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A Prospective Study of Lifestyle Factors and Bone Health in Breast Cancer Patients Who Received Aromatase Inhibitors in an Integrated Healthcare Setting

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Abstract

Purpose: Fracture and osteoporosis are known side effects of aromatase inhibitors (AIs) for postmenopausal hormone receptor positive (HR+) breast cancer (BC) patients. How modifiable lifestyle factors impact fracture risk in these patients is relatively unknown.

Methods: We conducted a prospective cohort study to examine the association of lifestyle factors, focusing on physical activity, with risk of incident major osteoporotic fracture and osteoporosis in 2,152 HR+ BC patients diagnosed from 2006–2013 at Kaiser Permanente Northern California and who received AIs. Patients self-reported lifestyle factors at study entry and at six-month follow-up. Fracture and osteoporosis outcomes were prospectively ascertained by physician-adjudication and bone mineral density (BMD) values, respectively. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated from multivariable proportional hazards regression. Models were adjusted for age, menopausal status, race/ethnicity, body mass index (BMI), AJCC stage, breast cancer treatment, prior osteoporosis, and prior major fracture.

Results: Over a median 6.1 years of follow-up after AI initiation, 165 women experienced an incident osteoporotic fracture and 243 women had osteoporosis. No associations were found between overall moderate-vigorous physical activity and fracture risk, although <150 minutes/week of aerobic exercise in the six months after BC diagnosis was associated with increased fracture risk (HR=2.42; 95% CI: 1.34, 4.37) compared to ≥150 minutes/week (meeting physical activity guidelines). Risk was also higher for never or infrequently engaging in aerobic exercise

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This study was approved by the KPNC Institutional Review Board and informed consent was obtained from all study participants.

This study was performed in accordance with the ethical standards in the principles of the Declaration of Helsinki.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

(HR=1.90; 95% CI: 1.05, 3.44). None or infrequent overall moderate-vigorous physical activity in the six months before BC diagnosis was associated with increased risk of osteoporosis (HR=1.94; 95% CI: 1.11; 3.37).

Conclusions: Moderate-vigorous physical activity during the immediate period after BC diagnosis, particularly aerobic exercise, was associated with lower risk of major osteoporotic fractures in women on AI therapy.

Implications for Cancer Survivors: Findings may inform fracture prevention in women on AI therapy through non-pharmacologic lifestyle-based strategies.

Keywords

breast cancer; aromatase inhibitor; hormone therapy; endocrine therapy; bone; major osteoporotic fracture; fragility fracture; osteoporosis; bone mineral density; physical activity; aerobic exercise; diet; smoking; alcohol; vitamin supplements

Introduction

Breast cancer patients may experience numerous side effects resulting from receipt of systemic adjuvant therapy, one of which is bone loss and fracture. The effectiveness of aromatase inhibitor (AI) treatment for postmenopausal women with hormone-receptor positive breast cancer is well-documented [1, 2]; however, there are known adverse effects on bone health [3, 4]. Specifically, since AIs block aromatase enzyme activity, circulating estrogen levels decline and promote bone loss through a net increase in bone resorption. Women with breast cancer who are treated with AIs are also found to have increased risk of bone fracture compared to those treated with tamoxifen [3, 5].

Various modifiable lifestyle factors that have been identified as potentially protective against fractures in healthy women may also be relevant to fracture risk in breast cancer patients. These include physical activity, diet, and supplement use. However, few studies have been conducted in breast cancer patients. In healthy female populations, physical activity has been found to reduce risk of fractures, though its effects have been primarily in relation to hip fractures [6–9]. For example, one prospective study of 9,704 women found an increasing linear trend with up to 36% reduction in risk for hip fracture for total physical activity and a 42% reduction for moderate to vigorous recreational activities [6]. Another study demonstrated that the relationship of hip fracture and overall and strenuous exercise varies by body mass index, with normal weight women at higher risk than obese women [8].

The associations of diet and supplement use with risk of fracture have been mixed. Some studies of healthy women have found positive associations between a more healthful diet and reduced risk of fractures [10], while others did not find any association [11–14]. Similarly, use of calcium and vitamin D supplements has been widely studied, yet while some studies support the use of these supplements to reduce fracture risk and bone loss [15–17], others found no protective effect [18–20].

Given the elevated risk of fracture in breast cancer patients on AIs, and lack of studies on how modifiable lifestyle factors might affect fracture risk in this patient population,

we investigated the association of lifestyle factors on risk of osteoporosis and major osteoporotic fractures in 2,157 women who received AI therapy for early-stage, hormone-receptor positive breast cancer in the Pathways Study, one of the largest prospective cohorts of breast cancer survivors to date. Our primary focus was on the role of physical activity on bone health, but we also examined the impact of diet, smoking, alcohol consumption, and supplement use.

Methods

Study Population

The Pathways Study is a prospective study of 4,505 women with newly diagnosed invasive breast cancer who are members of Kaiser Permanente Northern California (KPNC), a large, integrated health care delivery system covering over 4.3 million members in the San Francisco-Oakland Bay Area, Sacramento, and surrounding counties. Recruitment was from January 2006 to April 2013 through rapid case ascertainment procedures designed to enroll women prior to initiation of chemotherapy, as described elsewhere [21]. Eligibility criteria included: KPNC female members at least 21 years of age; no previous history of malignancy other than non-melanoma skin cancer; spoke English, Spanish, Cantonese, or Mandarin; and resided within a 65-mile radius of a field interviewer. The mean time from diagnosis to enrollment was 2.0 (±0.7) months.

For this bone health study [22], women were included if they were initially dispensed at least one hormonal therapy prescription of an AI (anastrozole, letrozole, exemestane) that was indicated for treatment of their first primary breast cancer. Complete hormonal therapy prescription data were obtained through December 2017. A total of 23 women who initiated hormonal therapy (AI or tamoxifen) after recurrence of their original breast cancer or second primary breast cancer were excluded. The final study population for analysis was 2,152 women.

Clinicopathologic Characteristics

Clinical and diagnostic tumor characteristics were obtained from the KPNC Cancer Registry approximately four months post-diagnosis [23]. These included: stage at diagnosis, estrogen/progesterone receptor (ER/PR) status, human epidermal growth factor receptor 2 (Her2) status, surgery type, and treatment received.

Self-reported Participant Information

The baseline interview was conducted at the time of enrollment, and included interviewer and self-administered questionnaires on sociodemographics, physical activity, diet, alcohol consumption, smoking, breast cancer risk factors, health history, and use of vitamin/mineral supplements. Follow-up assessments to update lifestyle information were conducted at 6, 24, and 72 months after the baseline interview. For this analysis, we used baseline data for all lifestyle factors listed in Table 1 and also included 6-month follow-up data for physical activity given our primary focus on this exposure.

Physical activity was assessed using the validated Arizona Activity Frequency Questionnaire (AAFQ) [24]. The questionnaire asked for activity levels in the six months before breast cancer diagnosis (baseline) and in the six months after breast cancer diagnosis (6-month follow-up). Frequency, duration, and intensity of activities over the past six months in four main domains were queried: household, recreational, transportation, and sedentary. Three types of moderate-vigorous physical activity were also defined: 1) aerobic exercise (running/jogging, stairmaster/elliptical runner, aerobic dance or exercise class, cross-country skiing, indoor/outdoor rowing or skiing, hiking, walking at fast pace, playing sports, golfing not using a cart, dancing), 2) resistance exercise (push-ups, calisthenics, floor exercise, core strengthening exercise, yoga, stretching, Tai Chi, pilates), and 3) weight-training exercise (weightlifting, free weights, circuit training). Given that swimming and biking are not considered weight-bearing exercises that benefit bone health, they were excluded from the aerobic exercise definition. Tertiles of overall moderate-vigorous activity in minutes per week based on the cohort distribution were created, as well as categories of meeting or not meeting the 2018 Physical Activity Guidelines for Americans of doing at least 150 minutes per week or more of moderate-vigorous intensity aerobic activity [25].

Diet, including frequency and portion size, was assessed over the past six months using a 139-item modified version of the Block 2005 food frequency questionnaire (FFQ) (NutritionQuest, Berkeley, CA). Alcohol consumption (beer, wine, and liquor), including frequency and portion size, was also asked on the FFQ. Using these dietary data, the Healthy Eating Index-2015 (HEI-2015) was calculated using data from the baseline interview. The HEI-2015 is comprised of 12 components that sum to a maximum total score of 100 [26, 27].

Pharmacy Data

Prescription drug data for nearly 100% of KPNC enrollees is recorded in the KPNC pharmacy database [28]. The pharmacy database was accessed to identify any outpatient dispensed prescriptions of AIs (anastrozole, letrozole, and exemestane) after breast cancer diagnosis. Dispensed prescriptions of bisphosphonates (BP) any time before breast cancer diagnosis were also captured. BPs are inhibitors of bone resorption and commonly prescribed to treat osteoporosis and other related conditions.

Bone Mineral Density, Osteoporosis and Fracture Outcomes

Bone mineral density (BMD) values for the femoral neck, total hip, and lumbar spine were extracted from the radiology reports of dual-energy x-ray absorptiometry (DXA) scans in the KPNC electronic health record (EHR). Validated algorithms were developed for this purpose and previously reported [22]. BMD T-scores were calculated based on the young adult female peak BMD derived from reference data in non-Hispanic white women, as previously described [29]. Incident osteoporosis was defined by a BMD T-score of −2.5 or below, using the lowest T-score of the three sites measured (femur, hip and spine) to determine osteoporosis after initiation of AI therapy. Women were excluded from the osteoporosis analysis if they had evidence of osteoporosis prior to AI initiation.

Incident osteoporotic fractures after AI initiation were obtained from the EHR using ICD-9 codes through September 30, 2015. Major osteoporotic fractures were defined as those at the humerus, wrist, hip or spine. All encounter data were then manually reviewed by a medical record abstractor and subsequently validated by the study endocrinologist (J. Lo). Fractures associated with major trauma, prevalent fractures, and pathologic fractures including bone metastases were flagged and removed from the fracture analysis.

History of osteoporosis (based on clinical diagnosis) and history of major osteoporotic fractures before breast cancer diagnosis were obtained from the EHR using ICD-9 codes with supplemental data on BP use as an indicator of history of osteoporosis, as previously described [22].

Statistical Analysis

Median and range for continuous variables and frequency and percentage for categorical variables were used to summarize the characteristics of the patient population. For estimation of lifestyle factors with fracture risk, Cox proportional hazards regression models were developed with and without adjustment for age, and then fully adjusted for age, menopausal status, race/ethnicity, body mass index (BMI), AJCC stage, breast cancer treatment, and prior osteoporosis and major fracture before breast cancer diagnosis. The time scale for regression analyses was defined as time since AI initiation with follow-up until event, disenrollment from the health plan, death, or end of study, whichever occurred first. Hazards ratios (HR) and 95% confidence intervals (CI) were reported. Delayed-entry Cox regression models were used to examine physical activity measures at 6-month follow-up and fracture risk. The proportional hazards assumption was examined by the scaled Schoenfeld residuals, and no violation was identified in any of the models.

Similarly, point and interval estimates of osteoporosis hazard ratios associated with lifestyle factors were obtained using Royston-Parmar proportional hazards regression models, a fully parametric regression approach which models the log of the baseline cumulative hazard function in terms of natural cubic splines [30]. The approach to estimation, however, accounted for left, right, and interval censoring due to the assessment of osteoporosis at the time of a DXA exam; the exact time of transition from normal BMD to osteoporosis was unknown. Women were considered left-censored if osteoporosis was diagnosed at the first DXA exam and right-censored if no osteoporosis was diagnosed at the last exam during follow-up. Women with a DXA exam negative for osteoporosis at an exam followed by an exam with an osteoporosis diagnosis were considered interval-censored, given that exact date of transition between the two time points was unknown. Women with no DXA exams during follow-up were excluded.. Models developed were unadjusted, age-adjusted, and fully-adjusted for age, menopausal status, race/ethnicity, BMI, AJCC stage, breast cancer treatment, and prior major fracture before breast cancer diagnosis. Analyses were conducted in SAS v.9.4.

Results

A total of 2,152 breast cancer patients in the Pathways Study were initially treated with AIs (84.5% anastrozole). Patients had a median age of 63 years (range 28–94) and were mostly

postmenopausal (93.4%) at breast cancer diagnosis (Table 1). Around 40.6% of patients had radiation therapy, 11.8% had chemotherapy, and 26.4% had both, and 4.6% of patients had any major fracture before breast cancer diagnosis. Over a median follow-up of 6.1 years (range 0.2–9.8) after AI initiation, there were 165 women who had an incident osteoporotic fracture and 243 women who had an incident osteoporosis diagnosis. Women who fractured compared with those who did not were more often prescribed letrozole (15.8% vs. 10.5%) and less exemestane (2.4% vs. 4.7%). Additionally, those who had a fracture were older (median age 69 years vs. 63 years) and postmenopausal (97.6% vs. 93.0%), of non-Hispanic white race (93.0% vs. 71.9%), and had a history of osteoporosis (12.7% vs. 4.8%) and prior major fracture (6.0% vs. 2.6%) within five years before breast cancer diagnosis. Fewer women who had a fracture were treated with chemotherapy and/or radiation therapy compared with women who did not have a fracture (68.5% vs. 79.7%).

Table 2 presents results examining the association of the lifestyle factors with risk of fracture, including overall moderate-vigorous physical activity and other lifestyle factors. No significant associations were observed for moderate-vigorous physical activity measured at baseline or at the 6-month follow-up in the fully adjusted models. In addition, none of the other lifestyle factors at breast cancer diagnosis, including the HEI-2015, smoking, alcohol intake, supplement use, and multivitamin use, were associated with risk of fracture, although being a current smoker compared to a never smoker was borderline associated with increased fracture risk in the fully adjusted model (HR=1.86; 95% CI: 0.98, 3.54) while being a former smoker was not (HR=1.03; 95% CI: 0.74, 1.42). Further adjustment for smoking status in the physical activity models produced similar results (data not shown).

Table 3 shows further examination of associations between type of moderate-vigorous physical activity (aerobic exercise, resistance exercise, and weight-training exercise) with subsequent fracture risk. At baseline for aerobic exercise, the lower two categories of the physical activity guidelines (when compared to the reference group of the highest level of activity at ≥150 minutes/week) were associated with fracture risk in the fully adjusted model (HRs=1.56–1.58). However, lower tertiles of aerobic exercise in minutes/week were not associated with fracture risk. When examining aerobic exercise at the 6-month follow-up, very little or no aerobic exercise was associated with increased risk of fracture compared to regular exercise in the fully adjusted model. Specifically, engaging in <150 minutes/week (HR=2.42; 95% CI: 1.34, 4.37) or no aerobic exercise (HR=1.90; 95% CI: 1.05, 3.44) was associated with at least twice the risk of fracture, compared to exercising ≥150 minutes/week. When examining by tertiles of aerobic exercise, a similar inverse trend of increasing risk with decreasing exercise was observed (p for trend = 0.002). No notable associations with fracture risk were observed for resistance exercise or weight-training exercise.

The associations of lifestyle factors with risk of osteoporosis during follow-up are presented in Table 4. Aside from physical activity, none of the other lifestyle factors at breast cancer diagnosis were significantly associated with risk of osteoporosis. Lower levels of overall moderate-vigorous physical activity at baseline and 6-month follow-up were associated with increased osteoporosis risk. Specifically, not engaging or very rarely engaging in moderate-vigorous physical activity at baseline compared to ≥150 minutes/week was associated with almost twice the risk of osteoporosis (HR=1.94; 95% CI: 1.11, 3.37) and

1.8 times the risk at 6-month follow-up (HR=1.83; 95% CI: 1.03, 3.24). Analysis by tertiles of moderate-vigorous activity at baseline (HR=1.34; 95% CI: 0.98, 1.85) and 6-month follow-up (HR=1.41; 95% CI: 0.93, 2.11) also showed a similar increased risk for the lowest tertile that was not statistically significant. Examining by type of moderate-vigorous activity reflected somewhat similar yet attenuated trends, specifically for aerobic exercise (Supplemental Table 1).

Discussion

In one of the largest prospective studies of 2,152 breast cancer survivors who received AI therapy for breast cancer, we found that not meeting the current physical activity guidelines of at least 150 minutes or more of aerobic exercise per week at 6-month follow-up was associated with potentially over two-fold increased risk of fracture in comparison to meeting the guidelines. Furthermore, not or very rarely engaging in overall moderate-vigorous physical activity at baseline or 6-month follow-up was associated with almost two-fold increased risk of osteoporosis by BMD. These results suggest that doing moderate-vigorous physical activity, especially aerobic exercise, is beneficial in bone health of breast cancer patients on AI therapy. As for the other lifestyle factors examined, including diet, smoking and supplement use, no associations were found.

Most lifestyle and fracture studies conducted to date have been in healthy female populations, and have reported varying positive effects of physical activity, as well as related factors like diet and supplement use [6–8]. Very few have been conducted in breast cancer patient populations. Our findings on low levels of aerobic exercise and increased risk of fracture are generally consistent with the recent findings reported from the Shanghai Breast Cancer Survivor Study (SBCSS) [9]. The SBCSS found that exercise was inversely associated with osteoporotic fractures in postmenopausal patients (HR = 0.56, 95% CI = 0.33 to 0.97, for ≥12.6 vs <4.5 MET-hours per week) following a dose-response pattern (P for trend=.035). They did not examine risk of fracture in women who were on AI therapy as their study population had a very modest proportion of women on AIs.

Several reasons have been hypothesized as to how exercise might improve bone health. Exercise can increase muscle strength, as well as coordination, mobility, and balance, which in turn can help prevent falls that may cause fractures [6]. Exercise may also enhance BMD or the structural integrity of bone, reducing the likelihood of fracture in the event of a fall [31–34]. Weight-bearing exercises including aerobic, resistance, and weight-training activities have also been shown to prevent loss of BMD in postmenopausal women, which could contribute to a reduced risk of osteoporotic fractures [35]. However, the evidence in pre- or post-menopausal patients with invasive breast cancer has been limited and mixed [36]. In general, these reviews underscored that it remains unclear what type of exercise, and at what intensity, duration, and frequency, is most beneficial to enhance bone health. However, we did identify a potential positive association of 150 minutes or more per week of regular aerobic exercise on reducing fracture risk. We did not observe any associations with resistance and weight-training exercises, although our sample size of women engaging in these activities was small and prevented us from drawing definitive conclusions on how these exercises might impact bone outcomes.

We were able to examine two important windows of physical activity assessment relative to breast cancer diagnosis which may have important clinical implications for subsequent osteoporotic fracture risk. Interestingly, we observed that general moderate-vigorous activity prior to breast cancer diagnosis was associated with reduced risk of osteoporosis by BMD, which might be indicative of a foundational, long-term lifestyle benefit of exercise on BMD, an important metric of bone health, in the survivorship period. We also saw that being active after diagnosis, which coincides with breast cancer treatment, but not before diagnosis, was associated with reduced risk of fracture. While the possible reasons underlying these observations remain unclear, the focus on aerobic exercise by women during the initial period after breast cancer diagnosis may have important implications for subsequent skeletal health. For instance, aerobic exercise maintained during AI therapy may partially mitigate the adverse pharmacologic effects of AI which reduce BMD through reductions in circulating estrogen levels. In support of this hypothesis, one small randomized control trial found that a 12-week exercise program increased estradiol levels and BMD in postmenopausal women with osteoporosis [37].

We also observed a possible negative effect of smoking on increased fracture risk, which is consistent with many prior studies in healthy populations [38, 39]. However, we did not see an association of smoking with osteoporosis, despite it being an established risk factor for osteoporosis [40]. Hip fracture risk among smokers, as compared to non-smokers, has been shown to be greater at all ages but increased from 17% at age 60 years to 71% at age 80 years [41]. Smoking affects musculoskeletal health via nicotine and other toxic substances in cigarettes [42, 43]. Specific mechanisms include reducing the blood supply to bones, slowing the production of bone-forming cells (osteoblasts) so that they make less bone, decreasing the absorption of calcium from the diet, and breaking down estrogen in the body more quickly.

We found no association between vitamin D and calcium supplementation and risk of fractures and osteoporosis in this population of women on AIs. This is not entirely surprising given that previous prospective studies in postmenopausal women have reported mixed results on the effectiveness of calcium and vitamin D supplements on preventing bone loss and fracture risk [17, 44–47]. Furthermore, women in our study are at an even higher risk of rapid bone loss caused by the AI therapy relative to healthy postmenopausal women.

Strengths of this study include a large contemporary breast cancer patient population on AIs, physician adjudicated chart review to identify and confirm osteoporotic fractures and to exclude traumatic and pathologic fractures, and detailed data collection on patient-reported lifestyle factors including physical activity. However, several limitations should be considered, including a relatively short median follow-up time of 6.1 years (compared to >10 years of follow-up in the SBCSS), and a subsequent modest number of osteoporotic fracture events which limited our statistical power to examine the association between lifestyle factors and fracture risk at the major sites. However, the association of aerobic physical activity and short-term fracture risk supports the importance of optimizing lifestyle factors, including aerobic exercise, to improve health outcomes in women receiving AI. A second limitation is that we cannot rule out the possible misclassification of osteoporosis by BMD at the start of AI initiation as not everyone had a prior DXA scan. Finally, among the

women who started their AI therapy before the 6-month follow-up (n=1,204, median time 4.6 months), it is possible that the physical activity assessment at the 6-month point does not completely reflect activity levels prior to AI initiation, as treatment side effects might have influenced subsequent physical activity, or being on an AI might have led women to avoid physical activity during this time period. Both scenarios could cause spurious associations between physical activity and bone outcomes. Finally, we cannot completely rule out residual confounding, yet we did adjust for major confounders of age at breast cancer diagnosis, receipt of breast cancer treatment, and history of osteoporosis and fracture before breast cancer diagnosis. When we also adjusted for smoking status at baseline, results did not change.

Conclusion

Engaging in moderate-vigorous physical activity in the six months after breast cancer diagnosis, particularly aerobic exercise, appears to possibly reduce the risk of major osteoporotic fractures in breast cancer survivors who received AI therapy. However, further prospective research studies conducted in larger populations with longer follow-up are necessary. In the interim, these results may help inform preventive health and lifestyle recommendations for optimizing skeletal health in breast cancer patients on AI therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of Pathways Study participants treated with aromatase inhibitors (n=2,152)

	Total N (%) n=2,152	No Fracture After AI Initiation N (%) n=1,987	Yes Fracture After AI Initiation* N (%) n=165	P-value†
Initially prescribed aromatase inhibitor				0.06
Anastrozole (Arimidex)	1,819 (84.5)	1,684 (84.8)	135 (81.8)	
Letrozole (Femara)	235 (10.9)	209 (10.5)	26 (15.8)	
Exemestane (Aromasin)	98 (4.6)	94 (4.7)	4 (2.4)	
Age at breast cancer diagnosis, years				<.0001
<50	79 (3.7)	77 (3.9)	2 (1.2)	
50–59	639 (29.7)	603 (30.3)	36 (21.8)	
60–69	890 (41.4)	842 (42.4)	48 (29.1)	
≥70	544 (25.3)	465 (23.4)	79 (47.9)	
median (range)	63.0 (28.0–94.0)	63.0 (28.0–93.0)	69.0 (47.0–94.0)	
Menopausal status at breast cancer diagnosis				0.02
Premenopausal	142 (6.6)	138 (7.0)	4 (2.4)	
Postmenopausal	2,010 (93.4)	1,849 (93.0)	161 (97.6)	
Race/ethnicity				0.01
White	1,565 (72.7)	1,428 (71.9)	137 (93.0)	
Black	122 (5.7)	117 (5.9)	5 (3.0)	
Asian	224 (10.4)	217 (10.9)	7 (4.2)	
Hispanic	199 (9.3)	184 (9.3)	15 (9.1)	
Other	42 (1.9)	41 (2.1)	1 (0.6)	
Body mass index at breast cancer diagnosis, kg/m ^{2}				0.52
<25	580 (26.9)	530 (26.7)	50 (30.3)	
25–29.9	699 (32.5)	645 (32.5)	54 (32.7)	
≥30	873 (40.6)	812 (40.9)	61 (37.0)	
median (range)	27.9 (13.7–62.0)	28.0 (13.7–62.0)	27.3 (18.1–53.1)	
AJCC stage				0.99
I	1,166 (54.2)	1,076 (54.2)	90 (54.6)	
II	746 (34.7)	689 (34.7)	57 (34.6)	
III	205 (9.5)	190 (9.6)	15 (9.1)	
IV	35 (1.6)	32 (1.6)	3 (1.8)	
ER/PR status				0.74
ER+/PR+	1,607 (74.7)	1,489 (74.9)	118 (71.5)	
ER+/PR−	542 (25.2)	495 (24.9)	47 (28.5)	
ER−/PR+	2 (0.1)	2 (0.1)	0	
Unknown	1 (0.05)	1 (0.05)	0	
HER2 status				0.09
Negative	1,867 (86.8)	1,725 (86.8)	142 (86.1)	
Positive	204 (9.5)	192 (9.7)	12 (7.3)	
Unknown	81 (3.8)	70 (3.5)	11 (6.6)	

	Total N (%) n=2,152	No Fracture After AI Initiation N (%) n=1,987	Yes Fracture After AI Initiation* N (%) n=165	P-value†
Breast cancer treatment				0.01
Chemotherapy	253 (11.8)	237 (11.9)	16 (9.7)	
Radiation therapy	873 (40.6)	815 (41.1)	58 (35.2)	
Both	568 (26.4)	529 (26.7)	39 (23.6)	
None	456 (21.2)	404 (20.35)	52 (31.5)	
Osteoporosis prior to breast cancer diagnosis‡				<.0001
No	1,987 (92.3)	1,851 (93.2)	136 (82.4)	
<5 years	117 (5.4)	96 (4.8)	21 (12.7)	
≥5 years	48 (2.2)	40 (2.0)	8 (4.9)	
Major osteoporotic fracture prior to breast cancer diagnosis‡				<.0001
No	2,053 (95.4)	1,907 (96.0)	146 (88.5)	
<5 years	62 (2.9)	52 (2.6)	10 (6.0)	
≥5 years	37 (1.7)	28 (1.4)	9 (5.5)	

*Osteoporotic fractures include all sites: hip, humerus, spine, and wrist

†From Pearson chi-square test

‡From ICD-9 codes [22]

Table 2.

Associations of lifestyle factors with major osteoporotic fracture in participants treated with aromatase inhibitors

	Fracture	No Fracture	Unadjusted model* HR (95% CI)	Age adjusted model* HR (95% CI)	Fully adjusted model*† HR (95% CI)
Moderate-Vigorous physical activity at baseline (minutes/week)					
Tertile 1 (0–139)	60	650	1.26 (0.87, 1.84)	1.06 (0.72, 1.55)	1.18 (0.79, 1.76)
Tertile 2 (140–386)	54	673	1.09 (0.74, 1.60)	1.03 (0.70, 1.52)	1.17 (0.79, 1.74)
Tertile 3 (387–2,790)	49	649	1.00	1.00	1.00
p for trend			0.22	0.78	0.43
Moderate-Vigorous physical activity at 6-month follow-up (minutes/week)					
Tertile 1 (0–101)	45	441	1.14 (0.72, 1.79)	0.92 (0.58, 1.46)	1.00 (0.61, 1.62)
Tertile 2 (102–308)	31	446	0.82 (0.50, 1.35)	0.79 (0.48, 1.29)	0.86 (0.52, 1.41)
Tertile 3 (309–2,070)	36	438	1.00	1.00	1.00
p for trend			0.27	0.83	0.59
Moderate-Vigorous physical activity at baseline					
median (range) = 248 (0–2,790)					
None≠	13	95	1.87 (1.05, 3.33)	1.25 (0.70, 2.25)	1.15 (0.62, 2.12)
<150 minutes/week	48	580	1.06 (0.75, 1.50)	0.97 (0.68, 1.36)	1.01 (0.71, 1.44)
≥150 minutes/week	102	1,297	1.00	1.00	1.00
Moderate-Vigorous physical activity at 6-month follow-up					
median (range) = 199 (0–2,070)					
None≠	8	111	0.96 (0.44, 2.10)	0.64 (0.29, 1.42)	0.60 (0.26, 1.39)
<150 minutes/week	44	439	1.20 (0.80, 1.81)	1.08 (0.72, 1.62)	1.16 (0.76, 1.76)
≥150 minutes/week	60	775	1.00	1.00	1.00
Healthy Eating Index (HEI-2015) at baseline					
Q1 (34–66)	32	418	1.00	1.00	1.00
Q2 (67–73)	37	413	1.14 (0.71, 1.84)	1.12 (0.70, 1.80)	1.19 (0.74, 1.93)
Q3 (74–79)	26	424	0.80 (0.48, 1.35)	0.78 (0.47, 1.31)	0.85 (0.50, 1.43)
Q4 (80–98)	36	414	1.08 (0.67, 1.75)	0.91 (0.56, 1.47)	0.92 (0.57, 1.49)
Smoking at breast cancer diagnosis					
Never	79	1,036	1.00	1.00	1.00
Former	74	837	1.13 (0.82, 1.56)	1.07 (0.78, 1.46)	1.03 (0.74, 1.42)
Current	11	107	1.40 (0.74, 2.63)	1.82 (0.97, 3.44)	1.86 (0.98, 3.54)
Alcohol intake at breast cancer diagnosis (grams/day)					
median (range) = 1.32 (0–129.26)					
None	9	156	1.00	1.00	1.00
Below median	52	661	1.37 (0.68, 2.76)	1.58 (0.78, 3.18)	1.67 (0.82, 3.39)
Above median	73	880	1.40 (0.70, 2.80)	1.70 (0.84, 3.41)	1.67 (0.82, 3.44)
Supplement use at breast cancer diagnosis					
None	1,475	120	1.00	1.00	1.00

	Fracture	No Fracture	Unadjusted model* HR (95% CI)	Age adjusted model* HR (95% CI)	Fully adjusted model*† HR (95% CI)
Calcium intake only	157	16	1.09 (0.64, 1.83)	1.03 (0.61, 1.73)	1.01 (0.60, 1.71)
Vitamin D intake only	235	17	1.18 (0.71, 1.96)	1.01 (0.60, 1.68)	1.02 (0.61, 1.70)
Both	92	11	1.75 (0.94, 3.24)	1.49 (0.80, 2.78)	1.42 (0.76, 2.66)
Multivitamin use at breast cancer diagnosis					
No	57	710	1.00	1.00	1.00
Yes	107	1255	1.05 (0.76, 1.45)	1.03 (0.74, 1.41)	1.03 (0.75, 1.43)

*Cox proportional hazards models with follow-up until fracture (event), disenrollment from health plan, death or end of study, whichever occurred first.

†Adjusted for age, menopausal status, race/ethnicity, BMI, AJCC stage, breast cancer treatment, prior osteoporosis, and prior major osteoporotic fracture

‡Includes never or less than once per month

Table 3.

Associations of types of baseline and 6-month follow-up moderate-vigorous physical activity with major osteoporotic fracture in participants treated with aromatase inhibitors

BASELINE	Fracture	No Fracture	Unadjusted model* HR (95% CI)	Age adjusted model* HR (95% CI)	Fully adjusted model*† HR (95% CI)
Aerobic Exercise (min/wk)					
Tertile 1 (4–68)	35	451	1.27 (0.74, 2.19)	1.32 (0.77, 2.27)	1.40 (0.81, 2.44)
Tertile 2 (69–180)	34	436	1.37 (0.80, 2.36)	1.30 (0.75, 2.24)	1.39 (0.80, 2.41)
Tertile 3 (181–1,838)	21	358	1.00	1.00	1.00
p for trend			0.43	0.34	0.26
Aerobic Exercise (min/wk)					
median (range) = 113 (4–1,838)					
None≠	73	727	1.80 (1.18, 2.76)	1.46 (0.95, 2.24)	1.58 (1.02, 2.47)
<150 minutes/week	60	715	1.44 (0.93, 2.23)	1.48 (0.95, 2.29)	1.56 (1.00, 2.44)
≥150 minutes/week	30	530	1.00	1.00	1.00
Resistance Exercise (min/wk)					
median (range) = 68 (4–750)					
None≠	101	1,257	0.98 (0.63, 1.52)	0.88 (0.57, 1.37)	0.96 (0.61, 1.51)
Below median	37	407	1.05 (0.63, 1.74)	1.11 (0.67, 1.84)	1.20 (0.72, 2.00)
Above median	25	307	1.00	1.00	1.00
Weight-training Exercise (min/wk)					
median (range) = 34 (4–450)					
None≠	129	1,639	0.99 (0.56, 1.75)	0.82 (0.46, 1.45)	0.88 (0.49, 1.59)
Below median	20	174	1.46 (0.72, 2.93)	1.49 (0.74, 3.00)	1.57 (0.78, 3.18)
Above median	13	156	1.00	1.00	1.00
6-MONTH FOLLOW-UP	**Fracture**	**No Fracture**	**Unadjusted model* HR (95% CI)**	**Age adjusted model* HR (95% CI)**	**Fully adjusted model*† HR (95% CI)**
Aerobic Exercise (min/wk)					
Tertile 1 (4–68)	35	284	2.79 (1.34, 5.81)	2.53 (1.21, 5.28)	2.85 (1.34, 6.08)
Tertile 2 (69–180)	17	282	1.42 (0.63, 3.18)	1.30 (0.58, 2.93)	1.42 (0.63, 3.23)

Tertile 3 (181–1,260)	9	217	1.00	1.00	1.00
p for trend			0.002	0.005	0.002
Aerobic Exercise (min/wk)					
median (range) = 103 (4–1,260)					
None‡	52	561	2.06 (1.16, 3.66)	1.73 (0.97, 3.09)	1.90 (1.05, 3.44)
<150 minutes/week	46	450	2.21 (1.23, 3.95)	2.13 (1.19, 3.82)	2.42 (1.34, 4.37)
≥150 minutes/week	15	333	1.00	1.00	1.00
Resistance Exercise (min/wk)					
median (range) = 68 (4–720)					
None‡	69	868	1.07 (0.61, 1.87)	0.95 (0.54, 1.66)	1.01 (0.57, 1.79)
Below median	28	262	1.44 (0.77, 2.69)	1.42 (0.76, 2.66)	1.49 (0.79, 2.82)
Above median	15	196	1.00	1.00	1.00
Weight-training Exercise (min/wk)					
median (range) = 34 (4–300)					
None‡	89	1,117	1.03 (0.48, 2.22)	0.86 (0.39, 1.84)	0.89 (0.40, 1.96)
Below median	15	111	1.74 (0.71, 4.28)	1.76 (0.72, 4.33)	1.72 (0.70, 4.24)
Above median	7	80	1.00	1.00	1.00

*Cox proportional hazards models with follow-up until fracture (event), disenrollment from health plan, death, or end of study, whichever occurred first

†Adjusted for age, menopausal status, race/ethnicity, BMI, AJCC stage, breast cancer treatment, prior osteoporosis, prior major osteoporotic fracture

‡Includes never or less than once per month

Table 4.

Associations of lifestyle factors with BMD-defined osteoporosis at any site in participants treated with aromatase inhibitors

		No	Unadjusted model*	Age adjusted model*	Fully adjusted model*†
	Osteoporosis	Osteoporosis	HR (95% CI)	HR (95% CI)	HR (95% CI)
Moderate-Vigorous physical activity at baseline (minutes/week)					
Tertile 1 (0–150)	83	467	0.91 (0.67, 1.23)	1.03 (0.76, 1.4)	1.34 (0.98, 1.85)
Tertile 2 (151–398)	73	490	0.81 (0.59, 1.1)	0.86 (0.63, 1.18)	0.99 (0.72, 1.36)
Tertile 3 (398–2,790)	82	456	1.00	1.00	1.00
p for trend			0.55	0.86	0.08
Moderate-Vigorous physical activity at 6-month follow-up (minutes/week)					
Tertile 1 (0–109)	54	321	0.93 (0.63, 1.36)	1.04 (0.71, 1.53)	1.41 (0.93, 2.11)
Tertile 2 (110–323)	59	332	1.03 (0.71, 1.5)	1.08 (0.74, 1.57)	1.23 (0.84, 1.80)
Tertile 3 (324–2,070)	52	318	1.00	1.00	1.00
p for trend			0.69	0.82	0.10
Moderate-Vigorous physical activity at baseline					
median (range) = 259 (0–2790)					
None‡	15	61	1.07 (0.63, 1.82)	1.57 (0.92, 2.68)	1.94 (1.11, 3.37)
<150 minutes/week	66	393	1.00 (0.75, 1.33)	1.06 (0.79, 1.41)	1.3 (0.97, 1.76)
≥150 minutes/week	157	959	1.00	1.00	1.00
Moderate-Vigorous physical activity at 6-month follow-up					
median (range) = 203 (0–2070)					
None‡	15	76	0.97 (0.56, 1.67)	1.26 (0.73, 2.18)	1.83 (1.03, 3.24)
<150 minutes/week	53	321	0.94 (0.67, 1.32)	0.98 (0.70, 1.37)	1.16 (0.82, 1.65)
≥150 minutes/week	97	574	1.00	1.00	1.00
Healthy Eating Index (HEI-2015) at baseline					
Q1 (42–66)	44	306	1.00	1.00	1.00
Q2 (67–73)	54	296	1.16 (0.78, 1.73)	1.21 (0.81, 1.8)	1.22 (0.82, 1.82)
Q3 (74–79)	60	290	1.22 (0.82, 1.8)	1.29 (0.87, 1.9)	1.23 (0.83, 1.82)
Q4 (80–98)	46	304	0.82 (0.54, 1.24)	0.96 (0.64, 1.46)	0.82 (0.54, 1.25)
Smoking at breast cancer diagnosis					
Never	135	725	1.00	1.00	1.00
Former	94	612	0.8 (0.61, 1.04)	0.84 (0.64, 1.09)	0.89 (0.68, 1.16)
Current	11	80	0.92 (0.5, 1.71)	0.86 (0.46, 1.59)	0.89 (0.48, 1.66)
Alcohol intake at breast cancer diagnosis					
median (range) = 1.44 (0–129.26)					
None	15	106	1.00	1.00	1.00
Below median	104	549	1.36 (0.79, 2.34)	1.31 (0.76, 2.25)	1.31 (0.76, 2.25)
Above median	93	557	1.23 (0.71, 2.11)	1.12 (0.65, 1.93)	0.99 (0.56, 1.72)
Supplement use at breast cancer diagnosis					
None	168	1,067	1.00	1.00	1.00

		No	Unadjusted model*	Age adjusted model*	Fully adjusted model*†
	Osteoporosis	Osteoporosis	HR (95% CI)	HR (95% CI)	HR (95% CI)
Calcium intake only	24	109	1.32 (0.86, 2.03)	1.32 (0.86, 2.03)	1.46 (0.95, 2.25)
Vitamin D intake only	30	157	1.08 (0.73, 1.6)	1.33 (0.9, 1.97)	1.35 (0.91, 2.01)
Both	15	72	1.12 (0.66, 1.89)	1.4 (0.82, 2.38)	1.44 (0.84, 2.45)
Multivitamin use at breast cancer diagnosis					
No	83	505	1.00	1.00	1.00
Yes	154	905	1.01 (0.77, 1.32)	1.02 (0.78, 1.34)	0.98 (0.75, 1.28)

*Royston-Parmar proportional hazards models using interval censoring with follow-up until osteoporosis, disenrollment from health plan, death, or end of study, whichever occurred first

†Adjusted for age, menopausal status, race/ethnicity, BMI, AJCC stage, breast cancer treatment, prior major osteoporotic fracture

‡Includes never or less than once per month