Changes in bone mineral density at 3 years in postmenopausal women receiving anastrozole and risedronate in the IBIS-II bone substudy: an international, double-blind, randomised, placebo-controlled trial

Ivana Sestak, Shalini Singh, Jack Cuzick, Glen M Blake, Rajesh Patel, Fatma Gossiel, Rob Coleman, Mitch Dowsett, John F Forbes, Anthony Howell, Richard Eastell

Lancet Oncol 2014; 15: 1460–68

Published Online November 11, 2014 http://dx.doi.org/10.1016/S1470-2045(14)71035-6

This publication has been corrected. The corrected version first appeared at thelancet.com/oncology on November 24, 2014

Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University London, London, UK (I Sestak PhD, S Singh PhD, Prof J Cuzick PhD); **Biomedical Engineering Department, King's College London, London, UK** (Prof G M Blake PhD); **Imperial College London, London, UK** (R Patel PhD); **Department of Human Metabolism** (F Gossiel MSc, Prof R Eastell PhD) **and Department of Oncology** (Prof R Coleman MD), **University of Sheffield, Sheffield, UK Academic Department of Biochemistry, Royal Marsden Hospital, London, UK** (Prof M Dowsett PhD); **University of Newcastle, Calvary Mater Hospital, Australia New Zealand Breast Cancer Trials Group Newcastle, Newcastle, NSW, Australia** (Prof J F Forbes MD); **and Genesis Breast Cancer Prevention Centre, Manchester, UK** (Prof A Howell MD)

Correspondence to: Dr Ivana Sestak, Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, UK **i.sestak@qmul.ac.uk**

Summary

Background Aromatase inhibitors prevent breast cancer in postmenopausal women at high risk of the disease but are associated with accelerated bone loss. We assessed effectiveness of oral risedronate for prevention of reduction in bone mineral density (BMD) after 3 years of follow-up in a subset of patients in the IBIS-II trial.

Methods The double-blind IBIS-II trial recruited 3864 healthy, postmenopausal women at increased risk of breast cancer and randomly allocated them oral anastrozole (1 mg/day) or matched placebo. 1410 (36%) postmenopausal women were then enrolled in a bone substudy and stratified at baseline according to their lowest baseline T score at spine or femoral neck (stratum I: T score at least –1·0; stratum II: T score at least –2·5 but less than –1·0; stratum III: T score less than –2·5 but greater than –4·0). Women in stratum I were monitored only; women in stratum III were all given risedronate (35 mg/week). Women in stratum II were randomly assigned (1:1) to risedronate (35 mg/week) or matched placebo by use of a block randomisation schedule via a web-based programme. The primary outcome of this per-protocol analysis (done with all women with a baseline and 3 year DXA assessment) was the effect of risedronate versus placebo for osteopenic women in stratum II randomly allocated to anastrozole (1 mg/day). Secondary outcomes included effect of anastrozole (1 mg/day) on BMD in women not receiving risedronate (strata I and II) and in osteoporotic women who were all treated with risedronate (stratum III). The trial is ongoing, but no longer recruiting. This trial is registered, number ISRCTN31488319.

Findings Between Feb 2, 2003, and Sept 30, 2010, 150 (58%) of 260 women in stratum II who had been randomly allocated to anastrozole and either risedronate or placebo had baseline and 3 year assessments. At the lumbar spine, 3 year mean BMD change for the 77 women receiving anastrozole/risedronate was 1·1% (95% CI 0·2 to 2·1) versus –2·6% (–4·0 to –1·3) for the 73 women receiving anastrozole/placebo (p<0·0001). For the total hip, 3 year mean BMD change for women receiving anastrozole/risedronate was –0·7% (–1·6 to 0·2) versus –3·5% (–4·6 to –2·3) for women receiving anastrozole/placebo (p=0·0001). 652 (65%) of 1008 women in strata I and II who were not randomly allocated to risedronate had both baseline and 3 year assessments. Women not receiving risedronate in stratum I and II who received anastrozole (310 women) had a significant BMD decrease after 3 years of follow-up compared with women who received placebo (342 women) at the lumbar spine (–4·0% [–4·5 to –3·4] *vs* –1·2% [–1·7 to –0·7], p<0·0001) and total hip (–4·0% [–4·4 to –3·6] *vs* –1·8% [–2·1 to –1·4], p<0·0001). 106 (79%) of 149 women in stratum III had a baseline and a 3 year assessment. The 46 women allocated to anastrozole had a modest BMD increase of 1·2% (–0·1 to 2·6) at the spine compared with a 3·9% (2·6 to 5·2) increase for the 60 women allocated to placebo (p=0·006). For the total hip, a small 0·3% (–0·9 to 1·5) increase was noted for women allocated anastrozole compared with a 1·5% (0·5 to 2·5) increase for women allocated placebo, but the difference was not significant (p=0·12). The most common adverse event reported was arthralgia (stratum I: 94 placebo and 114 anastrozole; stratum II: 39 placebo/placebo, 25 placebo/risedronate, 34 anastrozole/placebo, and 34 anastrozole/risedronate; stratum III: 21 placebo/risedronate, 17 anastrozole/risedronate). Other adverse events included hot flushes, alopecia, abdominal pain, and back pain.

Interpretation Risedronate counterbalances the effect of anastrozole-induced bone loss in osteopenic and osteoporotic women and might be offered in combination with anastrozole treatment to provide an improved risk–benefit profile.

Funding Cancer Research UK (C569/A5032), National Health and Medical Research Council Australia (GNT300755, GNT569213), Sanofi-Aventis, and AstraZeneca.

Introduction

Oestrogen has a major role in the regulation of skeletal homoeostasis, and therefore physiological decreases in oestrogen concentrations place postmenopausal women at high risk of osteoporosis (low bone mineral density [BMD]). Reduction in BMD in the first 7 years after the menopause is 1–3% per year at the spine and 1–2% per year at the hip.[1] Bone loss can be treated or prevented

with bisphosphonates, which increase BMD by inhibition of osteoclast-mediated bone resorption.[2,3]

This risk of BMD loss, and therefore fractures, is aggravated in postmenopausal women with breast cancer who are given an aromatase inhibitor as part of their treatment.[4,5] Aromatase inhibitors suppress oestrogen concentrations in postmenopausal women by inhibition of the conversion of androgens to oestrogens by the aromatase enzyme in soft tissues, especially fat. Studies from large adjuvant trials show significant BMD decreases and higher fracture rates in women receiving aromatase inhibitors compared with women on tamoxifen.[6–9] In the ATAC trial, anastrozole significantly decreased BMD at the lumbar spine (6·1%) and total hip (7·2%) after 5 years of follow-up, whereas a significant increase in BMD was noted with tamoxifen.[6] Similarly, the results from the BIG 1–98 confirmed a significant BMD loss and an increased fracture rate with letrozole compared with tamoxifen.[10] Most of the studies investigating the effect of aromatase inhibitors on bone density have been done in postmenopausal women with early breast cancer receiving adjuvant tamoxifen as a comparison group. Tamoxifen has a beneficial effect on BMD and it is therefore difficult to determine the true effect of aromatase inhibitors on BMD.

Two large prevention trials[11,12] comparing an aromatase inhibitor with placebo in postmenopausal women at high risk of development of breast cancer have recently reported their main findings. The MAP.3 trial,[11] which investigated exemestane for the prevention of breast cancer, reported a significant BMD loss at the lumbar spine and total hip with exemestane compared with placebo after 2 years of follow-up.[13] Overall, no increases in fractures with exemestane were reported, but the follow-up of 35 months was too short to make a firm conclusion about this endpoint. The IBIS-II trial[12] compared anastrozole with placebo in postmenopausal women at high risk of development of breast cancer and noted a significant reduction in breast cancer with anastrozole. Here we report the first results of a per-protocol analysis of the placebo-controlled IBIS-II bone substudy, which assesses the effect of 3 years of risedronate on BMD in postmenopausal women with healthy bone density, osteopenia, or osteoporosis.

Methods

Study design and participants

The IBIS-II trial recruited 3864 healthy, postmenopausal women at increased risk of breast cancer and randomly allocated them to receive either 1 mg/day oral anastrozole or matching placebo.[12] Eligible women were offered the opportunity to enter a bone substudy. Eligibility criteria for the main IBIS-II study have been summarised in detail elsewhere.[12] In brief, postmenopausal women aged 40–70 years were recruited from 44 centres from seven countries. Study sites were those in IBIS-II that consented to do dual energy x-ray absorptiometry (DXA) scans as part of the follow-up trial (appendix) and deemed postmenopausal when they were aged 60 years or older; had had a bilateral oophorectomy; were younger than 60 years, but had a uterus and amenorrhoea for at least 12 months; or were younger than 60 years, had no uterus, and had a concentration of follicle stimulating hormone of greater than 30 IU/L. Exclusion criteria for the main trial included premenopausal status, any previous diagnosis of invasive cancers, present use of selective oestrogen receptor modulators for more than 6 months, intention to continue with hormone-replacement therapy, evidence of severe osteoporosis (T score less than –4·0), and lack of physiological or psychological fitness. Women in the bone substudy were enrolled and stratified into three groups according to the lowest baseline T score at either femoral neck or lumbar spine. Women with healthy T score (at least –1·0) were entered into stratum I. Women who were osteopenic (T score at least –2·5 but less than –1·0) were entered into stratum II. Finally, osteoporotic women with a T score of less than –2·5 but greater than –4·0 or those with one to two low trauma fragility fractures (as assessed by spinal radiographs) were entered into stratum III. Spinal radiographs within the 2 years before randomisation were used to rule out low trauma fractures. Women were advised to take vitamin D and calcium supplements, but no specific doses were specified or required by study protocol. Exclusion criteria for the bone substudy included previous bilateral hip fractures or any type of metabolic bone disease. Furthermore, women who had regularly taken medication affecting bone metabolism within the past 12 months before study entry were also excluded. Finally, women who had a T score of less than –4·0 and those with more than two low trauma fractures, were excluded from the bone substudy and referred for further management. The trial was approved by the UK North West Multicentre Research Ethics Committee and was done in accordance with the Declaration of Helsinki, under the principles of good clinical practice. Participants provided written informed consent.

See Online for appendix

Randomisation and masking

Women in stratum II were randomly assigned to receive risedronate (35 mg/week) or matched placebo. Randomisation was done with randomly chosen blocks of size six, eight, or ten to maintain balance and was not stratified. The non-consecutive allocation sequence was generated by the IBIS-II programmer before the study started who also assigned the interventions to all women. All IBIS-II personnel, participants, and clinicians were masked to treatment allocation and only the IBIS-II trial statistician (IS) had access to unmasked data.

Procedures

All women entering the main IBIS-II study were required to have a DXA scan before study entry for stratification

and exclusion purposes. In the bone substudy, BMD was further assessed by follow-up DXA scans at the lumbar spine and total hip at 12, 36, and 60 months. Women who had a BMD loss of 6% or more at the 12 month visit were required to have a safety DXA scan at 24 months of follow-up. Similarly, women with a BMD loss of more than 10% at 36 months had a safety scan at 48 months, and those with a BMD loss of more than 16% at the 60 months visit had an interval scan at 72 months.

We calculated T scores with either the Lunar[14] or Hologic[15] manufacturer's reference ranges for the lumbar spine (L1 to L4) and the National Health and Nutrition Examination Survey (NHANES) III reference range for the femoral neck region.[16] All baseline and follow-up DXA scans were reviewed centrally by two clinical scientists with expertise in bone densitometry (GMB and RP) to ensure quality assurance. Regular phantom reports from all participating centres were reviewed and investigators were requested to use the same DXA machine whenever possible throughout the study.

Women in stratum I were monitored only. Women in stratum II of the bone substudy were randomly allocated to receive either 35 mg/week oral risedronate or matching placebo for 5 years. All women in stratum III (osteoporotic women) received oral risedronate (35 mg/week) for 5 years. Women in strata II and III were advised to take their allocated risedronate or matching placebo in an upright position upon waking in the morning on an empty stomach, and not to consume anything apart from water within the next 30 min to minimise risk of inactivation of the drug or oesophageal irritation. Women were allowed to have a dose reduction (ie, alternate weeks) or go on treatment holiday from risedronate if they developed severe adverse events potentially related to the trial medication.

For biomarker analyses, a 10 mL urine sample from the second void was collected at baseline and 12 months. We measured N-telopeptide of type I collagen (NTx) levels with the Ortho Clinical Diagnostics automated immunoassay (High Wycombe, UK). The interassay coefficient of variation for NTx was 6·4%. NTx was expressed as a ratio to creatinine (nmol bone collagen equivalent:mmol creatinine) and the interassay coefficient of variation for creatinine was 1·8%.

Outcomes

The primary objective of this analysis was to compare the effect of risedronate versus placebo on BMD between baseline and 3 years at both the lumbar spine and total hip in women taking anastrozole in stratum II. Secondary endpoints included the effect of anastrozole versus placebo at the total hip and lumbar spine on BMD in women in stratum I and stratum II who had not been randomly allocated to risedronate at 3 years; the effect of

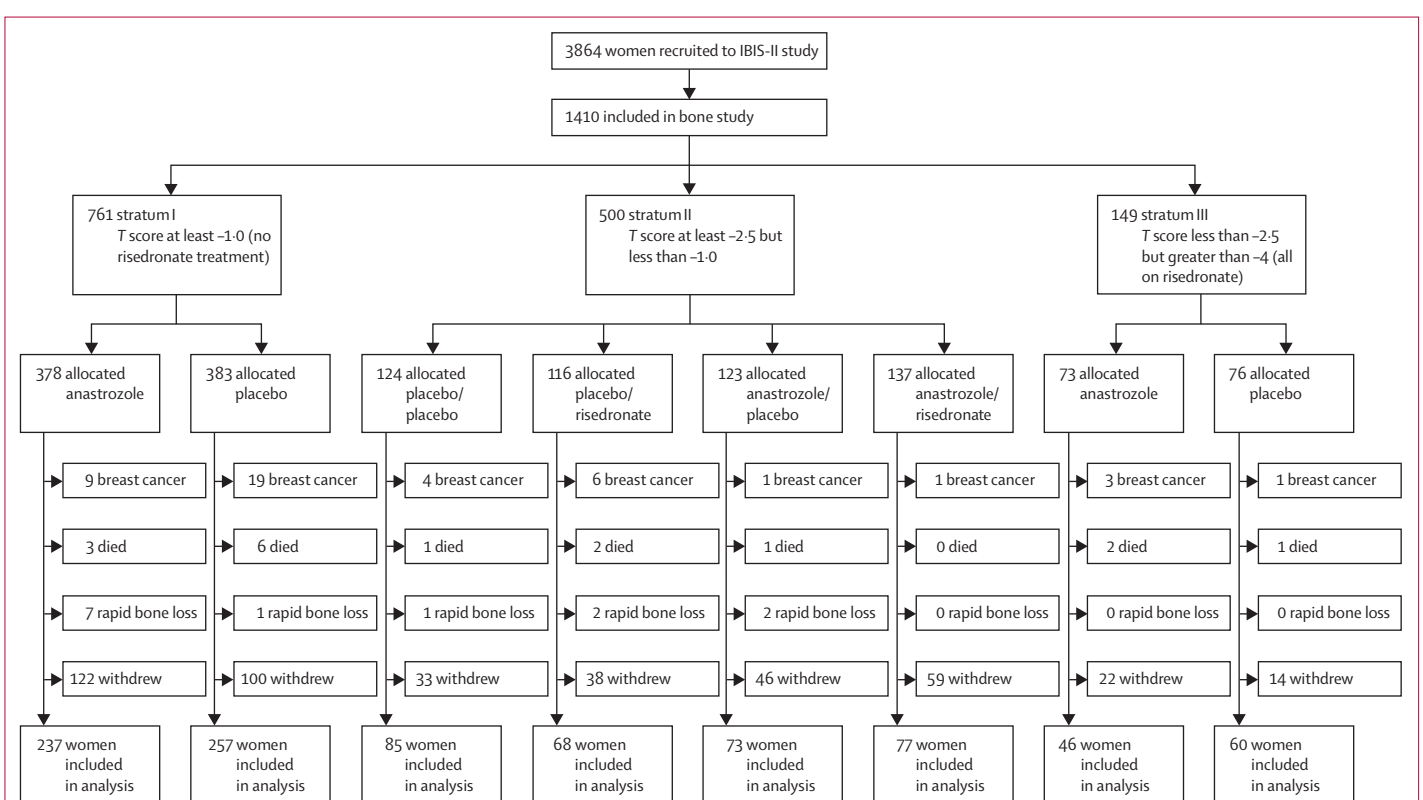

Figure 1: **IBIS-II bone substudy trial profile**

anastrozole versus placebo on BMD at the total hip and lumbar spine in women in stratum III at 3 years; and changes from baseline in biochemical markers (NTx to creatinine ratio) between baseline and 12 months of follow-up in all three strata.

Statistical analysis

All analyses were done on a per-protocol basis, in which women were included only if a baseline and 36 month DXA scan were available. In stratum II, our power calculations were designed to detect a difference of 1·6% between risedronate and placebo in women randomly allocated to anastrozole with 90% power. Power calculations for stratum I aimed to detect a difference of 1·4% between anastrozole and placebo with 90% power. Similar assumptions were made for women in stratum III, in which all women received risedronate.

Initial calculations suggested that we needed 500 women per strata. Recruiting osteoporotic women was difficult (number not achieved) whereas recruiting women with healthy bone was unproblematic. We thus entered postmenopausal women into the bone substudy until we had recruited 500 women into stratum II, which was needed to achieve power for primary objective. This analysis focuses on BMD changes between baseline and 36 months. Women ceased participation in the bone substudy if one of the following events occurred: withdrawal from main study, development of breast cancer, death, and if rapid bone loss occurred. These women were excluded from this analysis. We assessed normal distribution of all continuous variables with histograms and diagnostic distribution plots. All main results are expressed as percentage mean BMD changes at the total hip or lumbar spine between baseline and 36 months with corresponding 95% CIs. BMD changes and differences between treatment groups were assessed using *t* tests for two independent samples with corresponding 95% CI. For the NTx to creatinine ratio analysis, we report the estimated median (95% CI) percentage change from baseline to 12 months. We report two-sided p values, based on normal approximation, and all CIs at the 95% level. Analyses were done with STATA version 12.1.

This trial is registered, number ISRCTN31488319.

Role of the funding source

Sanofi-Aventis and AstraZeneca provided anastrozole and matched placebo. The sponsor or funding bodies of this study had no role in study design, collection of data or material, data analysis, interpretation of the data, or writing of the manuscript. IS had full access to all raw data. IS, JC, and RE had final responsibility to submit the report for publication.

Results

Between Feb 2, 2003, and Sept 30, 2010, we enrolled 1410 postmenopausal women into the bone substudy with a median follow-up of 3·0 years (IQR 2·95–3·09; figure 1). 761 (54%) women were stratified into stratum I, 500 (35%) into stratum II, and 149 (11%) into stratum III. Baseline and 36 month DXA scans were available for 903 (64%) women, who were included in this analysis (figure 1). No further DXA scans were done for women who withdrew from the main IBIS-II study (199 in stratum I, 127 in stratum II, 32 in stratum III), developed breast cancer (28 in stratum I, 12 in stratum II, four in stratum III), or died (nine in stratum I, four in stratum II, three in stratum III; no deaths were treatment related), and these women were excluded from the analysis (figure 1). 256 (72%) of the 358 women who withdrew from the main IBIS-II study did so before the 12 month follow-up visit (126 in stratum I, 112 in stratum II, 18 in stratum III) and therefore were excluded from this analysis. 55 women had a BMD decrease of more than 6% at the 12 month follow-up (36 in stratum I, 17 in stratum II, and two in stratum III). 13 of these women did not continue with the trial medication and were therefore excluded from this analysis (eight in stratum I, five in stratum II; figure 1). Only 76 (5%) of 1410 women withdrew from the bone substudy without first withdrawing from the main study (23 in stratum I, 49 in stratum II, and four in stratum III).

	Stratum I		Stratum II				Stratum III	
	Placebo (n=257)	Anastrozole (n=237)	Placebo/placebo (n=85)	Placebo/risedronate (n=68)	Anastrozole/placebo (n=73)	Anastrozole/risedronate (n=77)	Placebo/risedronate (n=60)	Anastrozole/risedronate (n=46)
Age (years)	58·7 (54·1–62·3)	58·4 (54·8–61·9)	59·4 (56·7–63·5)	60·8 (57·4–63·8)	60·2 (55·4–64·9)	60·0 (56·1–64·8)	61·9 (58·5–64·1)	59·3 (54·4–62·9)
Body-mass index (kg/m²)	28·7 (25·8–32·2)	28·6 (25·3–32·6)	27·1 (23·7–30·7)	26·4 (24·5–29·3)	26·3 (24·0–30·6)	26·4 (23·7–29·1)	26·3 (24·0–28·7)	25·4 (22·9–28·3)
Previous HRT use	129 (50%)	104 (44%)	35 (41%)	33 (45%)	31 (46%)	38 (49%)	23 (38%)	22 (48%)
Never smokers	156 (61%)	124 (52%)	54 (64%)	47 (64%)	39 (57%)	44 (57%)	37 (62%)	25 (54%)
Hysterectomy	80 (31%)	80 (34%)	21 (25%)	21 (29%)	21 (31%)	18 (23%)	18 (30%)	12 (26%)
Oophorectomy	47 (18%)	28 (12%)	8 (9%)	12 (16%)	11 (16%)	14 (18%)	3 (5%)	5 (11%)
Baseline T score	−0·22 (0·89)	−0·27 (0·82)	−1·40 (0·55)	−1·66 (0·53)	−1·44 (0·59)	−1·64 (0·62)	−2·64 (0·55)	−2·70 (0·56)

Data are median (IQR), n (%), or mean (SD). DXA=dual energy x-ray absorptiometry. HRT=hormone-replacement therapy.

Table 1: **Baseline characteristics for all postmenopausal women with a baseline and 36 month DXA scan available**

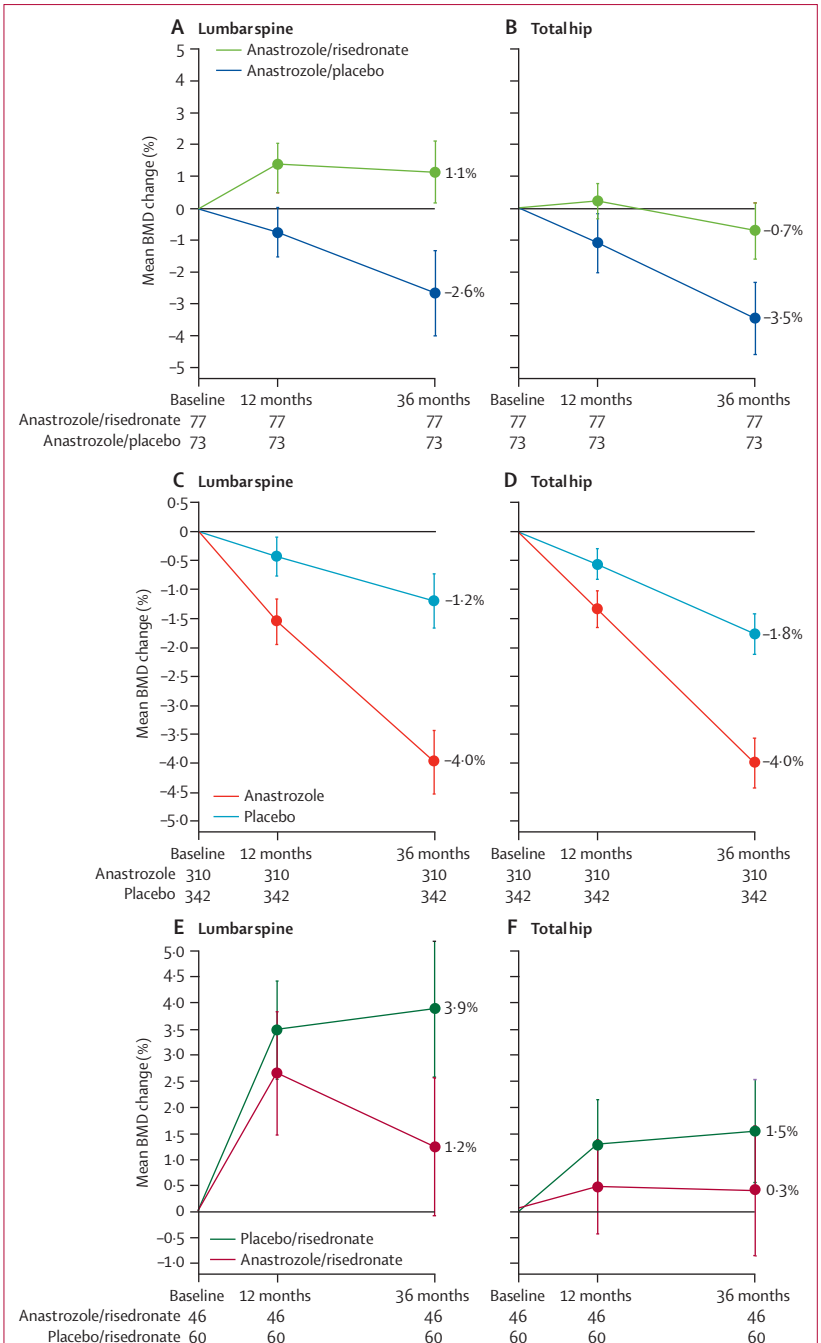

Figure 2: **Bone mineral density changes at lumbar spine and total hip at each follow-up visit**
(A–B) Women in stratum II receiving anastrozole who were randomly allocated to either risedronate or placebo. (C–D) Women in stratum I or II not receiving risedronate who were randomly allocated to either anastrozole or placebo. (E–F) Women in stratum III (all receiving risedronate) who were randomly allocated to either anastrozole or placebo. Error bars show 95% CIs.

Baseline characteristics for women with available baseline and 36 month DXA scans are shown in table 1. The baseline characteristics between women all receiving anastrozole and randomly allocated to risedronate versus placebo were evenly distributed and we noted no major differences (table 1). Similarly, for women in stratum I and II not receiving risedronate but randomly allocated to anastrozole versus placebo, we noted no substantial differences in baseline characteristics. Women in stratum III who were randomly allocated to receive placebo were older than were those randomly allocated to anastrozole (p=0·043; table 1). All other comparisons in this stratum were not substantially different between treatment groups. We compared baseline demographics and BMD for women included in this analysis with those who were excluded. No major differences between these two groups were noted for all baseline characteristics (data not shown).

In the analysis of women in stratum II who had all received anastrozole and either risedronate or placebo, 150 (58%) of 260 women had baseline and 36 month DXA scans available for analysis (77 anastrozole/risedronate *vs* 73 anastrozole/placebo). Women randomly allocated to anastrozole and receiving risedronate had a mean BMD increase of 1·1% (95% CI 0·2 to 2·1) at the lumbar spine after 36 months' follow-up compared with a mean decrease of –2·6% (–4·0 to –1·3) in those not receiving risedronate (p<0·0001; figure 2, appendix). We noted a linear decrease in BMD at the lumbar spine and total hip for women randomly allocated to anastrozole over 36 months' follow-up. Although BMD for the total hip decreased by only –0·7% (95% CI –1·6 to 0·2) for women on anastrozole and risedronate after 36 months' follow-up, the difference was significant compared with women on only anastrozole, who had a decrease of –3·5% (–4·6 to –2·3; p=0·0001; figure 2, appendix).

In the analysis of women in stratum I and II who were not randomly allocated to risedronate and received only anastrozole or placebo, 652 (65%) of 1008 had baseline and 36 month DXA scans. We noted a linear decrease in mean BMD for all groups between baseline and 36 months, irrespective of main randomisation (figure 2). However, we noted a significantly larger decrease at the lumbar spine or total hip for women randomly allocated to anastrozole compared with placebo (lumbar spine: –4·0% [95% CI –4·5 to –3·4] for anastrozole *vs* –1·2% [–1·7 to –0·7] for placebo, p<0·0001; total hip: –4·0% [–4·4 to –3·6] for anastrozole *vs* –1·8% [–2·1 to –1·4] for placebo; p=0·0001; figure 2, appendix).

In the analysis of women in stratum III who had all received risedronate and either anastrozole or placebo, 106 (71%) of 149 women had baseline and 36 month DXA scans. We noted the largest increase in mean percentage BMD at the lumbar spine for women randomly allocated to placebo (3·9% increase [95% CI 2·6 to 5·2]) whereas we noted a smaller increase for women randomly allocated to anastrozole (1·2% increase [–0·09 to 2·6]; p=0·006; figure 2, appendix). We noted a rapid increase in BMD with risedronate within the first 12 months of follow-up at the lumbar spine (figure 2). For the total hip, we noted an increase in mean percentage BMD in both treatment groups, with a

	Stratum I			Stratum II					Stratum III		
	Placebo (n=147)	Anastrozole (n=142)	p value	Placebo/ placebo (n=70)	Placebo/ risedronate (n=58)	Anastrozole/ placebo (n=69)	Anastrozole/ risedronate (n=67)	p value	Placebo/ risedronate (n=43)	Anastrozole/ risedronate (n=31)	p value
Baseline	37·3 (34·7 to 39·8)	39·1 (35·8 to 42·3)	0·3	43·0 (36·4 to 49·7)	43·0 (35·3 to 50·6)	43·1 (34·8 to 51·3)	44·3 (38·7 to 50·0)	0·8	50·7 (43·8 to 57·6)	52·2 (45·1 to 59·4)	0·8
12 months	34·9 (31·5 to 38·3)	49·5 (45·3 to 53·6)	<0·0001	44·1 (39·4 to 48·9)	24·6 (17·6 to 31·6)	55·6 (49·7 to 61·6)	33·7 (28·3 to 39·1)	<0·0001	23·5 (16·5 to 30·5)	32·7 (23·1 to 42·3)	0·1
Median change, %*	–1·9% (–4·8 to 1·0)	8·9% (4·4 to 13·4)	<0·0001	–1·8% (–6·7 to 3·2)	–16·1% (–18·6 to –13·6)	11·7% (6·2 to 17·1)	–13·0% (–17·5 to –8·5)	<0·0001	–25·4% (–35·6 to –15·2)	–19·0% (–26·1 to –11·9)	0·3
p value†	0·5	<0·0001	..	0·3	<0·0001	0·0013	0·0002	..	<0·0001	0·0002	..

Data are % (95% CI), unless otherwise stated. *Median of individual differences between baseline and 12 months. †Difference between baseline and 12 months.

Table 2: **Median baseline, 12 month, and median percentage changes for N-telopeptide to creatinine ratios**

	Stratum I		Stratum II				Stratum III	
	Placebo (n=257)	Anastrozole (n=237)	Placebo/ placebo (n=85)	Placebo/ risedronate (n=68)	Anastrozole/ placebo (n=73)	Anastrozole/ risedronate (n=77)	Placebo/ risedronate (n=60)	Anastrozole/ risedronate (n=46)
Arthralgia	94 (37%)	114 (48%)	39 (46%)	25 (37%)	34 (47%)	34 (44%)	21 (35%)	17 (37%)
Hot flush	24 (9%)	22 (9%)	7 (8%)	3 (4%)	5 (7%)	7 (9%)	5 (8%)	5 (11%)
Alopecia	13 (5%)	11 (5%)	2 (2%)	5 (7%)	3 (4%)	1 (1%)	1 (2%)	3 (7%)
Abdominal pain	6 (2%)	6 (3%)	5 (6%)	1 (1%)	1 (1%)	2 (3%)	4 (7%)	1 (2%)
Essential hypertension	6 (2%)	2 (1%)	0	1 (1%)	1 (1%)	0	0	0
Cataract	5 (2%)	2 (1%)	1 (1%)	1 (1%)	1 (1%)	0	1 (2%)	0
Arthritis	5 (2%)	2 (1%)	1 (1%)	1 (1%)	1 (1%)	0	1 (2%)	1 (2%)
Amnesia	1 (<1%)	3 (1%)	1 (1%)	0	0	1 (1%)	3 (5%)	3 (7%)
Anxiety	4 (2%)	2 (1%)	1 (1%)	0	0	0	0	0
Back pain	4 (2%)	8 (3%)	3 (4%)	1 (1%)	0	0	2 (3%)	2 (4%)
Abdominal distension	2 (1%)	0	1 (1%)	0	1 (1%)	1 (1%)	1 (2%)	1 (2%)
Depression	2 (1%)	0	0	0	0	0	0	0
Acute sinusitis	3 (1%)	0	0	0	0	0	0	0
Constipation	3 (1%)	0	0	0	1 (1%)	0	0	0
Cystitis	3 (1%)	0	0	0	2 (3%)	0	0	1 (2%)
Dyspepsia	2 (1%)	1 (<1%)	0	0	1 (1%)	0	0	1 (2%)
Acne	1 (<1%)	0	0	0	0	0	0	0
Angina pectoris	2 (1%)	2 (1%)	0	0	0	0	1 (2%)	0
Balance disorder	1 (<1%)	1 (<1%)	0	0	0	0	0	1 (2%)
Emotional disorder	0	1 (<1%)	0	0	1 (1%)	0	0	1 (2%)
Goitre	1 (<1%)	0	0	0	0	0	0	0
Gynaecological events	1 (<1%)	1 (<1%)	0	1 (1%)	0	1 (1%)	1 (2%)	1 (2%)
Total	183 (71%)	178 (75%)	61 (72%)	39 (57%)	52 (71%)	47 (61%)	41 (68%)	38 (83%)

See appendix for a breakdown of adverse events by severity.

Table 3: **Adverse events (any grade)**

smaller increase noted in women randomly allocated to anastrozole (anastrozole: 0·3% increase [95% CI –0·9 to 1·5] *vs* placebo: 1·5% increase [0·5 to 2·5]; p=0·12; figure 2, appendix).

Second void morning urine samples were analysed for NTx and creatinine in 866 women in the bone substudy. 627 (72%) women had a sample available at baseline and 12 months and these samples were the basis for this analysis (table 2). In stratum I, we noted a significant median increase of almost 9% after 12 months in women randomly allocated to anastrozole, but no difference with placebo (table 2). The difference between treatment groups for the yearly change in NTx to creatinine ratio was significant (p<0·0001; table 2). Women in stratum II who were randomly allocated to anastrozole but not to risedronate had a significant median increase in NTx to creatinine ratio of almost 12% by 12 months of follow-up whereas those randomly allocated to placebo did not

Panel: **Research in context**

Systematic review

We searched PubMed for randomly allocated trials in the preventive setting published in English before May 30, 2014, that investigated a bisphosphonate in women at high risk of breast cancer treated with an aromatase inhibitor. We used the search terms "breast cancer", "prevention", "high risk", "aromatase inhibitor", and "bisphosphonate". We identified no other breast cancer prevention trials investigating the effect of a bisphosphonate in combination with an aromatase inhibitor in postmenopausal women at high risk of development of the disease. However, we identified several trials in the adjuvant setting. We identified one other prevention trial[13] in postmenopausal women comparing exemestane with placebo that reported on bone mineral density changes in this study group, but did not investigate the use of a bisphosphonate.

Interpretation

Results from our trial provide the first evidence that risedronate prevents anastrozole-induced bone mineral density loss in postmenopausal women at high risk of development of breast cancer with osteopenia or osteoporosis. Risedronate was well tolerated and no serious adverse events associated with this drug were reported. Because aromatase inhibitors have emerged as a treatment option for the reduction of breast cancer risk for postmenopausal women, the concomitant use of a bisphosphonate is inevitable in this setting. However, long-term follow-up is required for the assessment of risedronate on fracture risk and for overall bone mineral density changes over the course of 5 years of anastrozole use.

show a significant change in this marker (table 2). By contrast, women who were randomly allocated to receive risedronate in stratum II had significant median decreases in NTx to creatinine ratios after 12 months of follow-up, irrespective of main treatment allocation (table 2). The differences in NTx to creatinine ratio between randomisation groups were significant after 12 months of follow-up in stratum II ($p<0·0001$). We noted decreases in NTx to creatinine concentrations were observed for both treatment groups for women in stratum III, but the difference was not significant (table 2).

639 (45%) of 1410 women in the IBIS-II bone substudy had adverse events (table 3). Incidence did not differ between treatment allocations within each stratum. No serious adverse events, such as osteonecrosis of the jaw or serious gastrointestinal problems, were reported after 3 years of follow-up with risedronate. Only 85 women had a treatment interruption from risedronate between baseline and 36 months (median 3 weeks [IQR 2–5]; 65 women in stratum II and 20 women in stratum III). By 36 months of follow-up, two women in stratum I (one anastrozole, one placebo) and 23 women in stratum II (six placebo/placebo, two placebo/risedronate, ten anastrozole/placebo, and five anastrozole/risedronate) developed osteoporosis and subsequently stopped trial medication to start open-label bisphosphonates. Overall, 128 fractures were reported by 109 women in the bone substudy (44 women in stratum I, 51 women in stratum II, and 14 women in stratum III). 57 (8%) of 711 women randomly allocated to anastrozole reported at least one fracture compared with 52 (7%) of 699 in the placebo group. The incidence rate for fractures in the anastrozole arm was 13·7 per 1000 woman-years compared with 12·6 per 1000 woman-years in the placebo arm ($p=0·70$). The number of fractures is too small at present to report stratum specific data, and further follow-up is needed.

Discussion

The mean percentage BMD loss in women on placebo in our study is similar to that reported in the overall population of similar age.[17] The IBIS-II results confirm that 3 years of anastrozole decreases BMD at the lumbar spine or total hip in healthy postmenopausal women, as previously reported (panel).[13] More importantly, our results show that risedronate counterbalances BMD loss induced by anastrozole in women with osteopenia or osteoporosis. Similar findings have been reported by two smaller studies in patients with breast cancer.[18,19] Both trials showed that the addition of a bisphosphonate normalises bone turnover in such patients receiving anastrozole after 2 years. Longer follow-up is needed to assess the fracture risk in healthy postmenopausal women receiving anastrozole. Risedronate was well tolerated and no serious adverse events, such as osteonecrosis of the jaw or serious gastrointestinal problems, were reported after 3 years of follow-up.

Bisphosphonates are well established drugs for the prevention of bone loss and reduction of fractures in postmenopausal women and men with osteoporosis.[2,20,21] Oral and intravenous bisphosphonates significantly reduce the incidence of vertebral and non-vertebral fractures.[22] In the adjuvant setting, anastrozole, letrozole, and exemestane have all been assessed in postmenopausal women with early breast cancer.[23–26] These trials have all shown significant BMD loss with these drugs, but have in common that the comparator was tamoxifen, which has been shown to have a beneficial effect on bone.[6,7,9] Zoledronic acid can prevent BMD loss induced by letrozole or anastrozole in postmenopausal women with breast cancer.[27–29] A small study assessing risedronate in women with breast cancer receiving anastrozole showed that this drug was effective in preventing anastrozole induced bone loss.[30] In a large review, the European guidelines[31] for the management of aromatase inhibitor induced bone loss concluded that the use of bisphosphonates for treatment of osteoporosis in postmenopausal women with breast cancer is safe and that these drugs are effective in the prevention of BMD loss because of endocrine therapy.

In the preventive setting, the bone substudy of the MAP.3 trial,[13] which compared exemestane with placebo, recently reported their results on bone density changes in a subgroup of women. Their primary endpoint was the comparison of percentage change in total volumetric BMD at the distal radius between baseline and 2 years of follow-up by quantitative CT. However, they also reported on BMD changes at the lumbar spine and total hip by DXA as a secondary objective, and reported that women

randomly allocated to exemestane had a significant decrease in BMD at all sites compared with placebo after 2 years of follow-up. The MAP.3 trial did not assess the use of a bisphosphonate in women receiving exemestane and therefore a direct comparison between the two trials in that respect is not possible.

Anastrozole resulted in significant increases in bone turnover whereas women on placebo showed little change after 12 months in those with healthy bone or osteopenic women and not receiving risedronate. Other studies, in the adjuvant setting, have also shown that aromatase inhibitors are associated with higher concentrations of bone resorption makers.[7,8,32] By contrast, those women who were randomly allocated to risedronate in stratum II or osteoporotic women (stratum III) receiving risedronate showed significant decreases in NTx to creatinine ratio by 12 months of follow-up.

Strengths of our analysis include an overall large sample size (1410 women), with a large proportion of women with osteopenia, long follow-up of 3 years, and a population that came from a large prevention trial with excellent clinical records. Furthermore, this trial is the first time that a bisphosphonate has been compared with a placebo in healthy postmenopausal woman at risk of development of breast cancer who are taking anastrozole as a preventive drug. This analysis reports on the 3 year BMD changes, but we will be able to present results after 5 years of treatment and are in the process of obtaining a DXA scan 2 years after treatment cessation to investigate whether BMD loss induced by anastrozole is regained.

Limitations of our study include the incomplete set of BMD data at 36 months (903 [64%] of 1410 women). Specifically for our primary objective, the number of women included in the analysis was small, but nevertheless we detected significant differences between the treatment groups. This finding is mainly attributable to withdrawal from the main IBIS-II study in the first 3 years and therefore our results might not be representative for the whole study population. However, only 5·4% of women withdrew from the bone substudy without first leaving the main study. A few participants were lost to follow-up because centres changed their DXA scanner to a different manufacturer. Wherever possible, this problem was mitigated by arranging for the women to be scanned on a similar machine at a different hospital. A further limitation of this study is the insufficient follow-up length for fracture risk assessment. DXA is the standard clinical technique for skeletal assessment of BMD changes and fracture risk, but does not take into account bone structure and microarchitecture of the bone. Bone structure, especially cortical structure of the bone, probably plays an important part in determination of bone strength,[13,33,34] but assessment of these bone structure changes was not possible.

To our knowledge, this analysis was the first to investigate the effect of risedronate on anastrozole-induced bone loss in healthy postmenopausal women in a placebo-controlled trial. Our findings confirm BMD loss induced by anastrozole in healthy postmenopausal women in the preventive setting. However, we also showed that risedronate counterbalances the effect of anastrozole-induced bone loss in osteopenic and osteoporotic women. Longer follow-up is needed to assess the risk of fracture with anastrozole in healthy postmenopausal women. Nevertheless, careful monitoring of bone density by DXA scans and the use of a bisphosphonate can control BMD loss induced by anastrozole in the preventive setting.

Contributors

IS, SS, JC, GMB, RP, RC, MD, JFF, AH, and RE designed the study and all authors interpreted the data. IS analysed the data and wrote the manuscript. All authors reviewed the report and approved the final version.

Declaration of interests

IS, SS, FG, GMB, RP, JFF, AH, and RE declare no competing interests. JC has received funding for the IBIS-II trial from Sanofi-Aventis and AstraZeneca, and is consultant for AstraZeneca. RC has given expert testimony for Novartis. MD has received grant support from AstraZeneca.

Acknowledgments

This study was funded in part by Cancer Research UK (C569/A5032) and National Health and Medical Research Council Australia (GNT300755, GNT569213), in part by Sanofi-Aventis and AstraZeneca, who also provided anastrozole and matching placebo. The study sponsor was Queen Mary University of London, UK. MD acknowledges support from the Royal Marsden National Cancer Research Institute Biomedical Research Centre.

References

1 Sowers MR, Zheng H, Jannausch ML, et al. Amount of bone loss in relation to time around the final menstrual period and follicle-stimulating hormone staging of the transmenopause. *J Clin Endocrinol Metab* 2010; **95:** 2155–62.

2 Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998; **280:** 2077–82.

3 Black DM, Cummings SR, Karpf DB, et al, for the Fracture Intervention Trial Research Group. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 1996; **348:** 1535–41.

4 Guise TA. Bone loss and fracture risk associated with cancer therapy. *Oncologist* 2006; **11:** 1121–31.

5 Leslie WD, Cowden EA, Maclean JP. Oestrogen and bone density: a comparison of tamoxifen and hypo-oestrogenaemia. *Nucl Med Commun* 1995; **16:** 698–702.

6 Eastell R, Adams JE, Coleman RE, et al. Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. *J Clin Oncol* 2008; **26:** 1051–57.

7 Eastell R, Hannon RA, Cuzick J, Dowsett M, Clack G, Adams JE. Effect of an aromatase inhibitor on bmd and bone turnover markers: 2-year results of the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial (18233230). *J Bone Miner Res* 2006; **21:** 1215–23.

8 Lonning PE, Geisler J, Krag LE, et al. Effects of exemestane administered for 2 years versus placebo on bone mineral density, bone biomarkers, and plasma lipids in patients with surgically resected early breast cancer. *J Clin Oncol* 2005; **23:** 5126–37.

9 Perez EA, Josse RG, Pritchard KI, et al. Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: a companion study to NCIC CTG MA.17. *J Clin Oncol* 2006; **24:** 3629–35.

10 Rabaglio M, Sun Z, Price KN, et al. Bone fractures among postmenopausal patients with endocrine-responsive early breast cancer treated with 5 years of letrozole or tamoxifen in the BIG 1–98 trial. *Ann Oncol* 2009; **20:** 1489–98.

11 Goss PE, Ingle JN, Ales-Martinez JE, et al. Exemestane for breast-cancer prevention in postmenopausal women. *N Engl J Med* 2011; **364:** 2381–91.

12 Cuzick J, Sestak I, Forbes JF, et al. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. *Lancet* 2014; **383:** 1041–48.

13 Cheung AM, Tile L, Cardew S, et al. Bone density and structure in healthy postmenopausal women treated with exemestane for the primary prevention of breast cancer: a nested substudy of the MAP.3 randomised controlled trial. *Lancet Oncol* 2012; **13:** 275–84.

14 GE Medical systems. DPX series operator's manual. GE Medical systems, 1998.

15 Kelly TL. Bone mineral density reference databases for American men and women. *J Bone Miner Res* 1990; **5** (suppl 1)**:** S249.

16 Looker AC, Wahner HW, Dunn WL, et al. Updated data on proximal femur bone mineral levels of US adults. *Osteoporos Int* 1998; **8:** 468–89.

17 Finkelstein JS, Brockwell SE, Mehta V, et al. Bone mineral density changes during the menopause transition in a multiethnic cohort of women. *J Clin Endocrinol Metab* 2008; **93:** 861–68.

18 Van Poznak C, Hannon RA, Mackey JR, et al. Prevention of aromatase inhibitor-induced bone loss using risedronate: the SABRE trial. *J Clin Oncol* 2010; **28:** 967–75.

19 Lester JE, Dodwell D, Purohit OP, et al. Prevention of anastrozole-induced bone loss with monthly oral ibandronate during adjuvant aromatase inhibitor therapy for breast cancer. *Clin Cancer Res* 2008; **14:** 6336–42.

20 Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007; **356:** 1809–22.

21 Wells G, Cranney A, Peterson J, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev* 2008; **1:** CD004523.

22 Khosla S, Bilezikian JP, Dempster DW, et al. Benefits and risks of bisphosphonate therapy for osteoporosis. *J Clin Endocrinol Metab* 2012; **97:** 2272–82.

23 Coleman RE. Effect of anastrozole on bone mieral density and bon fractures: results of the 'Arimidex' (anastrozole), tamoxifen, alone or in combination (ATAC) trial. *Eur J Cancer Suppl* 2004; **2:** 140: abstr 289.

24 Cuzick J, Sestak I, Baum M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. *Lancet Oncol* 2010; **11:** 1135–41.

25 Coleman RE, Banks LM, Girgis SI, et al. Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomised controlled study. *Lancet Oncol* 2007; **8:** 119–27.

26 Goss PE, Hershman DL, Cheung AM, et al. Effects of adjuvant exemestane versus anastrozole on bone mineral density for women with early breast cancer (MA.27B): a companion analysis of a randomised controlled trial. *Lancet Oncol* 2014; **15:** 474–82.

27 Coleman R, de Boer R, Eidtmann H, et al. Zoledronic acid (zoledronate) for postmenopausal women with early breast cancer receiving adjuvant letrozole (ZO-FAST study): final 60-month results. *Ann Oncol* 2013; **24:** 398–405.

28 Brufsky AM, Harker WG, Beck JT, et al. Final 5-year results of Z-FAST trial: adjuvant zoledronic acid maintains bone mass in postmenopausal breast cancer patients receiving letrozole. *Cancer* 2012; **118:** 1192–201.

29 Llombart A, Frassoldati A, Paija O, et al. Immediate administration of zoledronic acid reduces aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer: 12-month analysis of the E-ZO-FAST trial. *Clin Breast Cancer* 2012; **12:** 40–48.

30 Sergi G, Pintore G, Falci C, et al. Preventive effect of risedronate on bone loss and frailty fractures in elderly women treated with anastrozole for early breast cancer. *J Bone Miner Metab* 2012; **30:** 461–67.

31 Hadji P, Aapro MS, Body JJ, et al. Management of aromatase inhibitor-associated bone loss in postmenopausal women with breast cancer: practical guidance for prevention and treatment. *Ann Oncol* 2011; **22:** 2546–55.

32 Harper-Wynne C, Ross G, Sacks N, et al. Effects of the aromatase inhibitor letrozole on normal breast epithelial cell proliferation and metabolic indices in postmenopausal women: a pilot study for breast cancer prevention. *Cancer Epidemiol Biomarkers Prev* 2002; **11:** 614–21.

33 Vico L, Zouch M, Amirouche A, et al. High-resolution pQCT analysis at the distal radius and tibia discriminates patients with recent wrist and femoral neck fractures. *J Bone Miner Res* 2008; **23:** 1741–50.

34 Kazakia GJ, Burghardt AJ, Link TM, Majumdar S. Variations in morphological and biomechanical indices at the distal radius in subjects with identical BMD. *J Biomech* 2011; **44:** 257–66.