Aromatase inhibitors are associated with a higher fracture risk than tamoxifen: a systematic review and meta-analysis

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Abstract

Background: In this paper, our aim was to systematically evaluate published evidence of bone fracture risk associated with tamoxifen and aromatase inhibitors in women aged 65 and under, and diagnosed with nonmetastatic breast cancer.

Methods: We comprehensively searched MEDLINE, EMBASE and CINAHL databases from January 1997 through May 2015, and reference lists of the selected articles to identify English-language randomized controlled trials and cohort studies of fracture risk. Two independent reviewers screened articles and assessed methodological quality using Risk of Bias assessment for randomized controlled trials and the Newcastle–Ottawa Scale for cohort studies. Fracture risk was estimated as pooled risk ratios using a random-effects model and inverse variance method.

Results: Of 1926 identified articles, 21 independent studies fulfilled our selection criteria. Similar fracture risk was observed in women treated and not treated with tamoxifen [pooled risk ratio (RR) 0.95; 95% confidence interval (CI) 0.84–1.07]. A 35% (95% CI 1.21–1.51) higher fracture risk was observed in the aromatase inhibitor group compared with the tamoxifen group. A 17% (95% CI 1.07–1.28) higher fracture risk was observed in the aromatase inhibitor group than the no aromatase inhibitor group. Compared with the tamoxifen group, aromatase inhibitor-associated fracture risk increased by 33% (pooled RR 1.33; 95% CI 1.21–1.47) during the tamoxifen/aromatase inhibitor treatment period, but did not increase (pooled RR 0.99; 95% CI 0.72–1.37) during the post-tamoxifen/aromatase inhibitor treatment period.

Conclusions: Fracture risk is significantly higher in women treated with aromatase inhibitors, especially during the treatment period. Tamoxifen is not associated with lower fracture risk while tamoxifen could potentially preserve bone mass. Better osteoporosis management programs, especially during the treatment period, are needed for this group of women.

Keywords: aromatase inhibitors, breast cancer, fracture risk, hormonal treatment, tamoxifen, women

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Introduction

Adjuvant systemic treatments, such as chemotherapy and hormonal treatment, have been used widely to treat breast cancer.[1] Hormonal treatment is recommended for women with hormone receptor-positive breast cancer, accounting for at least two-thirds of all breast cancer cases.[2,3] The two most common hormonal treatments are tamoxifen and aromatase inhibitors (AIs).

Tamoxifen, a selective estrogen receptor modulator (SERM), was introduced in the 1970s. Tamoxifen is currently recommended to treat

early and advanced-stage breast cancer in premenopausal and postmenopausal women.[4] Tamoxifen is also an optional treatment in women with stage 0 (*in situ*) breast cancer.[5] Tamoxifen reduces the available estrogen to cancer cells by competitively inhibiting the binding of estrogen to the estrogen receptors on breast tissues. The effect of tamoxifen on bone tissues is inconsistent across studies and seems to differ by menopausal status. Tamoxifen caused a bone mineral density (BMD) decrease in healthy premenopausal women but a BMD increase in healthy postmenopausal women.[6] In women diagnosed with breast cancer, tamoxifen preserves bone mass in premenopausal women, and either slightly increases or decreases BMD in postmenopausal women.[7–12] Tamoxifen may have a beneficial effect on bone health in women diagnosed with breast cancer. However, tamoxifen has not been approved for the treatment or prevention of osteoporosis in any populations by the US Food and Drug Administration.

AIs were introduced in the early 2000s. AIs are currently recommended to treat early and advanced-stage breast cancer in postmenopausal women, especially women unable to tolerate tamoxifen or at higher risk of cancer relapse. AIs reduce the circulating estrogen levels by inhibiting the aromatase enzyme from converting androgen into estrogen in nonovarian tissues. AIs significantly increase bone loss[10,13] and are associated with higher fracture risks in several major trials.[14,15] However, AI-associated fracture risk has not been reviewed systematically.

The initial goal of this study was to determine the effects of adjuvant systemic breast cancer treatments on BMD changes and fracture risk, compared with locoregional treatments (i.e. surgery and radiation therapy) or no breast cancer treatment in women aged 65 and under. In women diagnosed with breast cancer, younger women (aged 65 and under) are less likely than older women to be assessed for fracture risk before fractures occur using 10-year fracture risk assessment tools or BMD testing. This is because cancer treatment-associated fracture risk is not universally recognized as an indicator in the 10-year fracture risk assessment tools and BMD testing.[16] Fractures, however, have a higher clinical impact on healthcare systems than BMD changes. Tamoxifen and AIs are used to treat breast cancer more often than other adjuvant systemic treatments. Hence, we focussed our research questions on the differential fracture risks associated with tamoxifen and AIs in younger women aged 65 years and under, and diagnosed with nonmetastatic breast cancer. This study is targeting younger women, as it is more challenging to identify high-risk young women before fractures occur.

Method

This was a systematic review with meta-analysis study using aggregate data from randomized controlled trials (RCTs) and cohort studies on fracture risks associated with tamoxifen and AIs in younger women aged 65 years and under, and diagnosed with nonmetastatic breast cancer. We registered the review protocol at PROSPERO (registration number CRD42015015604, available at: https://www.crd.york.ac.uk/PROSPERO/). We reported study results using criteria from the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA).[17] Article search was conducted by the first author. Study selection (NR/OT for title/abstract screening; WH/OT for full-text article review), study quality evaluation (WH/OT), and data extraction (WH/OT) were performed independently by two reviewers using Excel spreadsheets. Disagreements between reviewers were resolved by discussion. Persistent disagreements between reviewers were arbitrated by another designated team member (MD).

Search strategy

We searched PubMed, MEDLINE, CINAHL, EMBASE, and Cancerlit databases for article published from 1 January 1970 to 1 May 2015, on 3 May 2016. We included search terms "breast" and "wom*n OR female" and "tumor OR cancer OR neoplasm OR malignanc?" and "fracture OR BMD OR densit? OR densitometr? OR absorptiometry?". Studies were then limited to human studies and English language articles. Review articles were then excluded. The reference lists of the included articles were hand searched. Approximately 20% of included and excluded articles at each step of the article search were randomly reviewed to ensure proper article search strategies.

Study selection

Articles were initially screened by title and abstract, followed by full article reviews (Figure 1). Articles fulfilling the inclusion criteria: (a) RCTs or cohort studies;[18] (b) women diagnosed with nonmetastatic breast cancer; (c) at least one participant aged 65

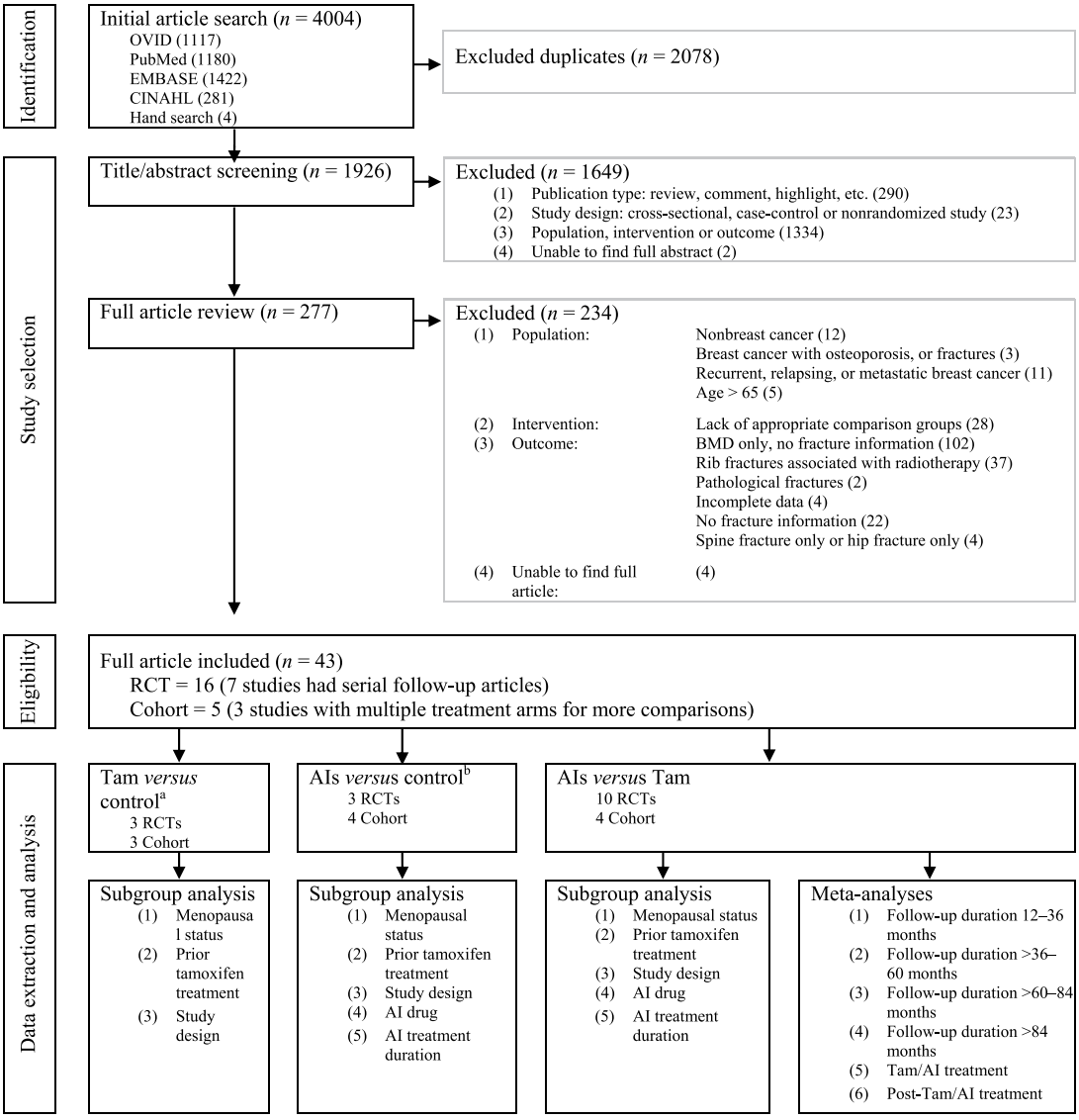

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram for systematic review of the fracture risks associated with breast cancer treatments.
[a]No tamoxifen;
[b]No AIs.
AIs, aromatase inhibitors; BMD, bone mineral density; RCT, randomized controlled trial; Tam, tamoxifen.

years and under at baseline; (d) breast cancer treatments of tamoxifen, AIs or both; and (e) fracture outcomes, were selected. We defined the outcomes in this study as count of fracture events or participants with fractures. Articles reporting pathological fractures or any specific fracture type (e.g. spine fracture only) were excluded.

Study quality assessment

We evaluated the methodological quality of the selected articles using two separate assessment tools suggested by the Cochrane Collaboration Review Group. RCTs were evaluated using the Cochrane Risk of Bias assessment tool. Each RCT was assessed and rated as 'low risk of bias', 'high risk of bias' or 'unknown risk of bias' in the seven domains of potential bias.[19,20] Cohort studies were evaluated in three categories using the Newcastle–Ottawa Scale with a range of zero to nine stars. Each cohort study was awarded a maximum of one star per item within the selection category with four items and outcome category with three items, and a maximum of two stars for the single item within the comparability category.[21,22]

Data extraction

Articles reporting data with the same follow-up times from the same independent study were collated (ID 5, 16, 18, 21, 30). We extracted data from each included study on method, participant, treatment, fracture outcome, and factors controlled for multivariate regression models. Fracture outcome information included definition of fractures, count of fracture events (allowing more than one fracture event per participant), count of participants who developed fractures, and relative measures consisting of odds ratios (ORs), risk ratios (RRs), incidence rate ratios (IRRs), or hazard ratios (HRs) using Cox regression models.

There were two articles (ID 12, 34) each reporting combined data from two independent studies.[23,24] Extracted data from each independent study were inadequate for meta-analysis. The authors of both articles were contacted by email but we were unable to obtain additional information on these four studies.

Data synthesis

Meta-analyses were undertaken to estimate the differential fracture risks of tamoxifen and AIs, and risks between tamoxifen and AI. Each fracture risk was stratified by three to five factors of menopausal status (prespecified), prior tamoxifen treatment, study design, AI treatment duration and AI drugs, using subgroup analysis. Menopausal status was determined using age in the two cohort studies with missing menopausal status information (ID 4, 35).

The time effect on differential fracture risk between tamoxifen and AI was evaluated by ranges of follow-up durations (12–36, >36–60, >60–84, >84 months) and treatment period (on- and post-Tam/AI treatment). Meta-analyses were conducted independently for each range of follow-up duration and treatment period. The Tam/AI-treatment period was defined as the time period when women were receiving tamoxifen or AIs during the study period.

For each independent study with serial follow-up data, the article with the longest follow-up duration was included for each individual meta-analysis to avoid double counting of study participants. For studies with multiple treatment arms, the arms were either grouped as a single pair-wise comparison (ID 13, 14) or a three-group comparison with each other (ID 35, 36, 37) of tamoxifen, AIs, and control group (no tamoxifen alone, no AIs alone, and no combination of tamoxifen and AIs). Articles with double-zero events (zero-cell counts in both intervention arms) were excluded from meta-analysis.[25]

Statistical analysis

Meta-analyses were restricted to studies reporting counts of participants with fractures and not fracture events. For RCTs included in meta-analysis, RRs with 95% confidence intervals (CIs) were calculated. For cohort studies included in meta-analysis, published adjusted hazard ratios (aHRs) with 95% CIs were used first. RRs were calculated for cohort studies without available aHRs. aHRs were treated as adjusted RRs due to the low incidence of fracture outcomes. Overall differential fracture risk was pooled as weighted RRs using a generic inverse variance method with random effects models. The weight of each study was based on the inverse of that study's variance. Statistical significance of the pooled RRs was evaluated using chi-square tests. Statistical heterogeneity was evaluated using Cochrane's Q statistic and quantified as I^2 measures. Sensitivity tests were conducted when combining RRs and aHRs. Funnel plots were not used to evaluate publication bias, as each analysis included less than ten studies.[26] All statistical tests were performed using RevMan 5.2 analysis software (The Cochrane Collaboration, Copenhagen, Denmark).[27]

Results

There were 4004 articles identified, of which 2078 were duplicate articles (Figure 1). This left 1926 unique articles for title/abstract screening. Of them, 1649 were excluded, leaving 277 articles for full article review. A total of 43 articles from 21 independent studies fulfilled our selection criteria and proceeded to methodological quality assessment.

Characteristics of included studies

Sixteen RCTs, four retrospective cohort studies, and one prospective cohort study were included (Table 1). All RCTs were designed to evaluate primary outcome of efficacy and secondary outcome of safety, including fractures, using intent-to-treat analysis with the exception of one study (ID 7). All cohort studies were designed to evaluate fracture outcomes. Seven of the 16 RCTs reported serial follow-up data. Eight of the 16 RCTs involved postmenopausal women only.

Mean or median age ranged from 43 to 67 years. Treatment dose was unknown in four cohort studies (ID 4, 11, 35, 36). Doses of tamoxifen were 20 mg/day in almost all studies, with one (ID 1) of 30 mg/day and two of 20–30 mg/day (ID 12, 15). Doses of AIs were consistent across all studies as follows: anastrozole (1 mg/day), letrozole (2.5 mg/day), and exemestane (25 mg/day). Treatment duration ranged from 12 to 72 months while follow-up duration ranged from 12 to 128 months. About 17–25% crossover was reported in a few studies (ID 25, 26). Fracture outcomes were measured as any self-reported fracture (15 studies), self-reported osteoporotic/minimal-trauma fracture (ID 1, 36), self-reported hospitalized fracture (ID 32), any fracture event in medical records (ID 11), or any fracture using data linkage (ID 4, 35).

Study quality assessment

High risk of bias was observed primarily in domains of blinding of participants, blinding of outcome assessors, incomplete data, and other biases (e.g. funding) among RCTs (Appendix Figure A, online only). Unblinding of participants and their outcome assessment was observed in at least half of the RCTs that were either open RCTs or unblinded during their study periods.

Financial support from pharmaceutical companies was noted in at least 80% of the RCTs. The quality of all cohort studies was consistently high with either seven or nine out of a maximum of nine stars (Appendix Table B, online only).

Tamoxifen

Three RCTs and three cohort studies compared fracture outcomes between women treated and not treated with tamoxifen (Table 2; Figure 2). One RCT with double-zero events was excluded from this meta-analysis. This analysis included 37,783 participants. Fracture risk did not differ between tamoxifen and no-tamoxifen groups (pooled RR 0.95; 95% CI 0.84–1.07). The statistical heterogeneity was low with an I^2 measure of 0% ($p = 0.72$). No statistical significance was reported in subgroup analyses.

Aromatase inhibitors

Three RCTs and four cohort studies compared fracture outcomes between women treated and not treated with AIs. All seven studies were included in this meta-analysis (Table 2; Figure 3). Data from the longest follow-up durations were selected for the two included studies (ID 6, 9). This analysis included 59,258 participants. A 17% (95% CI 1.07–1.28) higher fracture risk was observed in the AI group than the no-AI group. Statistical heterogeneity was low, with an I^2 measure of 8% ($p = 0.37$). No statistical significance was noted in subgroup analyses. Sensitivity analyses, excluding the Xu *et al.* study[65] (ID 37), resulted in a similar estimate of 16% RR increase with a zero I^2 measure across all analyses.

Comparison of aromatase inhibitors and tamoxifen

Ten RCTs and four cohort studies compared fracture outcomes between women treated with AIs and treated with tamoxifen (Table 2; Figure 4). Four studies (ID 12, 27, 34, 35) were excluded due to either missing data, double-zero events, or reporting combined data from more than one independent study. Data from the longest follow-up duration was selected for the five included studies (ID 14, 18, 26, 30, 32). This analysis included 20,403 participants. A 35% (95% CI 1.21–1.51) higher fracture risk was observed in the AI group compared with the tamoxifen group. The statistical heterogeneity was low with an I^2 measure of 12% ($p = 0.43$). No statistical significance was observed in subgroup analysis. Sensitivity analyses excluding the Xu *et al.* study[65] (ID 37) resulted in a similar estimate of 36% RR increase with a low I^2 measure (range 0–7) across all analyses.

Comparison of tamoxifen and aromatase inhibitors: time effect

Twenty articles from ten independent studies were included for these meta-analyses (Appendix Table C; Figure D, E, online only). Compared with the tamoxifen group, increased AI-associated fracture risk showed a downward trend when the range of follow-up duration increased. The pooled RRs were 1.47 (95% CI 1.28–1.68), 1.46 (1.27–1.68), 1.39 (1.23–1.57) and 1.32 (1.10–1.57) when the range of follow-up duration was 12–36, >36–60, >60–84 and >84 months, respectively. Compared with the tamoxifen group, AI-associated fracture risk increased by 33% (pooled RR 1.33; 95% CI 1.21–1.47) during the Tam/AI treatment period, but did not increase (pooled RR 0.99; 95% CI 0.72–1.37) during the post-Tam/AI treatment period. Sensitivity analysis excluding the Koopal *et al.*

Table 1. Summary of studies.

Study Information						Study participants (safety population)				Treatment		Published fracture outcomes - fracture				Meta-analysis	Factors
ID	**Study name Author, year (ref)**	**Design**	**Country**	**Data source**	**Median follow-up duration**	**Age (Years)[a]**	**Post-menopausal (%)**	**Prior tamoxifen [b] (duration)**	**No.**	**Arms**	**Duration**	**Type**	**Participants with fractures No.**	**Fracture events per 1000 PY**	**Risk measure (95% CI)**	**Risk Measure used in meta-analysis (95% CI)**	**Adjusted**
Tamoxifen vs. Control / placebo (reference)																	
1	Kristense, 1994[28]	RCT	Denmark	Self-report	44 M	57 (NR, 65)	100	N	20 23	Tam Control	24 M	Osteo-porotic	0 / – 0 / –	–	–	–	–
2	Love, 1994[29]	RCT	USA	Self-report	Mean 60.5 M	58 ± 4	100	N	70 70	Tam Placebo	24 M	Any	6 / 7 8 / 10	–	–	Calculated RR 0.75 (0.27, 2.05)	–
3	Sacco, 2003[30]	RCT	Italy	Self-report	52 M	61 ± 6	95	Y (24 M)	943 958	Tam Control	36 M	Any	8 / – 10 / –	–	–	Calculated RR 0.81 (0.32, 2.05)	-
Aromatase inhibitors (AIs) vs. Control / placebo (reference)																	
4	Mincey, 2006[31]	Cohort	US	Data-linkage	Range 1998- 2005	66 ± 11 64 ± 13	<100[c]	N	1354 11,014	AIs Control	–	Any	183 / – 1132 / –	86 / – 63.6 / –	aHR 1.21 (1.03, 1.43) IRR 1.35 (1.16, 1.58)	Published aHR 1.21 (1.03, 1.43)	Age, 1, 2, 3, 4
5	***MA 17*** Goss, 2003[32]; DeGrendele, 2003[33]	RCT	Multiple, 9	Self-report	2.4 Y	62 (NR)	100	Y (60 M)	2154 2145	AIs (Let) Placebo	60 Months	Any	77 / – 63 / –	–	–	–	–
6	***MA 17*** Goss, 2005[34]				30 M				2572 2577	AIs (Let) Placebo			137 / – 119 / –	–	–	Calculated RR 1.15 (0.94, 1.41)	–
7	***MA 17*** Goss, 2008[35]				1.1 Y[d] (after unblinding)				1579[e] 804	AIs (Let) Placebo			82 / – 25 / –	–	–	–	–
8	***Norwegian*** Lonning, 2005[36]	RCT	Norway	Self-report	24 M	59 (46–73)	100	N	73 74	AIs (Exe) Placebo	24 months	Any	4 / – 5 / –	–	–	–	–
9	***Norwegian*** Geisler, 2006[37]				36 M				73 74	AIs (Exe) Placebo			4 / – 5 / –	–	–	Calculated RR 0.81 (0.23, 2.90)	–
10	***NSABP (B-33)*** Mamounas, 2008 [38]	RCT	USA / Canada	Self-report	Till April 2004	60 (NR)	100	Y (57–66 M)	783 779	AIs (Exe) Placebo	60 months	Any	28 / – 20 / –	–	–	Calculated RR 1.39 (0.79, 2.45)	–
Aromatase inhibitors (AIs) vs. Tamoxifen (reference)																	
11	Koopal, 2015[39]	Cohort	Netherland	Charts + X-ray	Post-Tam/ AI (3.1 Y)	52 ± 7 (pre-m) 71 ± 10 (post-m)	0	N	39 92	AIs Tam	5.7 – 6 years	Any	4 / – 24 / –	–	–	Calculated RR 0.39 (0.15, 1.06)	–
12	***ABCSG – 8 /*** ARNO 95 Jakesz, 2005[23]	RCT	Germany / Austria,	Self-report	28 M	62 (41–80)	100	Y (24 M)	1602 1597	AIs (Ana) Tam	36 months	Any	34 / – 16 / –	–	OR 2.14 (1.14, 4.17)		–
13	***ABCSG-12*** Grant, 2009[40]	RCT	Austria	Self-report	47.8 M	45 (26–57)	0	N	903 900	AIs (Ana) Tam	36 months	Any	12 / – 12 / –	–	–	Calculated RR 1.00 (0.45, 2.21)	–
14	***ABCSG-12*** Grant, 2011[41]				62 M				903 900	AIs (Ana) Tam			13 / – 12 / –	–	–	Calculated RR 1.08 (0.50-2.35)	–

Table 1. (Continued)

Study Information						Study participants (safety population)				Treatment		Published fracture outcomes - fracture				Meta-analysis	Factors
ID	**Study name Author, year (ref)**	**Design**	**Country**	**Data source**	**Median follow-up duration**	**Age (Years)[a]**	**Post-menopausal (%)**	**Prior tamoxifen [b] (duration)**	**No.**	**Arms**	**Duration**	**Type**	**Participants with fractures No.**	**Fracture events per 1000 PY**	**Risk measure (95% CI)**	**Risk Measure used in meta-analysis (95% CI)**	**Adjusted**
Aromatase inhibitors (AIs) vs. Tamoxifen (reference)																	
15	***ARNO 95*** Kaufmann, 2007[42]	RCT	Germany	Self-report	30.1 M	61 (46–74)	100	Y (24 M)	445 452	AIs (Ana) Tam	36 months	Any	10 / – 10 / –	–	–	Calculated RR 1.02 (0.43, 2.42)	–
16	***ATAC*** Buzdar, 2002[43]; Fisher, 2002[44]; Baum, 2002[45]	RCT	Multiple, 21	Self-report	33.3 M	64 ± 9	100	N	3092 3094	AIs (Ana) Tam	60 months	Any	183 / – 115 / –	–	–	Calculated RR 1.59 (1.27,2.00)	–
17	***ATAC*** Baum, 2003[46]				42 M				3092 3093	AIs (Ana) Tam			219 / – 137 / –	–	–	Calculated RR 1.60 (1.30, 1.97)	–
18	***ATAC*** Howell, 2005[47]; Cuzick, 2007[48]				68 M				3092 3094	AIs (Ana) Tam			340 / – 237 / –	22.6 / – 15.6 / –	OR 1.49 (1.25, 1.77) HR 1.44 (1.21, 1.68)	Calculated RR 1.44 (1.23, 1.68)	–
19	***ATAC*** Arimidex, 2008[49]				100 M				3092 3094	AIs (Ana) Tam			–	–	–	–	–
					On Tam/AI				3092 3094	AIs (Ana) Tam			– / 375 – / 234	– / 29.3 – / 19	IRR 1.55 (1.31-1.83)	–	–
					Post Tam/AI				2496 2419	AIs (Ana) Tam			– / 146 – / 143	– / 15.6 – / 15.1	IRR 1.03 (0.81, 1.31)	–	–
20	***ATAC*** Cuzick, 2010[14]				120 M				3092 3094	AIs (Ana) Tam			–	–	–	–	–
					On Tam/AI				3092 3094				451 / – 351 / –	–	–	Calculated RR 1.29 (1.13, 1.46)	–
					Post-Tam/AI				2223 2246				110 / – 112 / –	–	–	Calculated RR 0.99 (0.77, 1.28)	–
21	***BIG 1-98*** Thurlimann, 2005[50]; Monnier, 2005[51]	RCT	Multiple, 27	Self-report	25.8 M	61 (38–90)	100	N	3975 3988	AIs (Let) Tam	60 M	Any	225 / – 159 / –	22 / – 15 / –	OR 1.44	Calculated RR 1.42 (1.16, 1.73)	–
22	***BIG 1-98*** Crivellari, 2008[52]				40.4 M				2448 2447	AIs (Let) Tam			196 / – 132 / –	–	–	–	–
23	***BIG 1-98*** Coates, 2007[53]				51 M				2448 2447	AIs (Let) Tam			211 / – 141 / –	–	–	Calculated RR 1.50 (1.22, 1.84)	–

(Continued)

Table 1. (Continued)

Study Information						Study participants (safety population)				Treatment		Published fracture outcomes - fracture				Meta-analysis	Factors
ID	Study name Author, year (ref)	Design	Country	Data source	Median follow-up duration	Age (Years)[a]	Post-menopausal (%)	Prior tamoxifen [b] (duration)	No.	Arms	Duration	Type	Participants with fractures No.	Fracture events per 1000 PY	Risk measure (95% CI)	Risk Measure used in meta-analysis (95% CI)	Adjusted
24	***BIG 1-98*** Rabaglio, 2009,[15]				On Tam/AI 60.3 M[f]				2448 2447	AIs (Let) Tam			228 / – 160 / –	25.2 / 27.1 18.1 / 18.7	HR 1.38 (1.13, 1.69) aHR 1.40 (1.14, 1.71)	Calculated RR 1.42 (1.17, 1.73)	Age, 5, 6, 7, 8, 9, 10
25	***BIG 1-98*** Mouridsen, 2009[54]				71 M				1540 1534	AIs (Let) Tam			–	–	–	–	–
					on Tam/AI (Y1–2)				1540 1534	AIs (Let) Tam			65 / – 50 / –	–	–	–	–
					on Tam/AI (Y 3–5)[g]				1540 1534	AIs (Let) Tam			90 / – 67 / –	–	–	–	–
					on Tam/AI (Y 1–5)				1540 1534	AIs (Let) Tam			150 / – 112 / –	–	–	–	–
26	***BIG 1-98*** Colleoni, 2011[55]				74 M				2448 2447	AIs (Let) Tam			244 / – 165 / –	–	–	Calculated RR 1.48 (1.22, 1.79)	–
27	***HOBOE*** Nuzzo, 2012[56]	RCT	Italy	Self-report	12 M	50 (29–80)	46	N	148 152	AIs (Let) Tam	60 M	Any	0 / 0 0 / 0	–	–	–	–
28	***IES*** Coombes, 2004[57]	RCT	Multiple, 37	Self-report	30.6 M	64 ± 8	100	Y (2.4 Y)	2305 2329	AIs (Exe) Tam	2-3 Y	Any	72 / – 53 / –	–	–	Calculated RR 1.37 (0.97, 1.95)	–
29	***IES*** Coleman, 2007[58]				58 M				2320 2338	AIs (Exe) Tam			162 / 188 115 / 143	17.6 / 20.1 13.2 / 16.0	OR 1.45 (1.13-1.87)	Calculated RR 1.42 (1.13, 1.79)	–
30	***IES*** Bliss, 2012[59]; Clomean, 2010[9]				91 M				2319 2338	AIs (Exe) Tam			249 / 280 190 / 214	–	OR[h] 1.36 (1.04, 1.76)	Calculated RR 1.32 (1.10, 1.58)	–
					On Tam/AI				2319 2338	AIs (Exe) Tam			113 / 117 86 / 83	– / 21 – / 12.3	OR[h] 1.39 (0.94, 2.06) HR[h] 1.39 (0.96, 2.01)	Calculated RR 1.37 (1.04, 1.81)	–
					Post Tam/AI				2105 2036	AIs (Exe) Tam			144 / 163 117 / 128	– / 20.3 – / 20.6	OR[h] 1.20 (0.86, 1.69) HR[h] 1.20 (0.89, 1.63)	Calculated RR 1.19 (0.94, 1.51)	–
31	***ITA*** Boccardo. 2005[60]	RCT	Italy	Self-report	36 M	63 (38–77)	100	Y (28 M)	223 225	AIs (Ana) Tam	2-3 Y	Any	2 / – 2 / –	–	–	Calculated RR 1.01 (0.14, 7.10)	–
32	***ITA*** Boccardo, 2013[61]				128 M				223 225	AIs (Ana) Tam		Hospital events,	4 / – 4 / –	–	–	Calculated RR 1.01 (0.26, 3.98)	–

Table 1. (Continued)

Study Information						Study participants (safety population)				Treatment		Published fracture outcomes - fracture				Meta-analysis	Factors
ID	**Study name Author, year (ref)**	**Design**	**Country**	**Data source**	**Median follow-up duration**	**Age (Years)[a]**	**Post-menopausal (%)**	**Prior tamoxifen [b] (duration)**	**No.**	**Arms**	**Duration**	**Type**	**Participants with fractures No.**	**Fracture events per 1000 PY**	**Risk measure (95% CI)**	**Risk Measure used in meta-analysis (95% CI)**	**Adjusted**
33	***N-SAS BC03*** Aihara, 2010[62]	RCT	Japan	Self-report	42 M	60 ± 7	100	Y (1-4 Y)	347 349	AIs (Ana) Tam	1-4 Y	Any	5 / – 9 / –	–	–	Calculated RR 0.56 (0.19, 1.65)	–
34	***TEXT / SOFT (IBCSG)*** Pagani, 2014[24]	RCT	Multiple	Self-report	68 M	43 ± NR	0	N	2318 2325	AIs (Exe) Tam	60 M	Any	158 / – 120 / –	–	–	–	–
Multiple treatment arms																	
35	Ligibel, 2012[63]	Cohort	US	Data linkage	30 M	67 ± NR	<100 c	N	Total 44,026	Tam Control	–	Any	–	26.8 / – 38.1 / –	aHR 0.93 (0.82-1.06)	Published aHR 0.93 (0.82-1.06)	Age, 1, 2, 3, 11, 12, 13, 14, 15
									Total 44,026	AIs Control				33.3 / – 38.1 / –	aHR 1.13 (1.02-1.25)	Published aHR 1.13 (1.02-1.25)	
									Total 44,026	AIs Tam				33.3 / – 26.8 / –		–	
36	Robinson, 2014[64]	Cohort	Australia	Self-report	Mean 5.7 Y	57 (27–87)	35	N	393 252	Tam Control	–	Minimal trauma	56 / – 30 / –	–	–	Calculated RR 1.20 (0.79-1.81)	–
									306 252	AIs Control			46 / – 30 / –		OR 1.31 (0.80, 2.14)	Calculated RR 1.26 (0.82-1.94)	–
									306 393	AIs Tam			46 / – 56 / –			Calculated RR 1.05 (0.74, 1.51)	–
37	Xu, 2014[65]	Cohort	China	Self-report	32.5 M	56 ± 8 61 ± 9	76–88	N	52 89	Tam Control	–	Any	1 / – 1 / –	–	aHR 2.64 (0.14, 48.73)	Published aHR 2.64 (0.14, 48.73)	10, 16, 17
						61 ± 7 61 ± 9			70 89	AIs Control			9 / – 1 / –		aHR 20.08 (1.7, 234.1)	Published aHR 20.08 (1.7, 234.1)	
						61 ± 7 56 ± 8			70 52	AIs Tam			9 / – 1 / –		–	Calculated RR 6.69 (0.87, 51.14)	

[a]Mean ± SD or median (range)
[b]Tamoxifen treatment prior to the study
[c]Menopausal status was determined based on age range
[d]Information of fracture outcome was collected for 1.1 years after unblinding on October 2003
[e]1579 participants crossed over from placebo group after unblinding
[f]Fracture data obtained from participants on medications only
[g]25.2% crossover
[h]99% confidence intervals

Abbreviations: *aHR* adjusted hazard ratio, *AIs* Aromatase inhibitors, *Ana* anatrozole, *CI* confidence interval, *Exe* Exemestane, *HR* hazard ratio, *IRR* incidence rate ratio, *Let* letrozole, *M* month, *No* number, *NR* not recorded, *OR* odds ratio, *pre-m* pre-menopausal, *post-m* post-menopausal, *ref* reference, *RCT* randomized controlled trail, *RR* risk ratio, *SD* standardized deviation, *Tam* Tamoxifen, *Y* year,
Study abbreviations: *ABCSG* Austrian Breast & Colorectal Cancer Study Group, *ARNO* Arimidex-Nolvadex, *ATAC* Arimidex, Tamoxifen, Alone or in Combination, *BIG* Breast International Group, *HOBOE* Hormonal Bone Effects, *IES* Intergroup Exemestane Study, *ITA* Italian Tamoxifen Anastrozole, *NSABP* National Surgical Adjuvant Breast and Bowel Project, *SOFT* Suppression of Ovarian Function Trial, *TEXT* Tamoxifen and Exemestane
Adjusted factor: 1 Charlson Comorbidity Index, 2 residential regions, 3 health plan, 4 income, 5 body mass index, 6 smoking, 7 osteoporosis, 8 fracture history, 9 hormonal replacement therapy, 10 bisphosphonates, 11 index year, 12 urban/rural status, 13 drug class, 14 education, 15 % of black, 16 age of diagnosis, 17 age of menopause

Table 2. Meta-analysis including subgroup analysis of aromatase inhibitors, tamoxifen, and control groups on fractures.

Treatment arms	Study (*n*)	Participant (*n*)	Pooled RR (95% CI)	*p* for effect	I^2 (%)[a]	*p* for subgroup differences	ID of article included
Tam *versus* control (no-Tam)[b]							
Total effect	5	37,783	0.95 (0.84, 1.07)	0.39	0	0	2, 3, 35, 36, 37
Subgroup analysis							
Menopausal status						0.65	
Premenopausal	0		–	–	–		–
Pre-/postmenopausal	4		0.95 (0.84, 1.08)	0.42	0		3, 35, 36, 37
Postmenopausal	1		0.75 (0.27, 2.05)	0.57	–		2
Prior tamoxifen treatment						0.74	
No	4		0.95 (0.84, 1.07)	0.41	0		2, 35, 36, 37
Yes	1		0.81 (0.32, 2.05)	0.66	–		3
Study design						0.58	
RCT	2		0.78 (0.40, 1.55)	0.48	0		2, 3
Cohort	3		0.95 (0.84, 1.08)	0.45	0		35, 36, 37
AIs *versus* control (no-AIs)[b]							
Total effect	7	59,258	**1.17 (1.07, 1.28)**	**<0.01**	8		4, 6, 9, 10, 35, 36, 37
Subgroup analysis							
Menopausal status						0.88	
Premenopausal	0		–	–	–		–
Pre-/postmenopausal	4		**1.19 (1.01, 1.41)**	**0.04**	49		4, 35, 36, 37
Postmenopausal	3		1.17 (0.97, 1.41)	0.10	0		6, 9, 10
Prior tamoxifen treatment						0.99	
No	5		**1.18 (1.02, 1.37)**	**0.03**	35		4, 9, 35, 36, 37
Yes	2		**1.18 (0.97, 1.42)**	**0.09**	0		6, 10
Study design						0.88	
RCT	3		1.17 (0.97, 1.41)	0.10	0		6, 9, 10
Cohort	4		**1.19 (1.01, 1.41)**	**0.04**	49		4, 35, 36, 37
AI treatment duration						0.57	
⩽48 months	2		1.18 (0.97, 1.42)	0.09	0		6, 10
60 months	1		0.81 (0.23, 2.90)	0.75	–		9
AI drug						0.93	

Table 2. (Continued)

Treatment arms	Study (*n*)	Participant (*n*)	Pooled RR (95% CI)	*p* for effect	I^2 (%)[a]	*p* for subgroup differences	ID of article included
Nonsteroidal (letrozole and anastrozole)	1		1.15 (0.94, 1.41)	0.16	–		6
Steroidal (exemestane)	2		1.27 (0.76, 2.14)	0.36	0		9, 10
Any AI	4		**1.19 (1.01, 1.41)**	**0.04**	49		35, 36, 37
AIs *versus* Tam[b]							
Total effect	9	20,403	**1.35 (1.21, 1.51)**	<**0.01**	12		14, 15, 18, 26, 30, 32, 33, 36, 37
Subgroup analysis							
Menopausal status						0.75	
Premenopausal	1		1.08 (0.5, 2.35)	0.85	–		14
Pre-/postmenopausal	2		2.00 (0.36, 11.21)	0.43	67		36, 37
Postmenopausal	6		**1.39 (1.26, 1.54)**	<**0.01**	0		15, 18, 26, 30, 32, 33
Prior tamoxifen treatment						0.5	
No	5		**1.38 (1.18, 1.62)**	<**0.01**	27		14, 18, 26, 36, 37
Yes	4		**1.27 (1.07, 1.51)**	<**0.01**	0		15, 30, 32, 33
Study design						0.68	
RCT	7		**1.39 (1.26, 1.53)**	<**0.01**	0		14, 15, 18, 26, 30, 32, 33
Cohort	2		2.00 (0.36, 11.21)	0.43	67		36, 37
AI treatment duration						0.19	
⩽48 months	5		**1.26 (1.07, 1.50)**	<**0.01**	0		14, 15, 30, 32, 33
60 months	2		**1.45 (1.29, 1.64)**	<**0.01**	0		18, 26
AI drug						0.76	
Nonsteroidal (letrozole and anastrozole)	6		**1.41 (1.26, 1.59)**	<**0.01**	0		14, 15, 18, 26, 32, 33
Steroidal (exemestane)	1		**1.32 (1.10, 1.58)**	<**0.01**	–		30
Any AI	2		2.00 (0.36, 11.21)	0.43	67		36, 37

Values in bold indicate statistical significance.
AI, aromatase inhibitor; CI, confidence interval; RCT, randomized controlled trial; RR, risk ratio; Tam, tamoxifen.
[a]For heterogeneity.
[b]Reference group.

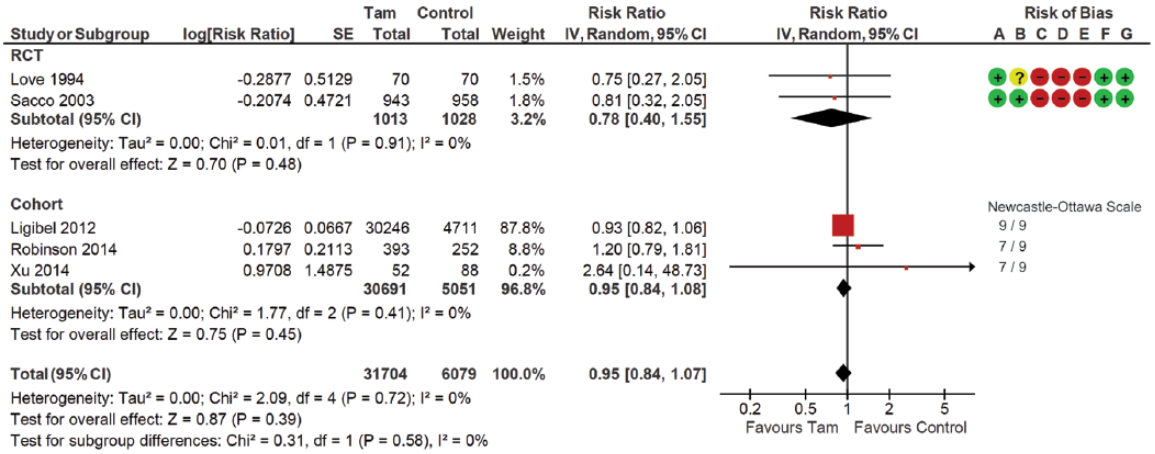

Figure 2. Forest plot of comparison for fracture risk between women treated with tamoxifen and not treated with tamoxifen (control) by study design subgroups.
The large diamond at the bottle of the table represents the pooled risk ratio of all studies. The width of the diamond represents with 95% CI. Results of study quality assessment were included.
Risk of bias: (A) random sequence generation (selection bias); (B) allocation concealment (selection bias); (C) blinding of participants and personnel (performance bias); (D) blinding of outcome asessment (detection bias); (E) incomplete outcome data (attrition bias); (F) selective reporting (reporting bias); (G) other bias.
⊕ Low risk of bias ? Unknown risk of bias ⊖ High risk of bias
CI, confidence interval; d.f., degrees of freedom; IV, inverse variance; RCT, randomized controlled trial; SE, standard error; Tam, tamoxifen.

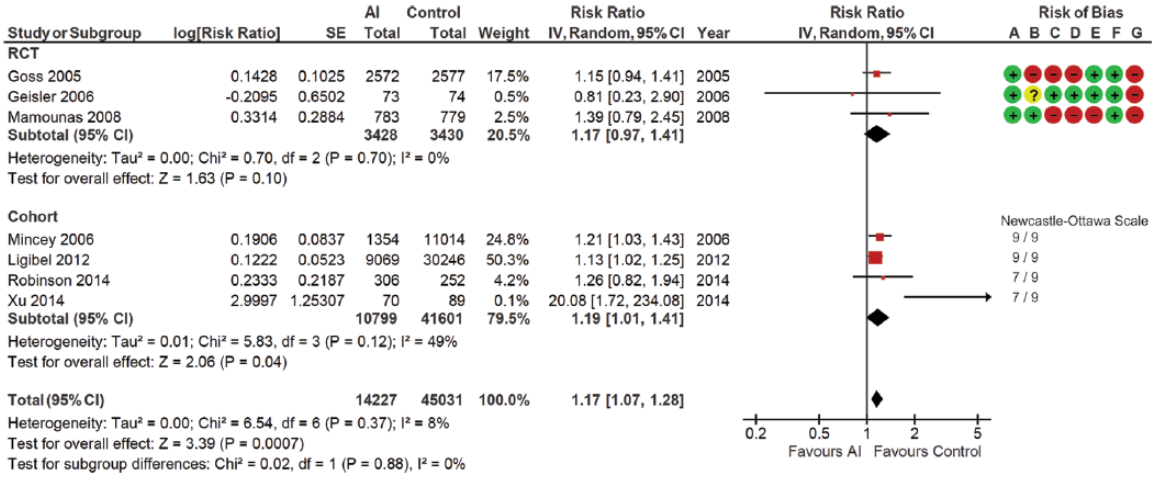

Figure 3. Forest plot of comparison for fracture risk between women treated with aromatase inhibitors and not treated with aromatase inhibitors (control) by study design subgroups.
The large diamond at the bottle of the table represents the pooled risk ratio of all studies. The width of the diamond represents with 95% CI. Results of study quality assessment were included.
Risk of bias: (A) random sequence generation (selection bias); (B) allocation concealment (selection bias); (C) blinding of participants and personnel (performance bias); (D) blinding of outcome asessment (detection bias); (E) incomplete outcome data (attrition bias); (F) selective reporting (reporting bias); (G) other bias.
⊕ Low risk of bias ? Unknown risk of bias ⊖ High risk of bias
AI, aromatase inhibitor; CI, confidence interval; d.f., degrees of freedom; IV, inverse variance; RCT, randomized controlled trial; SE, standard error.

study[39] (ID 11) resulted in a similar RR estimate (pooled RR 1.09; 95% CI 0.92–1.31) with a reduction of I^2 measure by 56% for the post-Tam/AI treatment period.

Discussion

This study systematically summarized fracture risks associated with tamoxifen and AIs in women diagnosed with breast cancer. Results showed that

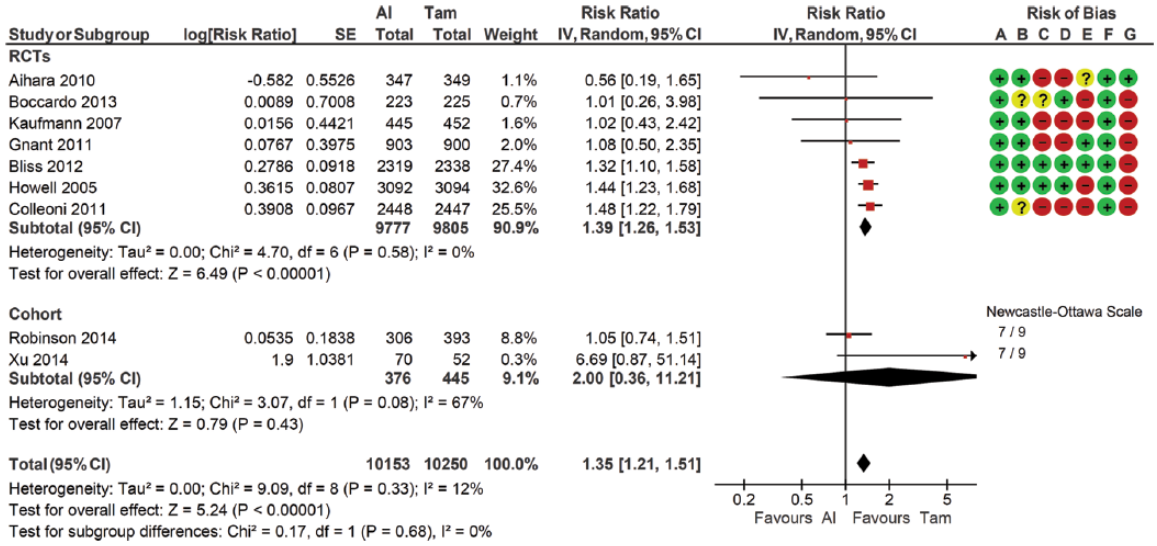

Figure 4. Forest plot of comparison for fracture risk between women treated with aromatase inhibitors and treated with tamoxifen by study design subgroups.
The large diamond at the bottle of the table represents the pooled risk ratio of all studies. The width of the diamond represents with 95% CI. Results of study quality assessment were included.
Risk of bias: (A) random sequence generation (selection bias); (B) allocation concealment (selection bias); (C) blinding of participants and personnel (performance bias); (D) blinding of outcome asessment (detection bias); (E) incomplete outcome data (attrition bias); (F) selective reporting (reporting bias); (G) other bias.
⊕ Low risk of bias ? Unknown risk of bias ⊖ High risk of bias
AI, aromatase inhibitor; CI, confidence interval; IV, inverse variance; RCT, randomized controlled trial; SE, standard error; Tam, tamoxifen.

fracture risk did not differ between women treated and not treated with tamoxifen. AI-associated fracture risk was 17 and 35% higher than the risks in the no-AI group and tamoxifen group, respectively. Compared with the tamoxifen group, increased AI-associated fracture risk trended down when the range of follow-up duration increased. AI-associated fracture risk increased by 30% during the Tam/AI treatment period but did not increase during the post-Tam/AI treatment period when compared with the tamoxifen group.

Our results showed that fracture risk did not differ between the tamoxifen and no-tamoxifen groups. This finding is consistent with the fact that tamoxifen has no effect on reducing vertebral or hip fractures in general populations.[66,67] By contrast, tamoxifen treatment for 1 year increased the risk of trochanteric fractures (HR 2.12; 95% CI 1.12–4.01) among 1716 postmenopausal women with nonmetastatic breast cancer during the 12-year follow up in the Danish Breast Cancer Cooperative Group (DBCG) trial.[68] While evidence shows that tamoxifen may preserve BMD, tamoxifen has not been approved for the treatment or prevention of osteoporosis in any population by the US Food and Drug Administration. Women who receive tamoxifen breast cancer treatment should not skip BMD testing recommended for women diagnosed with breast cancer.

Our analysis showed that AI-associated fracture risk increased by 17 and 35% when compared with the no-AI and tamoxifen groups respectively. The result in comparison with the tamoxifen group is consistent with the Early Breast Cancer Trialists Collaborative Group (EBCTCG) study (rate ratio 1.42; 95% CI 1.28–1.57),[69] with methodological differences in data type (aggregate *versus* individual), type of study included (RCTs and cohort *versus* RCTs only), effect size (RR *versus* rate ratio), outcome measure (number of participants with fractures *versus* number of fracture events) and data synthesis.

When comparing the AI with tamoxifen groups, differential fracture risks were higher without a statistical difference in the prior tamoxifen treatment subgroup (pooled RR 1.38; 95% CI 1.18–1.62) than the no prior tamoxifen treatment subgroup (pooled RR 1.27; 95% CI 1.07–1.51). This might be because prior tamoxifen treatment

may reduce AI-associated fracture risk. Or it may be because follow-up time was longer in the prior tamoxifen subgroup (30–128 months) than the no prior tamoxifen subgroup (32–74 months), and fracture risk decreased when follow-up duration increased.

AIs are given alone for 5 years or in sequence for 2–3 years before or after tamoxifen (sequential AI-Tam or sequential Tam-AI).[70] Sequential treatments, compared with either tamoxifen or AIs alone, reduce the exposure times of both tamoxifen and AIs, which may reduce the long-term side effects associated with either tamoxifen or AIs, such as fracture risk. Differential fracture risk between sequential AI-Tam and sequential Tam-AI treatments were not included nor compared in this study due to limited available data. However, the BIG-98 trial showed sequential AI-Tam treatment reducing fracture risk by 22% (calculated RR 0.78; 95% CI 0.62–0.99) compared with the sequential Tam-AI treatment in approximately 3000 participants during the 45-month follow up.[54]

Longer AI treatment duration did not affect fracture risk in our study, but increased fracture risk by 47% in the Amir *et al.* study in 2011.[71] This could be explained primary by different data synthesis methods. Our study evaluated the effect of AI treatment duration on differential fracture risk between AIs and tamoxifen. The Amir *et al.* study[71] evaluated differential fracture risk of AI treatment duration.

A steroid AI (exemestane) with irreversible binding properties may affect bone health differently than nonsteroidal AIs (letrozole and anastrozole) with reversible binding properties.[72] Our results showed no difference between steroidal and nonsteroidal AI subgroups when evaluating differential fracture risks of AIs, and between AIs and tamoxifen. This finding is consistent with findings from two other major trials; a bone substudy of the Tamoxifen Exemestane Adjuvant Multinational (TEAM) in Japan[73] and MA.27[74] comparing nonsteroidal anastrozole with steroidal exemestane.

While extracting and synthesizing data, we noted that fracture risk was not consistent over time. The RR decreased from 1.60 to 1.44 when the follow-up duration increased from 42 to 68 months in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial.[46,47] The IRRs decreased significantly from 1.55 during the Tam/AI treatment period to 1.03 during the post-Tam/AI treatment period in the ATAC trial.[49] In response to this, we evaluated the time effect on fracture risk by conducting four individual meta-analyses with four ranges of follow-up durations and two individual meta-analyses for Tam/AI treatment and post-Tam/AI treatment periods.

Our results showed that AI-associated fracture risk, compared with the tamoxifen group, increased by 33% (95% CI 1.21–1.47) during the Tam/AI treatment period but did not increase during the post-Tam/AI treatment period. This is consistent with the EBCTCG study which shows the AI-associated fracture risk increased by 43% (95% CI 1.30–1.57) during the first 4 years from treatment allocation (treatment period), but did not increase during the 5–9 years (primarily post-treatment period, 95% CI 0.61–1.18). This is also consistent with our other result: AI-associated fracture risk, compared with the tamoxifen group, decreased when follow-up duration increased and more participants entered their post-Tam/AI treatment periods. This also can be explained by changes in BMD but not fracture risks upon discontinuation of Tam/AI treatment. The median BMD changes during the first 24 months of the post-treatment period are either stable (hip) or increased (1.5–3.8% in spine) in the AI group, but decrease (1–1.9% in spine, 2.3–2.6% in hip) in the tamoxifen group, compared with the BMD in the final treatment year.[75] The fracture incidence rates (per 1000 person-years) in the AI group decreased significantly from 29.3 (95% CI 26.5–32.4) during the treatment period to 15.6 (95% CI 13.2–18.3) during the post-treatment period, while rates in the tamoxifen group were stable (treatment period: 19.0, 95% CI 16.7–21.5; post-treatment period: 15.1, 95% CI 12.8–17.8) in the ATAC trial (ID 19).[49] Contrasting this, the fracture incidence rates (per 1000 person-years) in the AI group were stable during both the treatment period (21.0; 95% CI 14.5–27.5) and post-treatment period (20.3; 95% CI 13.7–26.9), while rates in the tamoxifen group increased from 12.3 (95% CI 7.3–17.3) during the treatment period to 20.6 (95% CI 13.8–27.4) during the post-treatment period in the Intergroup Exemestane Study (IES).[9] The causes of differences in fracture risks between the treatment and post-treatment periods remain unclear. It may be due to the independent effect of AI on fracture risk, the independent effect of tamoxifen on fracture risk, or both effects combined.

Recommended osteoporosis management for women diagnosed with breast cancer is inconsistent across guidelines, which should include: (a) healthy lifestyles; (b) risk screening using predefined risk factors; (c) fracture risk assessment using BMD testing alone, Fracture Risk Assessment Tool (FRAX) alone or both; and (d) treatments.[76] It remains challenging to identify women at high fracture risk for treatment initiation before fractures occur. BMD measurements using dual-energy X-ray absorptiometry fail to identify everyone who will develop fractures[77,78] while promoting lifestyle modification[79] and willingness to initiate treatment.[80] Fracture risk assessment using FRAX in this population is limited by uncertain accuracy and potential underestimation. This is because FRAX was validated using population-based studies without considering the negative effects of breast cancer treatments on bones.[81] More recently, the role of bisphosphonates (such as zoledronic acid or clodronate) has shifted from being a fracture prevention treatment to an adjuvant treatment for postmenopausal women who are diagnosed with nonmetastatic breast cancer and candidates for adjuvant systemic treatments[82] due to their abilities to reduce bone recurrence and improve survival.

Similar estimates between RCTs and cohort subgroups were observed for fracture risk in our study and for treatment effects of other noncancer drugs in other studies.[83,84] This is likely because both RCTs and cohort studies included in this study had large participant populations, sufficient follow-up time, and low risk of bias.[85] Most included cohort studies reported relative measures adjusted for confounders, which further reduced selection bias. While at least 50% of included RCTs were unblinded to outcome assessment, it has a minimal effect on assessing objective outcomes including fractures.

Risk differences, differences in proportions of participants with fractures, between two treatments were not analyzed in this study due to significant variation in fracture rates (10 times), heterogeneous participant groups and baseline risk between studies. Number needed to treat, the average number of participants who need to be treated to prevent one fracture, was not estimated for the same reason.

All selected RCTs and cohort studies in this study reported relative measures as ORs, HRs or IRRs. RRs were selected to estimate effect sizes, as RRs are more appropriate measures and easier to interpret than ORs.[86,87] RRs were favored over HRs and IRRs, as RRs can be recalculated for almost all included articles except one. A generic inverse variance method with random effects model was selected in this study to account for different risk measures and heterogeneity across the included studies. Although we chose random effects models in this study, statistical heterogeneity was low (<15%) in the majority of our analyses except the analysis for post-Tam/AI treatment period and some subgroup analyses. Effect sizes were almost identical using either random or fixed effects models based on our internal analysis.

Mild to moderate statistical heterogeneity (27–67%) was noted in our meta-analyses. This statistical heterogeneity decreased significantly to 0–7% after excluding the Xu *et al*. study[65] (ID 37) or the Koopal *et al*. study[39] (ID 11). This statistical heterogeneity associated with both these studies could be explained primarily by uncontrolled confounders due to a lack of reported adjusted relative measures. These two studies also differed from most of the included studies in this review in study setting (one center *versus* national/multinational) and sample size.

Limitation

This review was limited by the relative low numbers of available articles on certain subgroups, especially premenopausal groups. When comparing AIs with tamoxifen, fracture risks did not differ among subgroups of premenopausal, a mixture of pre- and postmenopausal, and postmenopausal women. Only two included studies (ID 13, 34) involved 100% premenopausal women. However, the Tamoxifen and Exemestane Trial (TEXT)/Suppression Ovarian Functions (SOFT) study (ID 34) was not included in our reported meta-analysis, as it reported combined data from two independent studies, TEXT and SOFT. An internal analysis including data from the TEXT/SOFT study was conducted. It resulted in a similar RR estimate, with a slightly narrower 95% CI of 1.24–1.48.

Conclusion

Fracture risk is significantly higher in women treated with AIs, especially during the treatment period. Tamoxifen is not associated with lower fracture risk while tamoxifen could potentially preserve bone mass. Women who receive tamoxifen or

AI breast cancer treatment should be encouraged to have BMD testing as recommended for women diagnosed with breast cancer. Optimal osteoporosis management programs, especially during the treatment period, are needed for this group of women.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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