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Effect of Bisphosphonate Use on Risk of Postmenopausal Breast Cancer:

Results From the Randomized Clinical Trials of Alendronate and Zoledronic Acid

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Abstract

IMPORTANCE—Studies have shown that bisphosphonates may have antitumor and antimetastatic properties. Recently, observational studies have suggested a possible protective effect of bisphosphonates on breast cancer, but the effect of bisphosphonate use on risk of breast cancer has not been tested in randomized trials.

OBJECTIVE—To assess the relationship of postmenopausal breast cancer incidence and bisphosphonate use using data from 2 randomized (1:1), double-blind, placebo-controlled trials.

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Author Contributions: Dr Hue had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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DESIGN, SETTING, AND PARTICIPANTS—The Fracture Intervention Trial (FIT) randomly assigned 6459 women aged 55 to 81 years to alendronate or placebo for a mean follow-up of 3.8 years. The Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly–Pivotal Fracture Trial (HORIZON-PFT) randomly assigned 7765 women aged 65 to 89 years to annual intravenous zoledronic acid or placebo for a mean follow-up of 2.8 years. Data were collected at clinical centers in the United States (FIT and HORIZON-PFT) and in Asia and the Pacific, Europe, North America, and South America (HORIZON-PFT). Women, in either study, with recurrent breast cancer or who reported a history of breast cancer were excluded from analyses. In each trial, a blinded review was conducted of each cancer adverse event report to verify incident invasive breast cancer cases. The primary analysis compared events in the active vs placebo group using a log-rank test.

INTERVENTION—Alendronate vs placebo (FIT) or zoledronic acid vs placebo (HORIZON-PFT).

MAIN OUTCOMES AND MEASURES—Hazard ratio for incident breast cancer in the bisphosphonate treatment group compared to the placebo group.

RESULTS—There was no significant difference in the rate of breast cancer in FIT: 1.5% (n = 46) in the placebo group and 1.8% (n = 57) in the alendronate group (hazard ratio [HR], 1.24 [95% CI, 0.84–1.83]). In HORIZON-PFT, there was also no significant difference: 0.8% (n = 29) in the placebo group and 0.9% (n = 33) in the zoledronic acid group (HR, 1.15 [95% CI, 0.70–1.89]). There was also no significant difference when the data from FIT and HORIZON-PFT were pooled (HR, 1.20 [95% CI, 0.89–1.63]).

CONCLUSIONS AND RELEVANCE—These 2 randomized clinical trials do not support the findings from observational research. Contrary to the results from observational studies, we found that 3 to 4 years of bisphosphonate treatment did not decrease the risk of invasive postmenopausal breast cancer.

TRIAL REGISTRATION—clinicaltrials.gov Identifier: NCT00049829 (HORIZON-PFT).

The bisphosphonates alendronate sodium and zoledronic acid are frequently used to treat osteoporosis. In vitro studies suggest that bisphosphonates may induce cell death and inhibit the proliferation of estrogen-sensitive MCF-7 breast cancer cells.[1,2] Several trials in women receiving adjuvant treatment to improve bone mineral density (BMD) and/or improve survival found that high-dose zoledronic acid therapy increased breast cancer disease-free survival.[3–6] However, 1 adjuvant therapy trial found no significant difference in overall breast cancer disease-free survival with zoledronic acid therapy after a median follow-up of 59 months, but it did find a significant heterogeneity of treatment effect by menopausal status. A significant benefit in invasive breast cancer–free survival was seen in postmenopausal women receiving zoledronic acid, but this effect was not seen in the premenopausal-perimenopausal subgroup.[7] In addition, results from a 12-month combined analysis of data from 2 BMD–cancer recurrence trials demonstrated that when postmenopausal breast cancer survivors started using high-dose zoledronic acid with an aromatase inhibitor, they had significantly lower rates of breast cancer recurrence than women receiving an aromatase inhibitor who delayed the start of zoledronic acid use (until they had a decrease in BMD or a fracture).[8] This is contrary to the recently presented results

from a meta-analysis on recurrence using data from 36 adjuvant bisphosphonate trials (65% of the trials tested zoledronic acid). The investigators found that bisphosphonate use had no effect on local recurrence or contralateral breast cancer incidence.[9]

Observational studies have reported an association between bisphosphonate use and risk of breast cancer.[10–14] For example, in the Women's Health Initiative (WHI) observational study, women taking bisphosphonates (90% used alendronate) for treatment of osteoporosis had a 32% lower risk of invasive breast cancer after adjustment for several potential confounders.[15] A similar 39% lower risk was reported using data from the Breast Cancer in Northern Israel Study, a case-control study including 4039 patients with breast cancer and controls.[14] A meta-analysis of several observational studies also reported that use of bisphosphonates (mainly alendronate) was associated with a decreased risk of breast cancer.[16]

However, these observational study results may be confounded because among postmenopausal women, low levels of estrogen and high levels of sex hormone–binding globulin (SHBG) are strongly associated with both a decreased risk of estrogen receptor (ER)–positive breast cancer[17–22] and low BMD, as well as faster bone loss[23,24] and a higher risk of fracture,[20,25] which are all indications for prescribing bisphosphonates in osteoporotic women. This confounding may explain their findings of an association between the use of bisphosphonates for osteoporosis and a decreased risk of breast cancer in post-menopausal women. This confounding can only be avoided by testing the effect of bisphosphonate therapy on the risk of breast cancer in randomized trials. Therefore, we analyzed whether the use of bisphosphonates reduced the incidence of postmenopausal breast cancer in 2 large, multicenter, randomized, double-blind, placebo-controlled, phase 3 pivotal trials of alendronate and zoledronic acid.

Methods

Full details on the study design and methods for the Fracture Intervention Trial (FIT)[26–28] of alendronate and the Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly–Pivotal Fracture Trial (HORIZON-PFT) (ClinicalTrials.gov Identifier: NCT00049829)[29] have previously been published. The authors of this article were FIT and/or HORIZON-PFT investigators and had access to data from these trials. All trial participants provided written informed consent, and the appropriate protocol was approved by the institutional review boards at each participating center.

FIT

The FIT was a randomized (1:1) parallel-group double-blind placebo-controlled trial of daily oral alendronate sodium (5 mg/d for 2 years and 10 mg/d thereafter) for the treatment of osteoporosis in 6459 postmenopausal women aged 55 to 81 years without a menstrual period within the last 2 years (at the time of randomization) and a femoral neck BMD of no more than 0.68 g/cm^2 (corresponding to a T-score of −1.6 or less).[26–28] The trial was conducted at 11 academic clinical sites in the United States. High adherence, measured by means of pill counts and diaries, was defined as use of at least 70% (of expected). All participants also received calcium supplementation and 250 IU of vitamin D daily.

HORIZON-PFT

The HORIZON-PFT was a 3-year international (Asia and the Pacific, Europe, North America, and South America) randomized (1:1) parallel-group double-blind placebo-controlled trial in 7765 postmenopausal women aged 65 to 89 years with a femoral neck T-score of −2.5 or less with or without evidence of an existing vertebral fracture or a T-score of −1.5 or less with at least 2 mild or 1 moderate vertebral fractures.[29] Concomitant use of estrogen therapy, raloxifene hydrochloride, calcitonin, tibolone, tamoxifen citrate, dehydroepiandrosterone (s), ipriflavone, and medroxyprogesterone acetate at baseline or during the study was allowed. Women received annual intravenous infusions of either zoledronic acid 5 mg or placebo. Participants also received 400 to 1200 IU of vitamin D and 1000 to 1500 mg of calcium per day. This analysis was limited to women who received at least 1 infusion of zoledronic acid or placebo.

Verification of Incident Breast Cancer Cases

For this post hoc analysis, a search of the adverse event database (coded in FIT using Merck Clinical Events Dictionary and in HORIZON-PFT using Medical Dictionary for Regulatory Activities) was conducted for any report of breast cancer. For each reported adverse event of breast cancer, a review to verify incident cases was conducted by a single investigator (T.F.H.) blinded to treatment assignment. An incident case was defined as any new breast cancer event (not including ductal carcinoma in situ) occurring after randomization in the trials. Participants with recurrent breast cancer or those who reported a history of breast cancer were excluded from analyses.

Statistical Analysis

The primary analyses were performed using a log-rank test with Kaplan-Meier survival function estimates. Secondary analyses included Cox proportional hazards models to adjust for possible baseline covariates shown in previous research to be breast cancer risk factors including age, (current) smoking, (previous) hormone therapy use, body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), total hip BMD, race, country and/or region, and age at menopause. Modified intention-to-treat analyses were conducted separately for each trial, as well as a pooled analysis combining data from both trials. In the pooled analyses, we tested for possible interaction by study enrollment (FIT or HORIZON-PFT).

We also assessed prespecified subgroups for the following baseline variables: age (5-year categories), BMI categories (<18.5, 18.5–24.9, 25–29.9, ≥30), femoral neck and total hip BMD (T-scores ≤2.5 and >2.5). For each of these, the results were stratified by categories of each subgrouping variable and then interaction terms were included in the models (with each variable as continuous). In FIT, available variables from the Gail[30] 5-year breast cancer risk estimates model were also included in the subgrouping (note: Gail model variables were not available in HORIZON-PFT); available covariates in FIT included age, age at menarche, race, age at first birth, history of mother and/or sister with breast cancer (yes/no). The following Gail model variables were not collected in FIT and therefore not included in this multivariate model: history of breast biopsy, ductal carcinoma in situ, and lobular carcinoma in situ.

Statistical tests were conducted using SAS software, version 9.1 (SAS Institute), and were 2 sided, with $\alpha = .05$ considered statistically significant. Time to event (ie, follow-up time) began at randomization and ended at the date of the earliest of the following: first primary breast cancer adverse event, death, or last contact. The Kaplan-Meier method was used to estimate the cumulative incidence curves.

Results

FIT

A total of 6194 women without a history of breast cancer were included (Figure 1). Table 1 presents the baseline characteristics of the treatment groups. We confirmed 103 cases of invasive breast cancer reported over a mean (SD) of 3.8 (0.8) years of study follow-up. In each treatment group, 83% to 84% of participants adhered to treatment.

The incidence of breast cancer was 1.8% (n = 57) in the alendronate group and 1.5% (n = 46) in the placebo group (Table 2), for a hazard ratio (HR) of 1.24 (95% CI, 0.84–1.83; *P* = .28) for risk of breast cancer (Figure 2). Adjustment for baseline covariates did not significantly affect the results (HR, 1.17 [95% CI, 0.78–1.73]; *P* = .45). The multivariable analysis, including risk factors for breast cancer from the Gail model, also showed no evidence of difference between the alendronate and placebo groups (HR, 1.11 [95% CI, 0.71–1.73]; *P* = .64).

HORIZON-PFT

There were 7580 women without a history of breast cancer included in this analysis (Figure 3). Table 1 presents the baseline characteristics of study participants by treatment group assignment. A total of 62 confirmed invasive breast cancers were reported over the 3-year study period, with a mean (SD) follow-up of 2.8 (0.6) years. In each treatment group, 80% to 83% of participants had high adherence (ie, received all 3 scheduled annual infusions). Concomitant medications, including raloxifene, calcitonin, and estrogen therapy, were allowed and used by 21% of all HORIZON-PFT participants, but prevalence of use by medication type did not differ between the zoledronic acid and placebo groups during the trial. Trials have shown that raloxifene use is associated with decreased breast cancer risk,[31] whereas hormone therapy has been associated with an increased risk.[32] Because the use of these medications (assessed as a group or by individual medication) did not differ between the treatment groups in our randomized trial, no adjustments were made for concomitant medication use.

The incidence of breast cancer was 0.9% (n = 33) in the zoledronic acid group and 0.8% (n = 29) in the placebo group (Table 2), with an HR of 1.15 (95% CI, 0.70–1.89; *P* = .59) for risk of breast cancer when the zoledronic acid treatment group was compared with the placebo group (Figure 4). Adjustment for baseline covariates did not significantly affect the results (HR, 1.15 [95% CI, 0.70–1.91]; *P* = .58).

Pooled Trial Analyses

Because the overall numbers of events were relatively low in both trials, we pooled the data from both trials to increase the sample size but did not find any difference (from the separate FIT and HORIZON-PFT results) in effect. When the data from FIT and HORIZON-PFT were combined, the incidence of breast cancer was 1.3% (n = 90) in the bisphosphonate group (alendronate + zoledronic acid) and 1.1% (n = 75) in the placebo group (Table 2), with an HR of 1.20 (95% CI, 0.89–1.63; *P* = .24) for risk of breast cancer when the combined bisphosphonate group was compared with the combined placebo group. In addition, all results in FIT and HORIZON-PFT were similar when analyses were limited to those with high adherence to study treatment. We found no evidence of significant interaction in the pooled analyses by study enrollment (*P* for interaction = .81).

Subgroup Analyses

In FIT, no significant interactions were found for age, BMI, or femoral neck or total hip BMD. In HORIZON-PFT, there were also no significant interactions between assignment to zoledronic acid and subgroups of age, BMI, or femoral neck or total hip BMD.

Discussion

Three to four years of treatment with either alendronate or zoledronic acid, at doses used to treat osteoporosis, did not decrease the risk of incident postmenopausal breast cancer in our trials. These results from 2 large randomized clinical trials differ from the reports of a protective effect seen in several observational and case-control studies,[10–14] as well as a meta-analysis of those results,[16] which suggest that postmenopausal women taking bisphosphonate, mainly alendronate, had a 32% to 39% decreased risk of breast cancer. Our analyses found that treatment with neither alendronate nor the more potent zoledronic acid reduced the risk of breast cancer. The lower confidence bound for the relative hazard from our nonsignificant findings (0.89 from the pooled analysis of both trials, corresponding to an 11% risk reduction) is inconsistent with the 32% reduction seen in the meta-analyses of observational studies.[16]

The discrepancy between the observational studies and our randomized trial results may represent an example of confounding by indication.[33,34] Specifically, women with low bone density, fractures, and bone loss have substantially lower levels of estradiol and high SHBG.[20,23–25] Lower levels of estradiol and higher levels of SHBG are also strongly associated with a reduced risk of ER-positive breast cancer in postmenopausal women.[17–19,21,22] Thus, women with osteoporosis are likely to have a lower risk of ER-positive breast cancer. This parallels the discrepancy in results seen in other research of treatment effects, such as the strong associations observed between estrogen and progestin use and the reduction in the risk of cardiovascular disease in well-conducted observational studies[35–46] and the increased risk or lack of effect shown in the Heart and Estrogen/Progestin Replacement Study (HERS)[47] and WHI trials.[32] Our finding reinforces the importance of testing the efficacy of treatments in randomized trials.

The observational WHI study reported an association between bisphosphonate use and incident invasive breast cancer (HR, 0.68 [95% CI, 0.52–0.89]), adjusted for multiple factors associated with breast cancer risk, and was the only observational study that reported an assessment with an attempt to condition on sex hormone level (using a method of indirect adjustment). On the basis of a finding of a significant correlation ($r = 0.43$; $P < .001$) between hip fracture risk score (calculated without BMD) and total hip BMD in a subset of women with these measurements, WHI investigators adjusted for the risk score "to control for potential confounding by indication."[11](p3586) The "5-year risk of hip fracture" is a complex risk score that includes variables that may not be related to sex hormones, such as smoking and general health.[48] Therefore, the risk score included in their model may only partially adjust for the confounding influence of the prognostic sex hormone factor and residual confounding may have occurred. Randomized assignment to a bisphosphonate or placebo in FIT and HORIZON-PFT avoided this potential confounding.

It may be hypothesized that a longer duration of bisphosphonate use would result in a greater effect on breast cancer risk. However, the majority (52.5%) of WHI participants using a bisphosphonate reported taking it for less than a year. Only 10.4% of the WHI users had taken a bisphosphonate for at least 3 years.[49] The case-control study by Newcomb et al[13] found the greatest decrease in risk (adjusted odds ratio, 0.63 [95% CI, 0.42–0.95]; *P* for trend = .01) in women who took the drug for longer than 2 years, but they only had 118 women (2% of their cases and controls) who used a bisphosphonate for longer than 2 years. In contrast, both of our randomized trials (n = 13 774 pooled) included treatment with 3 to 4 years of bisphosphonate and we found no effect.

There are conflicting findings from adjuvant therapy trials with a high-dose bisphosphonate (eg, 4 mg of zoledronic acid used every 6 months) treatment. A number of trials have shown a reduction in risk of recurrent breast cancer or disease-free survival.[3–5,8,49] Conversely, a recent meta-analysis of 36 adjuvant bisphosphonate trials showed no effect on local recurrence or contralateral breast cancer incidence,[9] which is consistent with our finding. However, these adjuvant trial results do not apply to the prevention of incident breast cancer with the lower dose bisphosphonate treatment used for osteoporosis.

In addition to having longer treatment duration than the observational studies, our primary strength is the randomized, placebo-controlled designs of both FIT and HORIZON-PFT. Furthermore, both trials had high rates of treatment adherence (to both bisphosphonates and placebos). Despite these strengths, our studies have limitations. Because these trials were not designed to study breast cancer outcomes, a formal risk assessment for breast cancer was not performed at baseline and study mammograms were not conducted during follow-up. In our trials, incident invasive breast cancer cases were identified using adverse event reports and supporting medical records. Breast cancer cases were not centrally adjudicated, and pathology reports were not routinely collected for all cases. Therefore, we could not analyze results by estrogen-receptor status, but because more than 87% of breast cancer cases occurring in women 65 years and older are ER-positive[50] and the mean age of women in our trials was approximately 70 years, this implies that our breast cancer events were primarily ER-positive cases. Most women in our trials were white, and therefore our results might not be generalizable to other racial groups that have a higher risk of ER-negative cancer.

Another limitation is that we were only able to assess primary breast cancer risk because few women in FIT (n = 265) and HORIZON-PFT (n = 134) had a history of breast cancer; these participants were excluded from this analysis. In addition, we only analyzed the effect of the bisphosphonates, alendronate and zoledronic acid, on breast cancer risk. The use of FIT and HORIZON-PFT for this analysis seemed appropriate because alendronate was used by most participants in the observational studies,[11,16] which reported an association between bisphosphonate use and decreased breast cancer risk, and zoledronic acid was used in the adjuvant trials that have shown improved disease-free survival and/or reduced recurrence. Data from randomized trials of other bisphosphonates, such as ibandronate sodium or risedronate sodium, could also have been used for this analysis, but those bisphosphonates were not widely used in the observational research and were not used at all in the adjuvant studies published to date. Therefore, those other bisphosphonates may not be as relevant for a result comparison.

Conclusions

These data provide evidence that 3 to 4 years of treatment with bisphosphonate, alendronate or zoledronic acid, therapy does not reduce the risk of incident breast cancer in postmenopausal women. The discrepancy between our results and the reports of associations in observational studies may be an example of indication bias and illustrates the limitation and hazard of drawing conclusions about treatment effects from observational studies (even those that are very well done) and emphasizes the value of confirming such associations in randomized trials. The effect of bisphosphonate treatment on breast cancer risk in nonosteoporotic populations should be investigated in other randomized trials.

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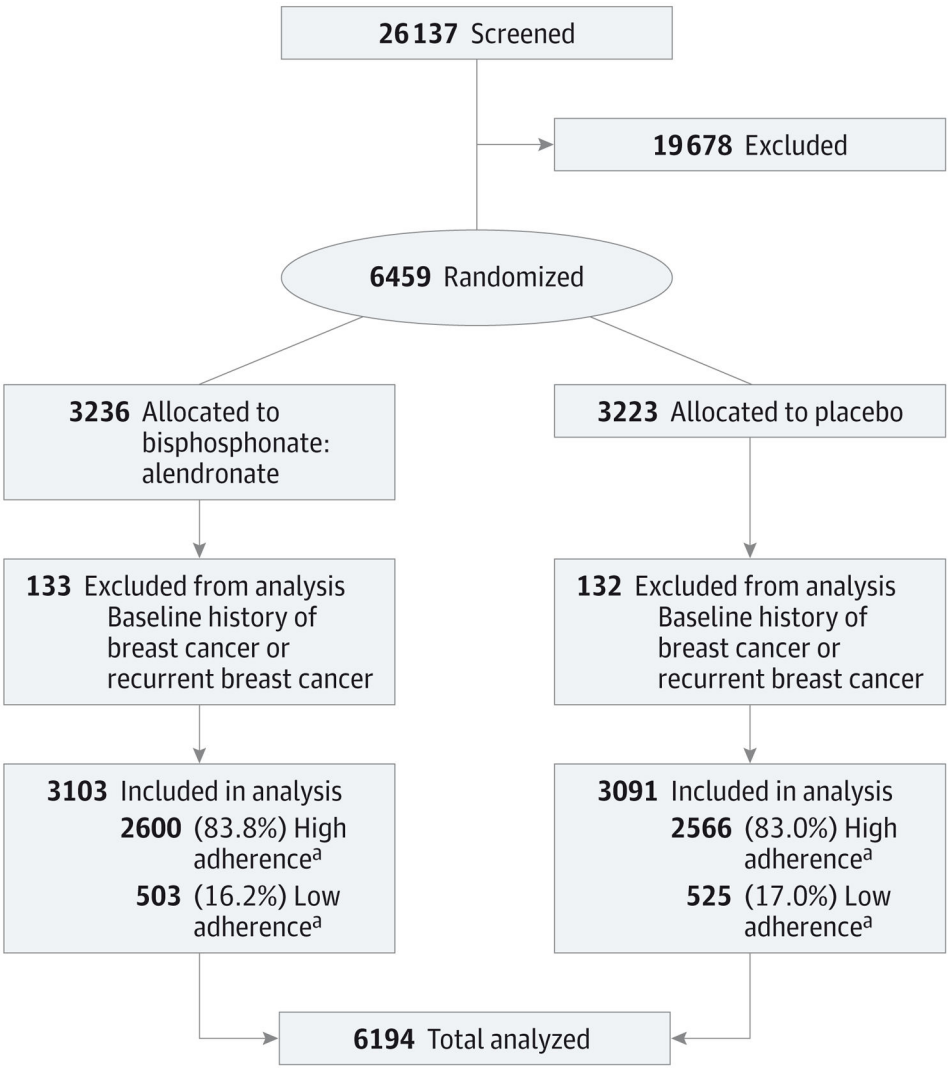

Figure 1.

Fracture Intervention Trial (FIT) Participant Flow Diagram

[a]Adherence was measured using pill counts at each study visit and the participant's self-reported therapy record. High study treatment adherence was defined as greater than 70% (of expected) study treatment use on the basis of pill counts and 75% or greater use of nonstudy concomitant medications on the basis of therapy.

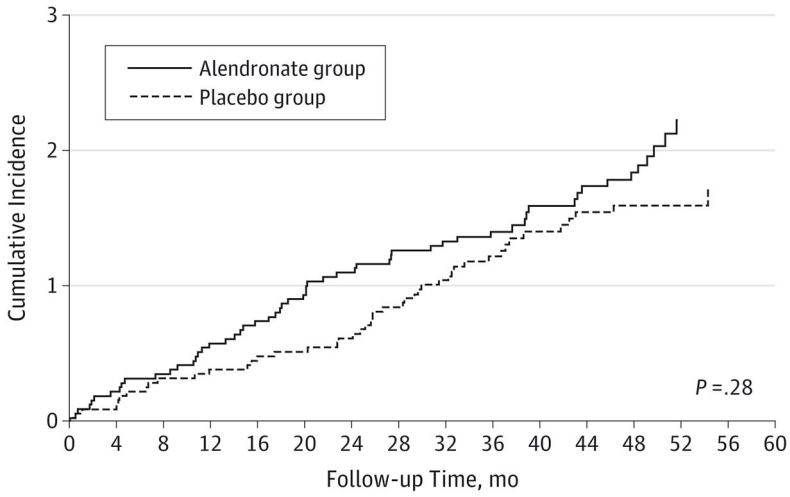

Figure 2.
Cumulative Incidence of Breast Cancer in the Fracture Intervention Trial (FIT)

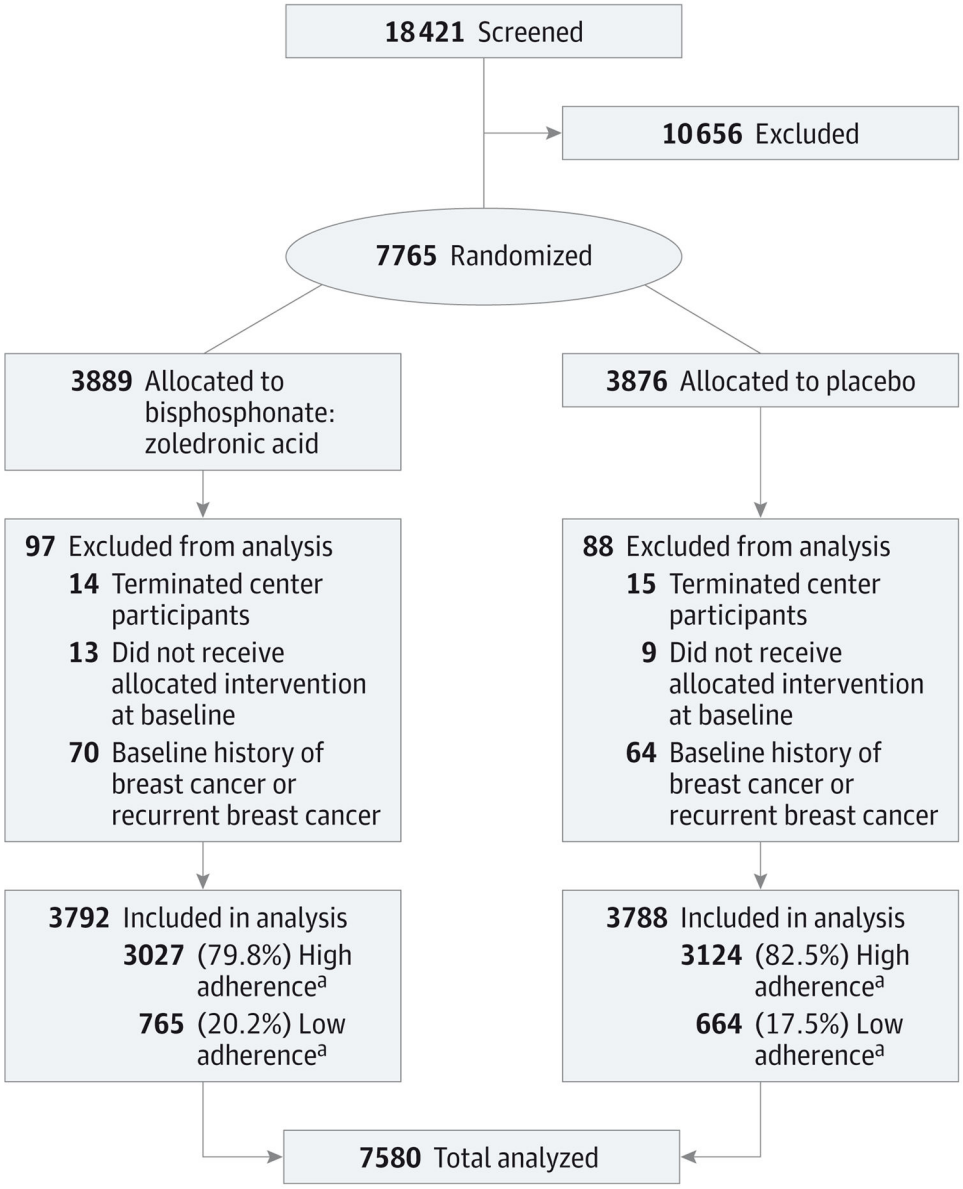

Figure 3. Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly–Pivotal Fracture Trial (HORIZON-PFT) Participant Flow Diagram

[a]Participants were randomized to either an annual intravenous administration of zoledronic acid 5 mg or placebo for 3 years (received at baseline, month 12, and month 24). High adherence was defined as receipt of all 3 treatment (zoledronic acid or placebo) doses. Low adherence was defined as receipt of 1 or 2 treatment doses.

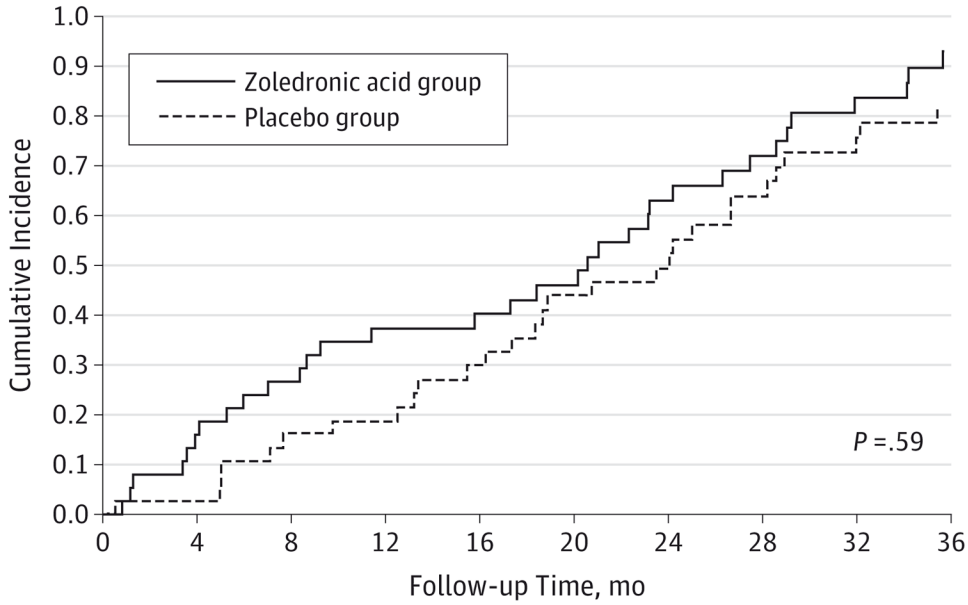

Figure 4.

Cumulative Incidence of Breast Cancer in Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly–Pivotal Fracture Trial (HORIZON-PFT)

Table 1

Baseline Characteristics by Treatment Assignment in the Fracture Intervention Trial (FIT) and Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly–Pivotal Fracture Trial (HORIZON-PFT)

	FIT		HORIZON-PFT	
Characteristic	**Alendronate (n = 3103)**	**Placebo (n = 3091)**	**Zoledronic Acid (n = 3792)**	**Placebo (n = 3788)**
Age				
Mean (SD), y	68.1 (6.2)	68.2 (6.1)	73.1 (5.3)	73.0 (5.4)
No. (%)				
<70 y	1754 (56.5)	1762 (57.0)	1117 (29.5)	1155 (30.5)
70–74 y	812 (26.2)	789 (25.5)	1212 (32.0)	1210 (31.9)
≥75 y	537 (17.3)	540 (17.5)	1463 (38.6)	1423 (37.6)
Race/ethnicity, No. (%)				
White	3006 (96.9)	2997 (97.0)	2978 (78.5)	2989 (78.9)
Asian/Pacific Islander	40 (1.3)	31 (0.7)	557 (14.7)	553 (14.6)
Hispanic	28 (0.9)	34 (1.1)	NA	NA
Black	16 (0.5)	21 (0.7)	NA	NA
Other	13 (0.4)	8 (0.3)	257 (6.8)	246 (6.5)
BMI, mean (SD)	25.1 (4.0)	25.3 (4.1)	25.1 (4.3)	25.4 (4.3)
Bone mineral density, mean (SD), g/cm^2				
Femoral neck	0.58 (0.06)	0.58 (0.06)	0.53 (0.06)	0.53 (0.07)
Total hip	0.69 (0.09)	0.69 (0.09)	0.65 (0.09)	0.65 (0.09)
Previous medication use, No. (%)				
Estrogen or estrogen plus progestin	1099 (35.4)	1052 (34.0)	805 (21.2)	799 (21.1)
Raloxifene	NA	NA	409 (10.8)	392 (10.3)
Oral bisphosphonate	NA	NA	546 (14.4)	538 (14.2)
Smoking status, No. (%)				
Never	1621 (52.2)	1660 (53.7)	NA	NA
Past	1136 (36.6)	1062 (34.4)	NA	NA
Current[a]	323 (10.4)	342 (11.1)	343 (8.9)	314 (8.2)

Characteristic	FIT		HORIZON-PFT	
	Alendronate (n = 3103)	Placebo (n = 3091)	Zoledronic Acid (n = 3792)	Placebo (n = 3788)
Unknown	23 (0.7)	27 (0.9)	0	0
Age at menarche, mean (SD), y	12.9 (1.4)	12.9 (1.4)	NA	NA
Age at menopause, mean (SD), y	47.4 (6.2)	47.3 (6.2)	48.0 (5.5)	47.9 (5.5)
Pregnancy, No. (%)				
Ever pregnant	2732 (88.1)	2700 (87.4)	NA	NA
Unknown	4 (0.1)	2 (0.1)		
Age at first birth, mean (SD), y	24.8 (4.6)	24.8 (4.5)	NA	NA
History of breast cancer in sister or mother, No. (%)	427 (13.4)	408 (13.2)	NA	NA

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not available or not applicable.

[a] In HORIZON-PFT, only current smoking status was collected.

Table 2

Breast Cancer Incidence by Treatment Assignment in the Fracture Intervention Trial (FIT) and Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly–Pivotal Fracture Trial (HORIZON-PFT): Bisphosphonate vs Placebo

Treatment Assignment	Treatment Group Allocation, No.	Follow-up Time, Person-years	Breast Cancer Cases, No. (%)	Unadjusted Hazard Ratio (95% CI)	*P* Value
FIT					
Alendronate	3103	11 637	57 (1.8)	1.24 (0.84–1.83)	.28
Placebo	3091	11 631	46 (1.5)	1 [Reference]	
HORIZON-PFT					
Zoledronic acid	3792	10 498	33 (0.9)	1.15 (0.70–1.89)	.59
Placebo	3788	10 582	29 (0.8)	1 [Reference]	
Pooled results					
Bisphosphonate	6895	22 135	90 (1.3)	1.20 (0.89–1.63)	.24
Placebo	6879	22 213	75 (1.1)	1 [Reference]	