremity. Notably, many vertebral fractures are considered to be asymptomatic and may only be discovered incidentally. Certainly, women with BC receive more imaging procedures than healthy controls generally do, which raises the possibility of ascertainment bias. Regarding postmenopausal women, we observed the most fractures in the forearm and the femur for both women treated with tamoxifen and healthy controls.

Generally, BC has been identified as a risk factor for subsequent fractures [18], although some studies have found positive associations with fracture risk at certain sites [19] and others have not [19–21]. In this context, it should be noted that self-reported vertebral fractures as well as ascertainment through administrative databases may be suspect because of the increased risk of confounders and indication bias [10]. Furthermore, various cancer-specific treatments interfere with bone turnover, leading to accelerated cancer treatment-

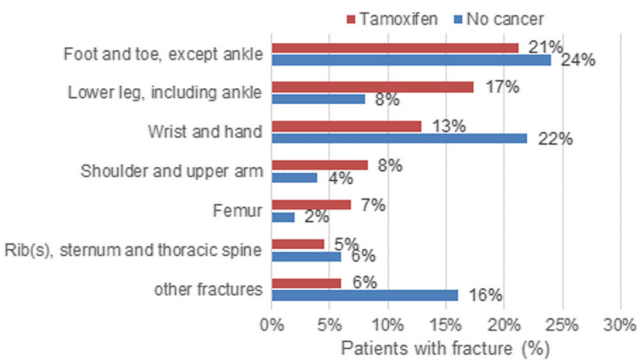

Fig. 4 Fracture sites in women aged 18–50 with breast cancer treated with tamoxifen and non-cancer controls

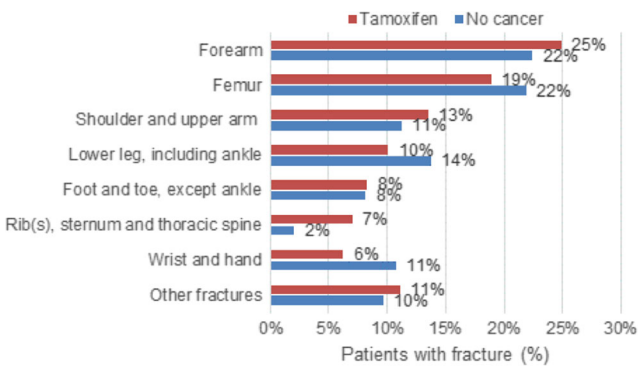

Fig. 5 Fracture sites in women aged 55–90 with breast cancer treated with tamoxifen and non-cancer controls

induced bone loss and increased fracture risk [22, 23]. Here, circulating estrogens represent the mediator for the increased risk of BC and in parallel a protective factor for cancer treatment-induced bone loss [24], while they directly influence bone metabolism via estrogen receptors on osteoblasts, osteoclasts, and osteocytes. Indirectly, estrogens have an impact on cytokines such as the transforming growth factor-ß, leptin, neuropeptide Y, tumor necrosis factor, insulin-like growth factor 1, and specific interleukins such as IL-1 and IL-6 [22, 25]. In this context, GnRH analogues, chemotherapy, and tamoxifen in premenopausal women as well as chemotherapy and aromatase inhibitors (AI) in postmenopausal women dysregulate this balance, mainly through interaction with serum estrogens, and result in BMD decrease as well as loss of the normal bone architecture [26, 27].

According to previous reports [10], after the exclusion of pathologic fractures and those detected incidentally, the overall fracture risk in tamoxifen users was significantly higher, at 2.5 and 1.4 times higher for pre- and postmenopausal women respectively compared to healthy controls. These findings highlight the impact of tamoxifen on fracture risk among breast cancer survivors since the overall fracture risk associated with BC was found to be non-significantly 1.19 times higher in a case-control study from Denmark [20] and also 1.3 times higher in the hip, spine, and wrist among prevalent BC cases in the Women's Health Observational Study [11]. Indeed, another study from Canada [28] even found a lower OR in the order of 0.86 for hip, spine, and wrist fractures in a case-control study, while Chen et al. [19] reported a HR of 1.02 for overall self-reported fracture risk after an incident of BC, as documented in the Women's Health Initiative. Similarly, a study by Utz et al. [29] also found no association between BC and non-pathologic fractures.

With regard to tamoxifen, Vestergaard et al. [12] investigated the fracture risk among BC survivors with fractures and confirmed a significant trend toward fewer fractures with increasing doses of tamoxifen, especially above 20 mg/day. While there was no association between the overall changes in fracture risk within the doses usually administered in this study, the authors reported an increased risk of hip fracture. In line with these findings, Kristensen and colleagues [30] also observed an increased risk of femoral fractures in BC patients receiving 30 mg/day of tamoxifen. According to the authors, the increase was not attributed to the pharmacological properties of tamoxifen but rather to factors determining the discontinuation of tamoxifen, such as progressive disease, e.g., bone metastases necessitating a more aggressive treatment approach such as AI or chemotherapy.

In accordance with previous reports [12], we did not find that tamoxifen had any protective effect with regard to non-vertebral fractures. In postmenopausal women, the prevalence of fracture at the femur was 19% in tamoxifen users compared to 22% in healthy controls. This finding is consistent with the absence of an effect of other SERMs such as raloxifene on the risk of non-vertebral fractures in postmenopausal women with osteoporosis [31]. As such, tamoxifen may not be effective in preventing non-vertebral fractures in women with BC. Notably, tamoxifen and raloxifene have an estrogen receptor alpha-selective partial agonist and antagonist function but a pure antagonist effect on estrogen receptor beta, which is commonly found in cortical bone [32]. Apart from this, tamoxifen is known for its strong affinity on the estrogen receptor alpha found in the axial skeleton, which might explain the reduction of vertebral fractures in some studies [33]. Generally, postmenopausal osteoporosis is a generalized phenomenon that affects both trabecular and cortical bone [34]. Still, the most common site of fracture in women with BC is the spine [35]. Although our findings do not support previous reports that tamoxifen may prevent cancer treatment-induced bone loss and reduce fracture risk in postmenopausal patients with early-stage hormone receptor-positive BC [4, 5, 36], neither does it seem to be harmful to bone health, like the use of aromatase inhibitors (AI) [37].

The present study is subject to certain limitations. First of all, no valid information on TNM status or documentation was available in the database. Furthermore, the assessment of comorbidity relied on the documentation of ICD codes by general practitioners and not oncologists. Moreover, no data was available regarding menopausal status, meaning that age-matched controls may not always have entered menopause or vice versa. Most importantly, there is a lack of data about chemotherapy or accompanying endocrine treatment with GnRH analogues, although GnRH analogues are infrequently used in the treatment of premenopausal women with BC in the UK. In this context, the recently published ProBONE II trial [38] showed a continuous decrease of bone mineral density over the entire study period in premenopausal patients receiving chemotherapy or endocrine treatment. Data regarding further fracture-related risk factors, such as parental history of hip fracture, socioeconomic status, or lifestyle (smoking, alcohol, physical activity) were not available. Another important aspect is the absence of information about patient persistence with regard to medication. As such, there was no possibility to consider the impact of persistence on fracture risk. However, we estimated persistence by counting the number of prescribed refills and considered patients with a follow-up time of at least 12 months after the index date. The major strengths of our study are the large size of the cohorts and the completeness of reporting. Finally, we provide data on facture risk in a large number of premenopausal patients and underline the negative aspects in this high-risk population. Considering that the number of long-term survivors of BC is steadily increasing, information about fracture risk, especially in younger premenopausal patients, is becoming extremely valuable.

In conclusion, tamoxifen does not seem to prevent fracture risk in postmenopausal women with BC compared to the

general population, while premenopausal patients showed an increased risk of fracture. Close surveillance is necessary for this high-risk population and cancer treatment-induced bone loss prevention should be considered as early as possible.

Compliance with ethical standards

Conflicts of interest None.

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