Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial

Jack Cuzick, Ivana Sestak, John F Forbes, Mitch Dowsett, Simon Cawthorn, Robert E Mansel, Sibylle Loibl, Bernardo Bonanni, D Gareth Evans, Anthony Howell, on behalf of the IBIS-II investigators*
risk of developing it to receive either anastrozole (1 mg daily) or matching placebo. The first analysis after a median follow-up of 60 months (IQR 36–85) reported a significant reduction in incidence of 53% for all breast cancer (including ductal carcinoma in situ). \(^6\) A 58% reduction in incidence of invasive oestrogen receptor-positive breast cancer and a 70% reduction in incidence of ductal carcinoma in situ was observed for anastrozole. As reported in adjuvant trials, \(^6\) the main adverse events with anastrozole were fractures, joint-related effects, and menopausal symptoms, which are associated with an almost complete elimination of oestrogen in postmenopausal women using aromatase inhibitors.

A long-term term reduction of breast cancer incidence for anastrozole or any aromatase inhibitor has not been established, as it has for tamoxifen. \(^1\) Such a result is likely to substantially improve the benefit-risk ratio, as side-effects are uncommon after treatment cessation. The objective of this study was to determine the long-term efficacy of anastrozole for preventing breast cancer (both invasive and ductal carcinoma in situ) in the post-treatment period.

Methods

Study design and participants

IBIS-II is an international, randomised, double-blind, placebo-controlled trial. Detailed study design and inclusion and exclusion criteria have previously been reported. \(^7\) In brief, high-risk postmenopausal women aged 40–70 years were recruited between Feb 2, 2003, and Jan 31, 2012, in 153 breast cancer treatment centres across 18 countries (appendix p 3). Specific risk criteria for entry were broad and have previously been reported. \(^7\) They were designed to include women aged 45–60 years who had a relative risk of breast cancer that was at least twice as high as that in the general population, those aged 60–70 years who had a risk that was at least 1.5 times higher, and those aged 40–44 years who had a risk that was at least four times higher. The exclusion criteria were being premenopausal, previous breast cancer including ductal carcinoma in situ diagnosed more than 6 months before trial entry, current or previous tamoxifen, raloxifene, or other SERM use for more than 6 months, or participation in IBIS-I, unless off-trial therapy for at least 5 years, intention to continue using oestrogen-based hormone replacement therapy, or previous or planned prophylactic mastectomy.

The trial was approved by the UK North West Multi-Centre Research Ethics Committee and was done in accordance with the Declaration of Helsinki (1996 revision), under the principles of good clinical practice. All participants provided written, informed consent to join the study, provide baseline and follow-up blood samples, and have their past and future health records examined, including access to mammograms and pathology material.

Randomisation and masking

Consenting eligible women were randomly assigned (1:1) to either anastrozole (1 mg per day, oral) or matching placebo daily for 5 years. Randomisation was stratified by country. All participants and medical personnel were blinded to treatment allocation, which was only held by the central study statistician. Unblinding was only permitted if the participant developed breast cancer, when a clinician considered there to be valid medical or
safety reasons, or the participant requested unblinding. Treatment allocation still remains largely blinded for investigators and participating women who have not developed breast or any other cancer (81·3% anastrozole vs 76·7% placebo, p=0·0053). A further analysis was planned to take place around 5 years after the last report, and this analysis is provided 6 years after that report. The decision to analyse the data was made without looking at the results beforehand.

Procedures
After treatment completion, women were followed on a yearly basis to collect data on breast cancer incidence, death, other cancers, and major adverse events (cardiovascular events, fractures). In the UK, these events were also collected through cancer registries and National Health Services (NHS Digital). In non-UK centres, annual questionnaire or annual clinic visits were used to collect these data.

Outcomes
The primary outcome was the development of histologically confirmed breast cancer—either invasive or non-invasive (ductal carcinoma in situ). Secondary outcomes were oestrogen receptor-positive breast cancer, breast cancer mortality, other cancers, cardiovascular disease, fractures, and all-cause mortality. Exploratory analyses reported treatment effects by more detailed breast cancer type, specific baseline patient characteristics (age, body-mass index [BMI], previous use of hormone replacement therapy, and previous lobular carcinoma in situ or atypical hyperplasia), and other major cancers by site.

Statistical analysis
All analyses were done on an intention-to-treat basis, including all randomly assigned patients. Analyses of the efficacy endpoints were based on hazard ratios (HRs) using Cox proportional hazard models, with corresponding 95% CIs, and survival curves were estimated using the Kaplan-Meier method. Only major adverse effects (other cancers, cardiovascular events, fractures, and deaths) were routinely collected after 5 years in all patients. Side-effects and secondary outcomes were compared between treatment groups using odds ratios (ORs) and Fisher exact significance tests. All p values were two-sided. All analyses were done using STATA version 15.1. This trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN31488319.

Role of the unding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
All women randomly assigned to treatment (N=3864, 1920 anastrozole and 1944 placebo) have been included in this analysis. 3704 (95·9%) were still at risk of developing breast cancer—either invasive or non-invasive (either breast cancer mortality, other cancers, cardiovascular events, fractures) at the last follow-up (anastrozole 11 339, placebo 11 028). Median follow-up for this analysis was 131 months (IQR 106–156), and 41 295 women-years of follow-up have been accrued (anastrozole 20 803, placebo 20 491), of which 22 367 women-years were accrued after 5 years of follow-up (anastrozole 11 339, placebo 11 028). Median age at study entry was 59·4 years (IQR 55·0–63·4), 1893 women (47·0%) had used hormone replacement therapy before entering the trial, and 2631 (68·1%) had a BMI of more than 25kg/m². Other baseline demographics (age, body-mass index [BMI], previous use of hormone replacement therapy, and previous lobular carcinoma in situ or atypical hyperplasia), and other major cancers by site.

Statistical analysis
All analyses were done on an intention-to-treat basis, including all randomly assigned patients. Analyses of the efficacy endpoints were based on hazard ratios (HRs) using Cox proportional hazard models, with corresponding 95% CIs, and survival curves were estimated using the Kaplan-Meier method. Only major adverse effects (other cancers, cardiovascular events, fractures, and deaths) were routinely collected after 5 years in all patients. Side-effects and secondary outcomes were compared between treatment groups using odds ratios (ORs) and Fisher exact significance tests. All p values were two-sided. All analyses were done using STATA version 15.1. This trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN31488319.

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Articles

Published online December 12, 2019   https://doi.org/10.1016/S0140-6736(19)32955-1

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non-proportional hazards was not significant (p=0.073).
After 12 years of follow-up, the estimated risk of
developing breast cancer was 8.8% (IQR 7.6–10.3) in
the placebo group compared with 5.3% (4.3–6.6) in the
anastrozole group (figure 1), and the number needed
to treat for 5 years to prevent one breast cancer was 29.
Overall 203 (81.2%) of the breast cancers were invasive,
and 151 (74.4%) of these were reported as oestrogen
receptor-positive. A 54% reduction in incidence with
anastrozole was observed for oestrogen receptor-positive
cancers (HR 0.46, 95% CI 0.33–0.65, p=0.0001), with
a larger 61% reduction in the first 5 years (0.39, 0.23–0.66,
p=0.0001; figure 2), followed by a 48% reduction (0.52,
0.33–0.83, p=0.0062). A small, non-significant reduction
in incidence was observed for invasive oestrogen receptor-
negative breast cancer in the anastrozole group (0.77,
0.41–1.44, p=0.41; figure 2). A significant reduction
in incidence for anastrozole was also found for ductal
in situ cancer (0.41, 0.22–0.79, p=0.0081), in particular for
lesions known to be oestrogen-positive (0.22, 0.07–0.65).

No clear heterogeneity or trend was observed for
differences in the preventive effect of anastrozole by
other tumour characteristics (appendix p 2). Anastrozole
reduced incidence of invasive HER2-negative cancers by
43% (HR 0.57, 95% CI 0.41–0.78), which was similar to
that for invasive HER2-positive cancers (0.52, 0.23–1.17;
appendix p 2).
Explosoratory analyses of baseline characteristics did not
show any significant heterogeneity by age, BMI, previous
hormone replacement therapy use, or previous lobular
hormone replacement therapy use, or previous lobular
invasive cancers (43 vs 73 cases, 0.59, 0.39–0.87, p=0.0058), and no effect
on other specific cancers was apparent (appendix p 2).
Reductions in incidence did not differ between treatment
groups for women with a BMI of more than 30 kg/m²
or who took hormone replacement therapy before
trial entry.
Overall, a 28% reduction in cancer incidence at non-
breast sites occurred (147 vs 200 cases, OR 0.72, 95% CI
0.57–0.91, p=0.0042; table 2). Secondary analyses
showed that this reduction was driven largely by a
reduction in the incidence of non-melanoma skin cancer
(43 vs 73 cases, 0.59, 0.39–0.87, p=0.0058), and no effect
on other specific cancers was apparent (table 2).
In particular, no reduction in the incidence of endometrial
cancer occurred due to oestrogen deprivation from
anastrozole, although oestrogen is thought to be a major
driver of this cancer.11 Additionally, the early reduction
seen for colorectal cancers1 has not been extended with
longer follow-up.
No effect was seen on any other major adverse event
(table 3). In particular, there was no excess of fractures
overall (380 vs 373, OR 1.04, 95% CI 0.88–1.22). A small
non-significant increase in number of events during the
active treatment period (198 vs 186, 1.09, 0.87–1.35) was
counterbalanced by slight reduction of events after
treatment was completed (182 vs 187, 0.98, 0.79–1.23).
Myocardial infarctions were evenly distributed between

<table>
<thead>
<tr>
<th>Table 2: Cancers other than breast</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anastrozole, N=1920, n (%)</strong></td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td><strong>Skin</strong></td>
</tr>
<tr>
<td><strong>Non-melanoma</strong></td>
</tr>
<tr>
<td><strong>Melanoma</strong></td>
</tr>
<tr>
<td><strong>Gynaecological</strong></td>
</tr>
<tr>
<td><strong>Endometrial</strong></td>
</tr>
<tr>
<td><strong>Ovarian</strong></td>
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<tr>
<td><strong>Respiratory</strong></td>
</tr>
<tr>
<td><strong>Lung</strong></td>
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<tr>
<td><strong>Gastrointestinal</strong></td>
</tr>
<tr>
<td><strong>Colorectal</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3: Major adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fractures</strong></td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
</tr>
<tr>
<td><strong>Deep vein thrombosis</strong></td>
</tr>
<tr>
<td><strong>Pulmonary embolism</strong></td>
</tr>
<tr>
<td><strong>Transient ischaemic attack</strong></td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
</tr>
</tbody>
</table>

*In the absence of pulmonary embolism. 1. In the absence of stroke. Numbers in parentheses refer to events occurring in the post-treatment period (>5-year follow-up).
treatment groups (table 3), and no differences in number of events were observed in the first 5 years (eight vs eight) or in follow-up after treatment (eight vs six). Numbers of deep vein thromboses were slightly increased in the placebo group, with no differences observed in the two periods (table 3). Cases of pulmonary embolism were non-significantly more frequent with anastrozole but no differences were observed during treatment compared with after treatment (table 3). Transient ischaemic attacks and strokes were non-significantly more common with anastrozole compared with placebo (46 vs 36, p=0.24).

Other less serious side-effects observed in the first 5 years during treatment with anastrozole, including arthralgia, joint stiffness, hot flushes, night sweats, vulvovaginal dryness, hypertension, and dry eyes, were not collected after the 5-year treatment period. However, even within the treatment period they were most common in the first year of treatment, so it is unlikely that there will be material differences in the post-treatment period. All participants have now completed treatment and full 5-year adherence was 74.6% for anastrozole compared with 77.0% for placebo (HR 0.91, 95% CI 0.79–1.01, p=0.081; appendix p 4), indicating that side-effects of anastrozole had little effect on treatment adherence. 139 (3.6%) women died during the study (69 anastrozole vs 70 placebo; table 4), with no difference between the two treatment groups (HR 0.96, 95% CI 0.69–1.34, p=0.82). Overall, no effect of anastrozole was seen for breast cancer-specific mortality (three anastrozole vs two placebo), but numbers are very small. Given the small number of deaths and the relatively young median age at entry (59.4 years), substantially longer follow-up will be needed to determine whether anastrozole affects breast cancer and other cause mortality. Deaths from cancers other than breast did not differ between treatment groups (p=0.39).

Discussion
This updated analysis of the IBIS-II trial provides additional support for the use of anastrozole in breast cancer prevention for high-risk postmenopausal women. The large 61% reduction in breast cancer incidence in the first 5 years has been maintained in subsequent follow-up to 12 years. The significant 36% reduction during post-treatment follow-up was not significantly smaller than during treatment, and still greater than that observed for tamoxifen, which has produced a roughly constant 29% reduction for 20 years.1 The number needed to treat to prevent one breast cancer during the first 12 years of follow-up was 29, which compares favourably with the 58 needed for tamoxifen at that time.1 Very few deaths from breast cancer have occurred to date, but it is too early to expect an effect on this outcome, which is a limitation of this analysis. The reduction with anastrozole was primarily seen in oestrogen receptor-positive cancers, which suggests that the effect on mortality will be smaller than that for incidence. The effects were greatest for oestrogen receptor-positive tumours, but an unexpected and non-significant 27% reduction was also seen for receptor-negative cancers, which will need further follow-up to validate.

The previously observed reduction of other cancers with anastrozole, notably non-melanoma skin cancer, has continued with longer follow up. No other side-effects have been identified with longer follow-up, and the small 11% excess of fractures during the active treatment period has not continued after 5 years of follow-up. A limitation of this analysis is that routine collection of less serious side-effects was not done after the 5-year treatment period.

All women have completed the active follow-up period of the trial and now are followed for long-term outcomes by various methods. In the UK, long-term data are collected through national registries for deaths, cancers, and major predefined adverse events, so we are confident that data are complete. Additionally, we still collect data through annual questionnaires where appropriate. For international centres, annual questionnaires were used to collect information on all primary and secondary outcomes. However, data on lesser side-effects, such as hot flushes and musculoskeletal events, were only collected during the 5-year treatment period.

In conclusion, these updated results show a continuing long-term effect of 5 years of anastrozole treatment in preventing breast cancer in high-risk postmenopausal women. No new major adverse events were identified. Overall, our data substantially strengthen the findings from our initial report after 5 years of follow-up.4 In the UK, the National Institute for Health and Care Excellence has now recommended the use of anastrozole for breast cancer prevention in high-risk postmenopausal women,15 and in the USA, the US Preventive Services Task Force has also supported its use.16 The benefits of anastrozole, in terms of the reduction in risk of breast cancer in high-risk postmenopausal women, extend beyond the 5-year treatment period.

Table 4: Specific causes of death

<table>
<thead>
<tr>
<th>Category</th>
<th>Anastrozole, N=1920, n (%)</th>
<th>Placebo, N=1944, n (%)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>69 (3.6%)</td>
<td>70 (3.6%)</td>
<td>0.96 (0.69–1.34)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2 (0.1%)</td>
<td>3 (0.2%)</td>
<td>0.64 (0.11–3.88)</td>
</tr>
<tr>
<td>Other cancer</td>
<td>27 (1.4%)</td>
<td>34 (1.8%)</td>
<td>0.77 (0.47–1.28)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>13 (0.7%)</td>
<td>9 (0.5%)</td>
<td>1.41 (0.60–3.31)</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>27 (1.4%)</td>
<td>24 (1.2%)</td>
<td>1.10 (0.63–1.91)</td>
</tr>
</tbody>
</table>

Declaration of interests
JC reports grants from AstraZeneca, during the conduct of the study, and personal fees and royalties through Queen Mary University of London from Myriad Genetics, outside the submitted work. IS reports...
personal fees from Myriad Genetics, Nanostring Technologies, and Pfizer, outside the submitted work. MD reports personal fees personal fees and royalties through the Institute for Cancer Research for development of abiraterone from Radius, AbbVie, GI Technologies Orion, and H3 Biomedicine, personal fees from Myriad Genetics, and Nanostring Technologies, and grants from Pfizer and Radius, all outside the submitted work. SL reports personal fees from AstraZeneca, Celgene, and Puma Samsung, grants and personal fees from Pfizer, Novartis, and Roche, and grants from Cepheid and Arogen, all outside the submitted work. DGE reports personal fees from AstraZeneca. All other authors declare no competing interests.

Data sharing
Data will be available according to IBIS-II’s data sharing plan. Requests for specific analyses or data can be submitted by email to j.cuzick@qmul.ac.uk. Details for data sharing policy and application process can be found on the website of Queen Mary University London.

Acknowledgments
This study was funded by Cancer Research UK (C569/A5032), the National Health and Medical Research Council Australia (GNT300755, GNT569213), the Breast Cancer Research Foundation (EMSR1C3R), Manchester National Institute for Health Research Biomedical Research Centre (ES-BRC-1215–20007), Sanofi Aventis, and AstraZeneca. AstraZeneca provided anastrozole and matching placebo. The study sponsor was Queen Mary University of London.

References
Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplementary Table 1: Number of breast cancer events and hazard ratios according to treatment allocation and follow-up period.

<table>
<thead>
<tr>
<th></th>
<th>Anastrozole (N=1920)</th>
<th>Placebo (N=1944)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>59.5 (55.0-63.5)</td>
<td>59.4 (55.1-66.3)</td>
</tr>
<tr>
<td>Age at menarche (years), median (IQR)</td>
<td>13.0 (12.2-14.0)</td>
<td>13.0 (12.2-14.0)</td>
</tr>
<tr>
<td>Age at first child birth (years), median (IQR)</td>
<td>24 (21-27)</td>
<td>24 (21-27)</td>
</tr>
<tr>
<td>Age at menopause (years), median (IQR)</td>
<td>50 (45-52)</td>
<td>49 (45-52)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.4 (24.2-31.1)</td>
<td>27.3 (24.4-31.2)</td>
</tr>
<tr>
<td>Previous HRT use</td>
<td>893 (47.0%)</td>
<td>910 (47.2%)</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>631 (33.2%)</td>
<td>656 (34.0%)</td>
</tr>
<tr>
<td>Family history (non-exclusive)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two or more relatives with breast/ovarian cancer</td>
<td>956 (49.8%)</td>
<td>938 (48.3%)</td>
</tr>
<tr>
<td>One relative with breast cancer at age ≤ 50</td>
<td>675 (35.3%)</td>
<td>653 (33.7%)</td>
</tr>
<tr>
<td>One relative with bilateral breast cancer</td>
<td>166 (8.6%)</td>
<td>141 (7.3%)</td>
</tr>
<tr>
<td>LCIS/Atypical hyperplasia</td>
<td>154 (8.0%)</td>
<td>190 (9.8%)</td>
</tr>
<tr>
<td>DCIS (treated with mastectomy)</td>
<td>160 (8.3%)</td>
<td>166 (8.5%)</td>
</tr>
</tbody>
</table>

IQR=Interquartile Range, kg=kilogram, m=meter, LCIS=lobular carcinoma in situ, DCIS=ductal carcinoma in situ
### Supplementary Table 2: Number of invasive breast cancer events and hazard ratios according to treatment allocation and subgroups.

<table>
<thead>
<tr>
<th>Nodal status</th>
<th>Number of events (anastrozole vs. placebo)</th>
<th>HR (95% CI)</th>
<th>P-heterogeneity/P-trend (1df)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>35 vs. 88</td>
<td>0.39 (0.27-0.58)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>26 vs. 32</td>
<td>0.80 (0.48-1.34)</td>
<td>0.083</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumour grade</th>
<th>Number of events (anastrozole vs. placebo)</th>
<th>HR (95% CI)</th>
<th>P-heterogeneity/P-trend (1df)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>14 vs. 17</td>
<td>0.81 (0.40-1.65)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>33 vs. 72</td>
<td>0.45 (0.30-0.68)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>21 vs. 39</td>
<td>0.53 (0.31-0.91)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumour size</th>
<th>Number of events (anastrozole vs. placebo)</th>
<th>HR (95% CI)</th>
<th>P-heterogeneity/P-trend (1df)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10mm</td>
<td>17 vs. 41</td>
<td>0.41 (0.23-0.72)</td>
<td></td>
</tr>
<tr>
<td>10-20mm</td>
<td>26 vs. 48</td>
<td>0.53 (0.33-0.86)</td>
<td></td>
</tr>
<tr>
<td>&gt;20mm</td>
<td>28 vs. 43</td>
<td>0.64 (0.40-1.03)</td>
<td>0.31</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>HER2 status</th>
<th>Number of events (anastrozole vs. placebo)</th>
<th>HR (95% CI)</th>
<th>P-heterogeneity/P-trend (1df)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>58 vs. 101</td>
<td>0.57 (0.41-0.78)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>9 vs. 17</td>
<td>0.52 (0.23-1.17)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of events (anastrozole vs. placebo)</th>
<th>HR (95% CI)</th>
<th>P-heterogeneity/P-trend (1df)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤55 years</td>
<td>17 vs. 32</td>
<td>0.51 (0.28-0.91)</td>
<td></td>
</tr>
<tr>
<td>55-60 years</td>
<td>13 vs. 44</td>
<td>0.32 (0.17-0.59)</td>
<td></td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>41 vs. 56</td>
<td>0.70 (0.47-1.05)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI</th>
<th>Number of events (anastrozole vs. placebo)</th>
<th>HR (95% CI)</th>
<th>P-heterogeneity/P-trend (1df)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤25 kg/m²</td>
<td>17 vs. 28</td>
<td>0.59 (0.32-1.07)</td>
<td></td>
</tr>
<tr>
<td>25-30 kg/m²</td>
<td>27 vs. 45</td>
<td>0.61 (0.38-0.98)</td>
<td></td>
</tr>
<tr>
<td>&gt;30 kg/m²</td>
<td>27 vs. 57</td>
<td>0.46 (0.29-0.73)</td>
<td>0.66</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>HRT</th>
<th>Number of events (anastrozole vs. placebo)</th>
<th>HR (95% CI)</th>
<th>P-heterogeneity/P-trend (1df)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>36 vs. 74</td>
<td>0.48 (0.32-0.71)</td>
<td></td>
</tr>
<tr>
<td>Prior</td>
<td>35 vs. 58</td>
<td>0.60 (0.39-0.91)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benign breast disease</th>
<th>Number of events (anastrozole vs. placebo)</th>
<th>HR (95% CI)</th>
<th>P-heterogeneity/P-trend (1df)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCIS or AH</td>
<td>8 vs. 23</td>
<td>0.34 (0.15-0.77)</td>
<td></td>
</tr>
<tr>
<td>No LCIS or AH</td>
<td>63 vs. 109</td>
<td>0.57 (0.42-0.78)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

HR=Hazard Ratio, CI=Confidence Intervals, df=degrees of freedom, BMI=Body Mass Index, LCIS=Lobular Carcinaoma in Situ, AH=Atypical Hyperplasia, HRT=Hormonal Replacement Therapy
Supplementary Figure 1: CONSORT diagram

3864 randomised

Intention To Treat:
1920 assigned to raloxifene
6 ineligible
(Premenopausal N=3
More than 2 spinal fractures N=2
DCIS/ER-negative N=1)

1914 received raloxifene
1866 at risk at five years

Intention To Treat:
1944 assigned to placebo
7 ineligible
(Premenopausal N=3
Breast cancer N=2
DCIS/ER-negative N=1
Adopted N=1)

1937 received placebo
1838 at risk at five years
Supplementary Figure 2: Five-year adherence (%) according to treatment allocation.

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.89 (0.79-1.01)</td>
<td>0.08</td>
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</tbody>
</table>

77.0% (75.1-78.8)
74.6% (72.6-76.5)
Appendix

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