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ORIGINAL REPORT

Tamoxifen Use and Osteoporotic Fracture Risk: A Population-Based Analysis

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ABSTRACT

Purpose
Although tamoxifen has been shown to increase bone mineral density in clinical trials, it is less clear whether this significantly affects fracture rates. Even fewer data are available on skeletal outcomes when tamoxifen is used outside of the context of a clinical trial. A population-based case-control study was undertaken to determine whether tamoxifen use is associated with osteoporotic fractures in routine clinical practice.

Patients and Methods
Population-based administrative data for the Province of Manitoba, Canada, were examined for tamoxifen use and nontraumatic fracture codes in women 50 years of age or older. Women with osteoporotic fractures (vertebral, wrist or hip; n = 11,096) from 1996 to 2004 were each compared with three controls without fracture, matched for age, ethnicity, and comorbidity (n = 33,209). Tamoxifen use was classified as never, past use, or current use.

Results
Lower osteoporotic fracture rates were associated with current tamoxifen use (univariate odds ratio [OR] = 0.68; 95% CI, 0.55 to 0.84). After controlling for demographic and medical diagnoses known to affect fracture risk, current use was associated with a significantly reduced overall osteoporotic fracture risk (adjusted OR = 0.68; 95% CI, 0.55 to 0.88) and of hip fractures (adjusted OR = 0.47; 95% CI, 0.28 to 0.77). Neither recent nor remote past tamoxifen use was associated with reduced osteoporotic fracture risk. Breast cancer was not independently associated with osteoporotic fractures (adjusted OR = 0.95; 95% CI, 0.81 to 1.12).

Conclusion
In a population-based case-control study, current tamoxifen use was associated with a substantial reduction in osteoporotic fractures.

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INTRODUCTION

Osteoporosis and its clinical expression, fragility fractures, have large public health implications. Worldwide, the number of fracture sufferers in 2000 was estimated at 56 million with approximately 9 million new osteoporotic fractures each year.[1] The worldwide prevalence and disability associated with osteoporotic fractures is projected to result in a loss of 5.8 million disability-adjusted life years. Osteoporosis costs $13.8 billion annually in the United States alone.[2]

Breast cancer survivors are at increased risk for osteoporosis[3] and all types of fractures.[4] This has been attributed to the effects of chemotherapy, ovarian failure, early menopause, and, recently, aromatase inhibitors (eg, letrozole). Despite widespread use for many years, it is not clear what effect adjuvant tamoxifen has on osteoporotic fractures rates. One breast cancer prevention study in women receiving tamoxifen or placebo found a reduction in fractures.[5] Three other prevention studies of tamoxifen versus placebo have not reported such an effect[6-8] but may be confounded by hormone replacement therapy or the age of participants included, and may be limited by smaller sample sizes. Tamoxifen adjuvant trials have not reported an effect on fractures.[9-11] There are data to show tamoxifen has a favorable effect on bone mineral density (BMD) in postmenopausal women[12] but it has been difficult to demonstrate that this translates into a reduced incidence of osteoporotic fracture.

Studies in breast cancer patients receiving adjuvant tamoxifen versus aromatase inhibitors have documented a reduced risk of fracture.[13-17] It is notable that placebo arms were not included, so the effect of aromatase inhibitors alone is not clear.

With greater use of aromatase inhibitors, it is important to establish the effect of tamoxifen alone on osteoporotic fractures so that the risk of fracture from aromatase inhibitors can be placed in the proper context. We therefore examined the effect of tamoxifen on osteoporotic fracture in a population-based case-control study.

PATIENTS AND METHODS

A case-control study was conducted using de-identified population-based administrative health data from the Manitoba Department of Health (Manitoba Health; Winnipeg, Manitoba, Canada) housed at the Manitoba Centre for Health Policy (MCHP) of the University of Manitoba.[18,19] Manitoba Health provides comprehensive health care coverage for essentially all residents of the Province of Manitoba. Because Manitoba residents are not obliged to pay premiums for this coverage, nonparticipation in the plan is rare and claims data are relatively complete for the entire population.

Manitoba Health maintains computerized databases of most physician services and all hospitalizations provided for all persons registered from the year 1970 until the present. All Manitoba residents have a unique personal health identification number (PHIN) through which all health system encounters are tracked. A computerized record of all outpatient pharmaceutical dispensations occurring since April 1, 1995, is also maintained allowing pharmacists to check for drug interactions, therapeutic duplications, and compliance information before dispensing a prescription drug. In addition to a unique numeric non-nominal personal identifier, each prescription record contains the date of dispensation; an exact identification of the dispensed drug, including substance, strength, route, and dosage form; the number of doses provided; the anticipated duration of the prescription in days; and a code for prescribing physician and dispensing pharmacy. All drugs are classified according to the Anatomic Therapeutic Chemical (ATC) system of the WHO Collaboration Centre for Drugs Statistics Methodology. The pharmacy database has been deemed accurate both for capture of drug dispensations and for capture of prescription details.[20] Each physician and hospital system contact includes information on date and type of service and diagnoses, which are coded using the International Classification of Diseases Ninth Clinical Modification (ICD-9-CM). The PHIN allows for linkage of physician and hospital records, prescription drug dispensations, and information on demographic characteristics contained in a population registry. A longitudinal record of a person's health service use can be created from these files. The accuracy of these administrative data has been established for a wide range of clinical disorders including fractures by the MCHP.[21]

This study was approved by the University of Manitoba Health Research Ethics Board. Access to data was granted by the Manitoba Health Information Privacy Committee.

Study Population

Women 50 years of age or older with a first osteoporotic fracture (ICD-9-CM code 805 for vertebral fracture without cord injury, ICD-9-CM code 813 for wrist fracture, and ICD-9-CM code 820-821 for hip fracture plus a physician claim for hip fracture reduction or fixation) from April 1, 1996, to March 31, 2004, were selected as cases for the study. Age and sex were taken from the registry at of the date of fracture. Each case was randomly matched to three controls by year of birth (within 5 years), ethnicity (Aboriginal *v* non-Aboriginal) and a comorbidity index as defined herein (0, 1 to 2, 3 to 5, or $\geq$ 6 ambulatory diagnostic groups in the year before the case fracture).

Aboriginal ethnicity was primarily determined by the Canadian Government's Status Verification System maintained by First Nations and Inuit Health Branch and Indian and Northern Affairs Canada, with a treaty status code in the Manitoba Health registry providing a secondary indicator of ethnicity.[22] The Johns Hopkins Ambulatory Care Group system was used to develop an index of population comorbidity.[23] This system has been validated by MCHP to predict premature mortality and use of medical services in Manitoba.[24] Ambulatory diagnostic groups (ADGs) represent 32 comorbidity clusters of ICD-9-CM diagnostic codes. Depending on the ICD-9-CM codes an individual receives over a period of 1 year, the number of ADGs can range from 0 to 32. For this study, the number of ADGs was grouped as none (0), 1 to 2, 3 to 5, and 6 or more using a previous definition.[25] The controls were assigned the same index date as that of their matched fracture case.

Cases and controls were eligible for inclusion in the study if they had coverage for health services from Manitoba Health for the entire period from April 1, 1998, to March 31, 2004, or until death unless death occurred during drug exposure and before fracture, at which point the participant was excluded. Other exclusions included residence in a long-term care facility because prescription drug dispensations are maintained for outpatients only, and osteoporosis drug use in the year before the index date (selective estrogen-receptor modulators, natural and semisynthetic estrogens, bisphosphonates, parathyroid hormones, and salmon calcitonin).

Exposure to tamoxifen was categorized as never used, remote past use, recent past use, and current use. The categories were mutually exclusive. Current users had at least one dispensation within 120 days preceding the index date of the fracture. Recent past users had at least one dispensation in the 121 to 365 days preceding the case's index date and remote past users had at least one dispensation before 365 days preceding the index date. Nonusers had no recorded dispensations.

Ascertainment of Potential Confounders

Potential confounders included in this study were variables that could be accessed from the administrative data and which had been previously associated with risk of fracture.[26] In particular, we controlled for specific diagnostic definitions from ICD-9-CM codes from physician office visits and/or hospitalizations found during the 3 years before the patient's index date: breast cancer diagnosis, epilepsy, diabetes, ischemic heart disease, myocardial infarction, hypertension, rheumatoid arthritis, solid organ transplant, chronic obstructive pulmonary disease (COPD), substance abuse, depression, schizophrenia, dementia, and home care use. Measures of body mass index, BMD, current smoking status, activities of daily living score, and cognitive and physical impairment scores, which may represent potential confounders, cannot be assessed directly from the databases.

Region of residence (rural north, rural south, and urban Winnipeg) and neighborhood income quintiles (derived from 2001 Statistics Canada Census public-use files) were obtained for case and control participants. Mean household income for census enumeration areas was used to define quintiles from 1 [lowest] to 5 [highest], stratified separately for urban and rural residency.[27] Income quintiles were aggregated into lower and higher categories for statistical modeling.

Statistical Analysis

Conditional logistic regression analysis was used to calculate odds ratios (ORs) and 95% CIs. Sequential conditional logistic regression models estimated the probability of fracture controlling for demographic and confounding covariates as follows. The first (partially adjusted) model included demographic variables describing neighborhood income quintile (high income as reference), region of residence (urban as reference), and the interaction of income quintile and region of residence. The second (fully adjusted) model included all of the preceding and the potential confounding medical conditions listed previously. The likelihood ratio test confirmed a significant improvement in model fit with the fully adjusted over the partially adjusted model. Because of the nature of conditional logistic regression, matching variables of age, ethnicity, and ADG comorbidity index were not included as covariates in the model. All tabulations and statistical analysis used SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Table 1 summarizes the characteristics of 11,096 patients with osteoporotic fractures and 33,209 matched controls. A breast cancer diagnosis was present in 324 patients (2.9%) and 1,123 controls (3.4%). Approximately 72% of breast cancer patients had received tamoxifen at some time. The univariate OR for osteoporotic fracture was significantly lower in women with a diagnosis of breast cancer (OR = 0.86; 95% CI, 0.76 to 0.98). Current tamoxifen use was identified in 105 fracture cases (0.9%) and 459 controls (1.4%), and this was associated with lower osteoporotic fracture rates (OR = 0.68; 95% CI, 0.55 to 0.84). In contrast, remote or recent past tamoxifen use was unrelated to osteoporotic fractures.

Several potentially confounding diagnoses (epilepsy, rheumatoid arthritis, COPD, substance abuse, depression, schizophrenia, dementia, and home care use) were significantly associated with osteoporotic fractures in the unadjusted analyses (Table 1). Hypertension (OR = 0.90; 95% CI, 0.87 to 0.94) showed a small protective effect. Diabetes, ischemic heart disease, myocardial infarction, and solid organ transplant were not associated with the risk of fracture.

In partially adjusted models (Table 2) that controlled for sociodemographic variables, a significant protective association between

Table 1. Characteristics of Patients and Controls

Characteristic	Patients (n = 11,096)		Controls (n = 33,209)		Univariate Odds Ratio	95% CI
	No.	%	No.	%		
Age, years						
50-59	1,559	14.1	4,763	14.3	NA	
60-69	2,136	19.3	6,327	19.1		
70-79	3,293	29.7	10,113	30.5		
≥ 80	4,108	37.0	12,006	36.2		
Aboriginal ethnicity	484	4.4	1,436	4.3	NA	
No. of ADGs						
0	812	7.3	2,429	7.3	NA	
1-2	2,797	25.2	8,372	25.2		
3-5	4,207	37.9	12,604	38.0		
6 or more	3,280	29.6	9,804	29.5		
Fracture site						
Vertebral	2,019	18.2	0	0	NA	
Wrist	6,167	55.6	0	0		
Hip	2,910	26.2	0	0		
Residence						
Urban	6,556	59.1	19,079	57.5	Reference	
Rural south	4,161	37.5	13,072	39.4	**0.93**	**0.89 to 0.97**
Rural north	379	3.4	1,058	3.2	1.04	0.92 to 1.18
Income						
Lower	5,625	50.7	16,352	49.2	Reference	
Higher	5,471	49.3	16,857	50.8	0.97	0.94 to 1.01
Medical conditions						
Breast cancer diagnosis	324	2.9	1,123	3.4	**0.86**	**0.76 to 0.98**
Short-term diabetes	472	4.3	1,557	4.7	0.91	0.82 to 1.01
Long-term diabetes	1,169	10.5	3,357	10.1	1.04	0.97 to 1.12
Epilepsy	52	0.5	58	0.2	**2.68**	**1.84 to 3.90**
Ischemic heart disease	1,392	12.5	4,341	13.1	0.96	0.90 to 1.02
Myocardial infarction	328	3.0	954	2.9	1.03	0.91 to 1.17
Hypertension	4,049	36.5	13,394	40.3	**0.90**	**0.87 to 0.94**
Rheumatoid arthritis	237	2.1	581	1.7	**1.22**	**1.05 to 1.42**
Solid organ transplant	Suppressed		Suppressed		0.17	0.02 to 1.25
COPD	1,787	16.1	4,873	14.7	**1.10**	**1.04 to 1.16**
Substance abuse	277	2.5	392	1.2	**2.11**	**1.81 to 2.47**
Depression	1,190	10.7	2,605	7.8	**1.37**	**1.27 to 1.47**
Schizophrenia	105	0.9	142	0.4	**2.21**	**1.72 to 2.85**
Dementia	680	6.1	1,128	3.4	**1.80**	**1.64 to 1.99**
Home care use	2,906	26.2	5,941	17.9	**1.46**	**1.39 to 1.54**
Medication use						
Tamoxifen never used	10,869	97.95	32,399	97.56	Reference	
Remote past tamoxifen	81	0.73	228	0.69	1.06	0.82 to 1.37
Recent past tamoxifen	41	0.37	123	0.37	0.99	0.70 to 1.42
Current tamoxifen	105	0.95	459	1.38	**0.68**	**0.55 to 0.84**

NOTE. Cases and controls were matched according to sex, ethnicity, age, and number of ADGs. Statistically significant results ($P < .05$) are in bold. Counts for solid organ transplant recipients are suppressed because of small numbers (n < 5).
Abbreviations: NA, not applicable; AGD, ambulatory diagnostic group; COPD, chronic obstructive pulmonary disease.

Table 2. Adjusted Odds Ratios for Osteoporotic Fractures

Factor	Partially Adjusted Model			Fully Adjusted Model		
	Odds Ratio*	95% CI	*P*	Odds Ratio*	95% CI	*P*
Medication use						
Remote past tamoxifen	1.06	0.82 to 1.37	.6547	1.09	.83 to 1.43	.5400
Recent past tamoxifen	0.99	0.69 to 1.41	.9511	0.97	.66 to 1.41	.8643
Current tamoxifen	**0.68**	**0.55 to 0.85**	.0005	**0.69**	**.54 to .88**	.0033
Medical conditions						
Breast cancer diagnosis		NA		0.95	0.81 to 1.12	.5588
Short-term diabetes		NA		**0.89**	**0.80 to 0.99**	.0398
Long-term diabetes		NA		1.00	0.93 to 1.07	.9535
Epilepsy		NA		**2.27**	**1.55 to 3.32**	< .0001
Ischemic heart disease		NA		**0.91**	**0.85 to 0.98**	.0096
Myocardial infarction		NA		0.98	0.85 to 1.12	.7704
Hypertension		NA		**0.85**	**0.81 to 0.89**	< .0001
Rheumatoid arthritis		NA		1.13	0.97 to 1.33	.1164
Organ transplant		NA		0.14	0.02 to 1.02	.0518
COPD		NA		**1.08**	**1.01 to 1.14**	.0201
Substance abuse		NA		**1.72**	**1.46 to 2.03**	< .0001
Depression		NA		**1.30**	**1.20 to 1.40**	< .0001
Schizophrenia		NA		**1.69**	**1.31 to 2.19**	< .0001
Dementia		NA		**1.39**	**1.25 to 1.55**	< .0001
Home care use		NA		**1.79**	**1.68 to 1.91**	< .0001

NOTE. Statistically significant results ($P < .05$) are in bold.
Abbreviation: COPD, chronic obstructive pulmonary disease.
*Adjusted for demographic variables (income, region of residence, and the interaction of income with region of residence).

current tamoxifen use and osteoporotic fracture was observed (OR = 0.68; 95% CI, 0.55 to 0.85). Once again, past tamoxifen use showed no association with osteoporotic fracture rates. Full adjustment for breast cancer and other medical conditions did not weaken the protective effect of current tamoxifen use (OR = 0.69; 95% CI, 0.54 to 0.88).

The fully adjusted ORs for site specific fracture rates are shown in Figure 1. Women with hip fracture were significantly less likely to be current tamoxifen users (adjusted OR = 0.47; 95% CI, 0.28 to 0.77). ORs for wrist fractures alone (0.84; 95% CI, 0.60 to 1.18) and spine fractures alone (0.73; 95% CI, 0.43 to 1.25) showed a similar trend but were not statistically significant.

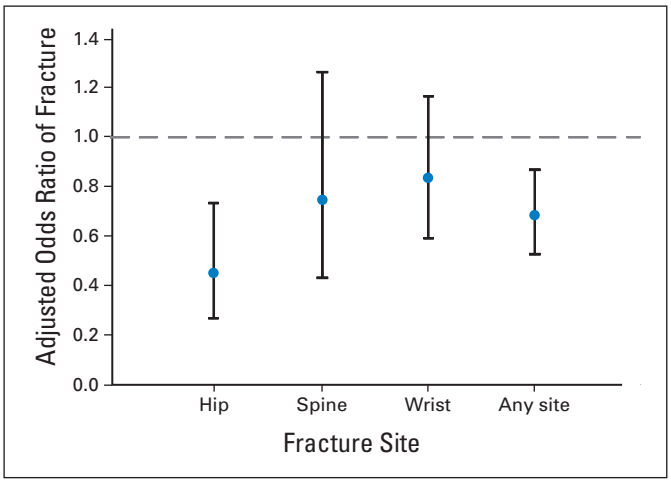

Fig 1. Adjusted odds ratios for fracture in current tamoxifen users according to fracture site.

DISCUSSION

Our study has shown a significant protective effect of current tamoxifen use on osteoporotic fractures. The strength of this effect was consistent across unadjusted and multiple adjusted analyses. In contrast, past tamoxifen use was unrelated to osteoporotic fractures. Tamoxifen users will be overwhelmingly breast cancer patients in our study because of low acceptance of tamoxifen for prevention.[28]

The possible confounding effect of a breast cancer diagnosis merits discussion. We found that breast cancer was less common in cases than in controls. Serum estrogen is a risk factor for breast cancer[29] and serum estrogen is expected to confer a reduced risk for osteoporotic fracture because of its effect on BMD.[30] BMD and breast cancer risk should therefore be associated, possibly confounding the effect of tamoxifen. An association between metacarpal BMD and breast cancer was demonstrated in women age 47 to 80 years in the Framingham study. After a median 22 years of follow-up, the age adjusted incidence rate ratio of breast cancer was highest among women in the upper quartile of bone mass (3.5; 95% CI, 1.8 to 6.8).[31] Therefore, it is possible that the reduced risk of osteoporotic fracture in tamoxifen users is because of prior endogenous estrogen exposure, which has resulted in both breast cancer with a subsequent need for tamoxifen and the reduced risk of fracture. The observation that past users are not protected from osteoporotic fractures whereas current users are suggests that such confounding can not fully account for the findings in our study.

In the fully adjusted model (Table 2) breast cancer was not associated with an increased risk of osteoporotic fracture. This finding is consistent with the Women's Health Initiative (WHI) study, which found no increased risk of hip fractures (adjusted hazard ratio [HR] = 0.93; 95% CI, 0.64 to 1.33) or clinical vertebral fractures for

women with a diagnosis of breast cancer after age 55 years (HR = 1.01; 95% CI, 0.72 to 1.42), although clinical vertebral fractures in women with breast cancer diagnosed before age 55 years (HR = 1.78; 95% CI, 1.28 to 2.46), forearm/wrist fractures (HR = 1.36; 95% CI, 1.16 to 1.59), and total fractures (HR = 1.31; 95% CI, 1.21 to 1.41) were increased.[4] Notably, only hip fractures were radiographically verified in the WHI study, and all other fractures were from self-report. Our use of physician and hospital diagnosis records are therefore likely to be more accurate for nonhip fractures. Data from the Surveillance, Epidemiology, and End Results (SEER) database show a reduced incidence of hip fracture (relative risk [RR] = 0.63; 95% CI, 0.43 to 0.94) in elderly breast cancer survivors.[32] There may be some discordance between osteoporotic fracture rates and total fractures in postmenopausal breast cancer survivors if tamoxifen only affects the former. A study of 352 breast cancer patients showed a five-fold increase in incident radiographic vertebral fracture versus controls but did not address clinical incidence.[33]

In a Danish study of 1,716 postmenopausal breast cancer patients randomly assigned to tamoxifen 30 mg/d for 1 year, there was no effect when all femoral fractures (HR = 1.08; 95% CI, 0.74 to 1.55) or femoral neck fractures were considered (HR = 0.86; 95% CI, 0.51 to 1.42), but the hazard ratio for the trochanteric fracture subgroup with tamoxifen was 2.12 (95% CI, 1.12 to 4.01). Most fractures in this study occurred years after tamoxifen was discontinued.[31]

Not all potential confounding factors are considered in our models. Proxy variables (eg, COPD for smoking, home care use for functional status, dementia diagnosis for cognitive function) were included where possible. Adjustment for the presence of multiple medical conditions did not appreciably alter the protective effect of current tamoxifen use, which argues against major confounding.

The choice of fracture diagnosis codes was intentionally limited to those types of fracture most clearly related to osteoporosis and does not include all types of fractures. It is possible that women with vertebral or hip fractures resulting from metastatic breast cancer would be included as cases thereby diluting the proportion of cases resulting from osteoporosis. If fractures resulting metastases occurred while patients were receiving tamoxifen for advanced disease, this would reduce the possibility of detecting a significant protective effect for current use on osteoporotic fractures. We recognize that, during the years of this study, some tamoxifen use would have been for metastatic disease. Fractures resulting from metastases occurring after the cessation of adjuvant tamoxifen would make it more difficult to demonstrate any late protective effect. The presence of osseous metastases could not be excluded by determining pamidronate use because it is administered in hospital outpatient clinic settings and is not captured by the provincial drug database. Oral clodronate, administered for osseous metastases, would be an exclusion from the study. Finally, the majority of case fractures (56%) are wrist fractures, which are unlikely to be related to metastases.

At 7 years' follow-up in National Surgical Adjuvant Breast and Bowel Project (NSABP) P1, the largest placebo-controlled tamoxifen trial of any sort (N = 13,388) tamoxifen reduced all fractures in women 50 years of age or older (RR = 0.71; 95% CI, 0.52 to 0.97)[5] and hip, spine, and Colles' fractures (RR = 0.68; 95% CI, 0.51 to 0.92). In the NSABP P2 study,[34] the total number and specific sites of fracture was similar for tamoxifen versus raloxifene, which is known to reduce vertebral fractures versus placebo.[35,36] Prevention studies include no breast cancer patients by definition, and the findings may not be generalizable to patients taking tamoxifen.

Preservation of BMD by tamoxifen in postmenopausal women should be associated with a reduced risk for osteoporotic fracture. BMD is a surrogate measurement for osteoporotic fracture risk, and can be demonstrated earlier and with a smaller sample size than is required to show a reduced fracture rate. Tamoxifen preserves BMD in the lumbar spine over 5 years of treatment in postmenopausal women,[37] and in the femoral neck.[38] A review of the effect of tamoxifen on BMD found 27 peer-reviewed articles that investigated the relationship of tamoxifen and bone health in postmenopausal women.[12] The authors concluded that tamoxifen protected against bone loss in the hip and spine but not the wrist. A prevention trial BMD substudy demonstrated that tamoxifen accelerates bone loss in premenopausal women.[39]

There has been no large adjuvant study of aromatase inhibitors versus placebo except for National Cancer Institute of Canada (NCIC) MA.17,[40] but all patients in this trial were treated initially with tamoxifen. After 30 months of letrozole versus placebo, there was no difference in the incidence of clinical fractures (5.3% *v* 4.6%; $P = .25$), but new cases of osteoporosis were more common (8.1% *v* 6.0%; $P = .003$) with letrozole. Our study suggests any protective effect of prior tamoxifen use would be gone quickly after treatment was changed to letrozole.

The increased fracture risk seen with adjuvant aromatase inhibitors versus tamoxifen in clinical trials should be considered in the context of a possible protective effect of adjuvant tamoxifen on osteoporotic fracture. Our study suggests such a protective effect.

In a population-based case-control study of osteoporotic fracture in women 50 years of age and older, current use of tamoxifen was significantly higher in the controls, suggesting a protective effect of the drug. The effect was significant for all osteoporotic fractures combined and for hip fractures as a specific subgroup, and was independent of other diagnoses including breast cancer itself. However, because of the nature of the case-control design, causality cannot be inferred. The association of tamoxifen use with a reduced risk of osteoporotic fracture appears to be limited to the time a woman is actually taking the drug, and does not persist after the drug has been discontinued.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Colleen Metge, Lisa Lix, Heather J. Prior, William D. Leslie
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