Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial

Jack Cuzick, Ivana Sestak, John F Forbes, Mitch Dowsett, Jill Knox, Simon Cawthorn, Christobel Saunders, Nicola Roche, Robert E Mansel, Gunter von Minckwitz, Bernardo Bonanni, Tiina Palva, Anthony Howell, on behalf of the IBIS-II investigators*

Summary
Background Aromatase inhibitors effectively prevent breast cancer recurrence and development of new contralateral tumours in postmenopausal women. We assessed the efficacy and safety of the aromatase inhibitor anastrozole for prevention of breast cancer in postmenopausal women who are at high risk of the disease.

Methods Between Feb 2, 2003, and Jan 31, 2012, we recruited postmenopausal women aged 40–70 years from 18 countries into an international, double-blind, randomised placebo-controlled trial. To be eligible, women had to be at increased risk of breast cancer (judged on the basis of specific criteria). Eligible women were randomly assigned (1:1) by central computer allocation to receive 1 mg oral anastrozole or matching placebo every day for 5 years. Randomisation was stratified by country and was done with blocks (size six, eight, or ten). All trial personnel, participants, and clinicians were masked to treatment allocation; only the trial statistician was unmasked. The primary endpoint was histologically confirmed breast cancer (invasive cancers or non-invasive ductal carcinoma in situ). Analyses were done by intention to treat. This trial is registered, number ISRCTN31488319.

Findings 1920 women were randomly assigned to receive anastrozole and 1944 to placebo. After a median follow-up of 5·0 years (IQR 3·0–7·1), 40 women in the anastrozole group (2%) and 85 in the placebo group (4%) had developed breast cancer (hazard ratio 0·47, 95% CI 0·32–0·68, p<0·0001). The predicted cumulative incidence of all breast cancers at 5·0 years (IQR 3·0–7·1), 40 women in the anastrozole group (2%) and 85 in the placebo group (4%) had developed breast cancer risk. Oestrogen production is driven by the aromatase enzyme, which converts androgens to oestrogens. Trials in the adjuvant setting have shown that aromatase inhibitors more effectively prevent breast cancer recurrence and also development of new contralateral tumours in postmenopausal women than does tamoxifen. In a meta-analysis, tamoxifen and three other selective oestrogen receptor modulators were shown to reduce the frequency of oestrogen-receptor-positive tumours by 51% overall, but no effect was reported for oestrogen-receptor-negative tumours. The reduction in contralateral tumours has proved an important surrogate for the preventive effects of tamoxifen and has been confirmed in a trial of the aromatase inhibitor exemestane, but whether this reduction extends to other agents is unclear.

One study of the preventive effects of an aromatase inhibitor has been done in high-risk women without breast cancer: in the MAP.3 trial, exemestane was compared with placebo in postmenopausal women. Exemestane significantly reduced the incidence of all breast cancer by 53% and invasive breast cancer by 65% after a median follow-up of 3 years. No serious side-effects of exemestane were recorded, but median follow-up was fairly short for detection of any serious adverse events. Here, we report the first results from the International Breast Cancer Intervention Study II (IBIS-II), in which the efficacy and safety of the aromatase inhibitor anastrozole was assessed in a large, randomised, double-blind trial of high-risk postmenopausal women.
inhibitor anastrozole for prevention of breast cancer are being compared with placebo.

**Methods**

**Study design and participants**

IBIS-II is an international, double-blind, randomised placebo-controlled trial. Between Feb 2, 2003, and Jan 31, 2012, postmenopausal women aged 40–70 years were recruited in 153 centres in 18 countries (appendix).

Women were deemed to be postmenopausal when they were aged 60 years or older; had had a bilateral oophorectomy; were younger than 60 years, but had a uterus and had had amenorrhoea for at least 12 months; or were aged less than 60 years, had no uterus, and had a concentration of follicle stimulating hormone of greater than 30 IU/L. Entry criteria were designed to include women aged 45–60 years who had a relative risk of breast cancer that was at least two times higher than 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 four times higher. Full eligibility criteria are listed in the appendix; to be eligible, women had to meet at least one of the criteria. Women who did not meet other eligibility criteria were included if the Tyrer-Cuzick model indicated a 10-year risk of breast cancer of more than 5%.

Exclusion criteria were: premenopausal status; any previous diagnosis of breast cancer (except for oestrogen-receptor-positive ductal carcinoma in situ diagnosed less than 6 months previously and treated by mastectomy); any invasive cancer in the previous 5 years (except for non-melanoma skin cancer or cervical cancer); present or previous use of selective oestrogen receptor modulators for more than 6 months (unless as part of IBIS-I and treatment was completed at least 5 years before study entry); intention to continue hormone replacement therapy; prophylactic mastectomy; evidence of severe osteoporosis (T score <-4 or more than two vertebral fractures); life expectancy of fewer than 10 years; psychologically or physiologically unfit for the study; or a history of gluten or lactose intolerance, or both.

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.

**Randomisation and masking**

Eligible women were randomly assigned (1:1) by central computer allocation to either anastrozole or matching placebo. Randomisation was stratified by country and was done with randomly chosen randomisation blocks (size six, eight, or ten) to maintain balance. All IBIS-II personnel, participants, and clinicians were masked to treatment allocation; only the trial statistician had access to unblinded data.

**Procedures**

Women received 1 mg oral anastrozole or matching placebo every day for 5 years. The primary endpoint was histologically confirmed breast cancer (invasive cancers or non-invasive ductal carcinoma in situ). Secondary endpoints were oestrogen-receptor-positive breast cancer, breast cancer mortality, other cancers, cardiovascular disease, fractures, adverse events, and deaths not due to breast cancer.
Women visited local clinics at baseline, 6 months, and 12 months, and then annually until the 5-year follow-up point. At baseline—after enrolment but before randomisation—women had a mammogram and physical breast examination to exclude any pre-existing breast cancer, unless they had undergone these procedures within 12 months before enrolment. Mammograms were then done at least every 2 years. Women also had a dual energy x-ray absorptiometry scan and two spinal radiographs in the lateral dimensions at baseline to assess bone density, unless they had undergone these procedures within 2 years before enrolment. Follow-up after 5 years varied and consisted of a mixture of clinic visits, annual questionnaires, and also record linkage systems in the UK. Blood samples were taken at baseline, after 1 year, and after 5 years for assessment of potential biomarkers. A detailed exploration of changes in bone mineral density, fractures, and use of bisphosphonates will be reported elsewhere.

Statistical analysis
Analyses were done on an intention-to-treat basis. A secondary per-protocol sensitivity analysis was done after some enrolled women were subsequently identified as ineligible. Initial assumptions for power calculation were based on an incidence of six cases of breast cancer per 1000 women per year, and a compliance-adjusted reduction in incidence of breast cancer of 50% with anastrozole. This calculation led to a sample size of 4000 women. However, interim figures indicated that incidence of breast cancer was higher than predicted: the overall event rate was 6·6 cases of breast cancer per 1000 women per year, and a 50% reduction in the anastrozole group, would translate to nine cases of breast cancer per 1000 women per year. Therefore, the sample size was reduced to 3500 women. The expected number of new cancers after a median of 5 years of follow-up for a total trial size of 3500 women was 78 in the placebo group and 39 in the anastrozole group, leading to a power in excess of 90% for a 5% significance level.

Analyses of the efficacy endpoints were based on hazard ratios (HRs). Cox proportional hazards models were used to derive HRs with 95% CIs. Survival curves were estimated with the Kaplan-Meier method. Results are presented for predefined or common (affecting at least 5% of participants) adverse events, or those for which a significant difference between groups was recorded (with a α of 0·02). Side-effects and secondary endpoints were compared with relative risks. Adherence was calculated by the Kaplan-Meier method, with censoring at breast cancer occurrence, death, 5 years of follow-up, or the cutoff date. Fisher’s exact tests were used to compare frequency of adverse events when appropriate. All p values were two sided. All analyses were done in Stata (version 12.1).

This trial is registered, number ISRCTN31488319.
randomisation (figure 1) and were excluded from a secondary per-protocol analysis. No new cancers occurred in this group and the omission of these women did not change the results (data not shown).

The cutoff date for analysis was May 15, 2013. Median follow-up was 5.0 years (IQR 3.0–7.1). 19,399 women-years of follow-up had been accrued (9,727 in the anastrozole group vs 9,672 in the placebo group). At the time of data

<table>
<thead>
<tr>
<th>Grade*</th>
<th>Number of women</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>7</td>
<td>0.86 (0.31–2.38)</td>
<td>0.01</td>
</tr>
<tr>
<td>Intermediate</td>
<td>16</td>
<td>0.55 (0.30–1.01)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>9</td>
<td>0.35 (0.16–0.74)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nodal status</th>
<th>Number of women</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>12</td>
<td>0.75 (0.35–1.58)</td>
<td>0.08</td>
</tr>
<tr>
<td>Negative</td>
<td>18</td>
<td>0.41 (0.23–0.70)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumour size</th>
<th>Number of women</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>x10 mm</td>
<td>11</td>
<td>0.58 (0.27–1.21)</td>
<td>0.1</td>
</tr>
<tr>
<td>10–20 mm</td>
<td>8</td>
<td>0.28 (0.13–0.62)</td>
<td></td>
</tr>
<tr>
<td>&gt;20 mm</td>
<td>13</td>
<td>0.76 (0.37–1.56)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oestrogen-receptor status*</th>
<th>Number of women</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>20</td>
<td>0.42 (0.25–0.75)</td>
<td>0.08</td>
</tr>
<tr>
<td>Negative</td>
<td>11</td>
<td>0.78 (0.35–1.72)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progesterone-receptor status*</th>
<th>Number of women</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>28</td>
<td>0.44 (0.17–1.07)</td>
<td>0.2</td>
</tr>
<tr>
<td>Negative</td>
<td>26</td>
<td>0.61 (0.37–1.03)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>7-year risk in placebo group*</th>
<th>Number of women who developed breast cancer</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>41%</td>
<td>20</td>
<td>0.47 (0.28–0.80)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>67%</td>
<td>44</td>
<td>0.46 (0.27–0.78)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Body-mass index (kg/m²)</th>
<th>7-year risk in placebo group*</th>
<th>Number of women who developed breast cancer</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>47%</td>
<td>10</td>
<td>0.43 (0.20–0.90)</td>
</tr>
<tr>
<td>25–30</td>
<td>52%</td>
<td>14</td>
<td>0.49 (0.26–0.94)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>5%</td>
<td>16</td>
<td>0.47 (0.26–0.85)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lobular carcinoma in situ or atypical hyperplasia</th>
<th>7-year risk in placebo group*</th>
<th>Number of women who developed breast cancer</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>49%</td>
<td>35</td>
<td>0.52 (0.31–0.78)</td>
</tr>
<tr>
<td>Yes</td>
<td>51%</td>
<td>19</td>
<td>0.31 (0.12–0.84)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ductal carcinoma in situ</th>
<th>7-year risk in placebo group*</th>
<th>Number of women who developed breast cancer</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>52%</td>
<td>34</td>
<td>0.47 (0.31–0.71)</td>
</tr>
<tr>
<td>Yes</td>
<td>48%</td>
<td>19</td>
<td>0.44 (0.17–1.15)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous use of hormone replacement therapy</th>
<th>7-year risk in placebo group*</th>
<th>Number of women who developed breast cancer</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>6%</td>
<td>17</td>
<td>0.36 (0.20–0.62)</td>
</tr>
<tr>
<td>Yes</td>
<td>5%</td>
<td>38</td>
<td>0.61 (0.37–1.03)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Less than 12 months before enrolment</th>
<th>7-year risk in placebo group*</th>
<th>Number of women who developed breast cancer</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>9%</td>
<td>3</td>
<td>0.30 (0.08–1.07)</td>
</tr>
<tr>
<td>Yes</td>
<td>1%</td>
<td>12</td>
<td>0.68 (0.35–1.31)</td>
</tr>
</tbody>
</table>
lock, 979 women (51%) in the anastrozole group and 975 (50%) in the placebo group had completed 5 years of treatment. We estimated full 5-year adherence to be 68% in the anastrozole group versus 72% in the placebo group (p=0·0047; appendix). The main reasons for treatment discontinuation were adverse events (375 [20%] in the anastrozole group; 298 [15%] in the placebo group) and patient refusal (94 [5%] in the anastrozole group; 98 [5%] in the placebo group). At the cutoff date, 357 women (19%) in the anastrozole group and 450 (23%) in the placebo group were continuing with treatment.

Significantly more breast cancers (including ductal carcinoma in situ) were recorded during follow-up in the placebo group than in the anastrozole group (HR 0·47, 95% CI 0·32–0·68; p<0·0001; figure 2). The predicted cumulative incidence of all breast cancers after 7 years in the placebo group was double that in the anastrozole group versus 72% in the anastrozole group versus 72% in the placebo group (p=0·0001; figure 2). We recorded no evidence of heterogeneity for invasive cancers (p=0·3). 35 deaths had been reported by data cutoff (table 2). No specific causes were more common in one group than in the other (p=0·836; table 2). Overall frequency of cancers other than breast cancer was significantly higher in the placebo group than in the anastrozole group (table 3). Notably, gastrointestinal cancers (p=0·05) and skin cancers overall (p=0·05) were more common in the placebo group than in the anastrozole group (table 3).

Many adverse events were reported (table 4). Total number of fractures and number of fractures in specific sites did not differ significantly by group (table 4). 627 (16%) women were taking a bisphosphonate during the trial and concomitant use was similar between treatment groups (330 [17%] in anastrozole group vs 297 [15%] in placebo group). Musculoskeletal adverse events were reported in significantly more women in the anastrozole group than in the placebo group (p=0·0001; table 4). We recorded no significant difference between groups for mild (p=0·9) or severe (p=0·06) arthralgia, but moderate arthralgia was more common with anastrozole than with placebo (p=0·01; table 4). Carpal tunnel syndrome and joint stiffness were both significantly more common in the anastrozole group than in the placebo group (table 4). Vaso-motor symptoms were common in both groups, but significantly more frequent with anastrozole than placebo (p<0·0001; table 4). Significantly more women taking anastrozole than those taking placebo reported dry eyes (table 4). Vaginal or uterine

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>Anastrozole group (n=1920)</th>
<th>Placebo group (n=1944)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin cancer</td>
<td>14 (1%)</td>
<td>27 (1%)</td>
<td>0·53 (0·28–0·99)</td>
</tr>
<tr>
<td>Non-melanoma</td>
<td>10 (1%)</td>
<td>20 (1%)</td>
<td>0·51 (0·24–1·08)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>4 (1%)</td>
<td>7 (1%)</td>
<td>0·58 (0·17–1·97)</td>
</tr>
<tr>
<td>Gastrointestinal cancer</td>
<td>4 (1%)</td>
<td>12 (2%)</td>
<td>0·34 (0·11–1·04)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>3 (1%)</td>
<td>11 (2%)</td>
<td>0·28 (0·08–0·99)</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>3 (1%)</td>
<td>5 (1%)</td>
<td>0·61 (0·15–2·54)</td>
</tr>
<tr>
<td>Leukaemia, lymphoma, or myeloma</td>
<td>4 (1%)</td>
<td>7 (1%)</td>
<td>0·58 (0·17–1·97)</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>0</td>
<td>2 (1%)</td>
<td>0·41 (0·08–2·08)</td>
</tr>
<tr>
<td>Cancer of the urinary tract</td>
<td>2 (1%)</td>
<td>5 (1%)</td>
<td>1·01 (0·25–4·04)</td>
</tr>
<tr>
<td>Cancer of the nervous system</td>
<td>3 (1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>4 (1%)</td>
<td>4 (1%)</td>
<td>1·01 (0·25–4·04)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>4 (1%)</td>
<td>7 (1%)</td>
<td>0·58 (0·17–1·97)</td>
</tr>
<tr>
<td>Vaginal cancer</td>
<td>1 (1%)</td>
<td>0</td>
<td>..</td>
</tr>
<tr>
<td>Carcinomatosis</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>1·01 (0·06–16·18)</td>
</tr>
<tr>
<td>Total*</td>
<td>40 (2%)</td>
<td>70 (4%)</td>
<td>0·58 (0·39–0·85)</td>
</tr>
</tbody>
</table>

Data are n (%), unless otherwise stated. *p=0·005

Table 3: Frequency of cancers other than breast cancer

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>Anastrozole group (n=1920)</th>
<th>Placebo group (n=1944)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>2 (&lt;1%)</td>
<td>0</td>
<td>..</td>
</tr>
<tr>
<td>Other cancer</td>
<td>7 (&lt;1%)</td>
<td>10 (1%)</td>
<td>..</td>
</tr>
<tr>
<td>Cerebrovascular accident or stroke</td>
<td>2 (&lt;1%)</td>
<td>2 (&lt;1%)</td>
<td>..</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>3 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>..</td>
</tr>
<tr>
<td>Other</td>
<td>4 (&lt;1%)</td>
<td>4 (&lt;1%)</td>
<td>..</td>
</tr>
<tr>
<td>Total*</td>
<td>18 (1%)</td>
<td>17 (1%)</td>
<td>..</td>
</tr>
</tbody>
</table>

Table 2: Causes of death

Anastrozole reduced frequency of high-grade tumours significantly more effectively than it reduced frequency of low-grade tumours (figure 4). We recorded no significant heterogeneity in the effect of anastrozole in different subgroups, but larger differences were noted for oestrogen-receptor-positive, progesterone-receptor-positive, and node-negative tumours (figure 4). When models were adjusted for age, body-mass index, previous use of hormone replacement therapy, and smoking status, we recorded similar HRs as for univariate analyses (data not shown). Further details for ductal carcinoma in situ according to treatment allocation are shown in the appendix.

Further exploratory analyses did not show any heterogeneity according to subgroups divided by age, body-mass index, previous use of hormone replacement therapy, and ductal carcinoma in situ, although non-significantly larger effects were recorded for women with lobular carcinoma in situ or atypical hyperplasia and those who had not previously used hormone replacement therapy (figure 5). In the placebo group, the highest 7-year cumulative incidences were recorded for lobular carcinoma in situ or atypical hyperplasia (12.1%), followed by ductal carcinoma in situ (9.7%), and none of these lesions (4.1%).
In women at high risk. Our results are similar to those recorded with exemestane in the MAP.3 trial. The reduction in incidence that we have reported is greater than that recorded for selective oestrogen receptor modulators such as tamoxifen. The effect of tamoxifen has been shown to persist for at least 10 years, and further follow-up is needed to establish whether anastrozole has such a sustained effect. We noted reductions in frequency of breast cancer in most subgroups of participants, although anastrozole’s effect

### Table 4: Adverse events of any severity reported at any time

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Anastrozole group (n=1920)</th>
<th>Placebo group (n=1944)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>1709 (89%)</td>
<td>1723 (89%)</td>
<td>1.00 (0.98–1.03)</td>
</tr>
<tr>
<td>Fractures</td>
<td>164 (9%)</td>
<td>149 (8%)</td>
<td>1.11 (0.90–1.38)</td>
</tr>
<tr>
<td>Arm</td>
<td>66 (3%)</td>
<td>61 (3%)</td>
<td>1.10 (0.78–1.54)</td>
</tr>
<tr>
<td>Leg</td>
<td>65 (3%)</td>
<td>57 (3%)</td>
<td>1.15 (0.81–1.64)</td>
</tr>
<tr>
<td>Rib, spine, or collarbone</td>
<td>23 (1%)</td>
<td>18 (1%)</td>
<td>1.29 (0.70–2.39)</td>
</tr>
<tr>
<td>Pelvic or hip</td>
<td>9 (&lt;1%)</td>
<td>10 (1%)</td>
<td>0.91 (0.37–2.24)</td>
</tr>
<tr>
<td>Skull</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>1.01 (0.06–1.83)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>1226 (64%)</td>
<td>1124 (58%)</td>
<td>1.03 (1.05–1.16)</td>
</tr>
<tr>
<td>Arthralgia*</td>
<td>972 (51%)</td>
<td>894 (46%)</td>
<td>1.04 (0.93–1.20)</td>
</tr>
<tr>
<td>Mild</td>
<td>385 (20%)</td>
<td>386 (20%)</td>
<td>1.01 (0.81–1.29)</td>
</tr>
<tr>
<td>Moderate</td>
<td>422 (22%)</td>
<td>363 (19%)</td>
<td>1.18 (0.47–1.33)</td>
</tr>
<tr>
<td>Severe</td>
<td>151 (8%)</td>
<td>123 (6%)</td>
<td>1.24 (0.99–1.56)</td>
</tr>
<tr>
<td>Joint stiffness</td>
<td>143 (7%)</td>
<td>96 (5%)</td>
<td>1.51 (1.17–1.94)</td>
</tr>
<tr>
<td>Pain in hand or foot</td>
<td>178 (9%)</td>
<td>147 (8%)</td>
<td>1.23 (0.99–1.51)</td>
</tr>
<tr>
<td>Cervical tunnel syndrome or nerve compression</td>
<td>67 (3%)</td>
<td>43 (2%)</td>
<td>1.58 (1.08–2.30)</td>
</tr>
<tr>
<td>Vascular</td>
<td>1090 (57%)</td>
<td>961 (49%)</td>
<td>1.15 (1.08–1.22)</td>
</tr>
<tr>
<td>Mild</td>
<td>550 (29%)</td>
<td>504 (26%)</td>
<td>1.10 (1.00–1.21)</td>
</tr>
<tr>
<td>Moderate</td>
<td>390 (20%)</td>
<td>330 (17%)</td>
<td>1.20 (1.05–1.37)</td>
</tr>
<tr>
<td>Severe</td>
<td>150 (8%)</td>
<td>127 (7%)</td>
<td>1.20 (0.95–1.50)</td>
</tr>
<tr>
<td>Gynaecological</td>
<td>460 (24%)</td>
<td>423 (22%)</td>
<td>1.09 (0.98–1.24)</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>357 (19%)</td>
<td>304 (16%)</td>
<td>1.19 (1.03–1.37)</td>
</tr>
<tr>
<td>Haemorrhage or bleeding</td>
<td>65 (3%)</td>
<td>81 (4%)</td>
<td>0.82 (0.60–1.13)</td>
</tr>
<tr>
<td>Vaginal or uterine prolapse</td>
<td>13 (1%)</td>
<td>31 (2%)</td>
<td>0.42 (0.22–0.81)</td>
</tr>
<tr>
<td>Vulvovaginal pruritus</td>
<td>40 (2%)</td>
<td>60 (3%)</td>
<td>0.68 (0.45–1.00)</td>
</tr>
<tr>
<td>Vascular</td>
<td>152 (8%)</td>
<td>127 (7%)</td>
<td>1.27 (0.97–1.52)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>89 (5%)</td>
<td>55 (3%)</td>
<td>1.64 (1.28–2.18)</td>
</tr>
<tr>
<td>Myocardial infarction or cardiac failure</td>
<td>8 (&lt;1%)</td>
<td>9 (&lt;1%)</td>
<td>0.90 (0.35–2.32)</td>
</tr>
<tr>
<td>Thrombosis or embolism</td>
<td>19 (1%)</td>
<td>17 (1%)</td>
<td>1.13 (0.59–2.17)</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>9 (&lt;1%)</td>
<td>8 (&lt;1%)</td>
<td>1.14 (0.44–2.95)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>3 (&lt;1%)</td>
<td>6 (&lt;1%)</td>
<td>0.51 (0.13–2.02)</td>
</tr>
<tr>
<td>Eye</td>
<td>348 (18%)</td>
<td>335 (17%)</td>
<td>1.05 (0.92–1.21)</td>
</tr>
<tr>
<td>Dry eyes</td>
<td>83 (4%)</td>
<td>58 (3%)</td>
<td>1.45 (1.04–2.01)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>12 (1%)</td>
<td>5 (&lt;1%)</td>
<td>2.43 (0.86–8.88)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>12 (1%)</td>
<td>24 (1%)</td>
<td>0.51 (0.25–1.00)</td>
</tr>
<tr>
<td>Cataract</td>
<td>90 (5%)</td>
<td>95 (5%)</td>
<td>0.96 (0.72–1.27)</td>
</tr>
<tr>
<td>Infections</td>
<td>230 (12%)</td>
<td>217 (11%)</td>
<td>1.07 (0.90–1.28)</td>
</tr>
<tr>
<td>Influenza</td>
<td>25 (1%)</td>
<td>12 (1%)</td>
<td>2.31 (1.06–4.70)</td>
</tr>
<tr>
<td>Otitis media</td>
<td>18 (1%)</td>
<td>6 (&lt;1%)</td>
<td>3.04 (1.21–7.64)</td>
</tr>
</tbody>
</table>

Data are n (%), unless otherwise stated. Details of any reported adverse event were recorded at every follow-up visit. Adverse events shown here are those that were predefined, common (affecting at least 5% of participants), or differed significantly (p <0.02) between groups. *Assessments of severity broadly based on Common Terminology Criteria for Adverse Events, but some discretion used by clinicians. †Hot flushes or night sweats.
seemed to be increased in women with lobular carcinoma in situ or atypical hyperplasia. This increased effect was also shown in two prevention trials of tamoxifen.\(^\text{14,27,28}\) An intriguing finding in our study was that anastrozole’s effect seemed to be greatest for high-grade tumours. Although highly significant, this finding could have been a result of chance, because other indicators of aggressive or fast growing tumours (eg, node positivity and large tumour size) were not differentially affected.

As in MAP,\(^3\) we recorded no significant differences between groups for cardiovascular events, but musculoskeletal and vasomotor symptoms were increased with anastrozole. Additionally, frequency of carpal tunnel syndrome was significantly higher with anastrozole, as was noted in the ATAC trial,\(^6\) although the disorder was still fairly rare. The high frequency of musculoskeletal and vasomotor symptoms in the placebo group is notable, because they are usually linked with an aromatase inhibitor in non-randomised comparisons.\(^7\) We have also confirmed an increase in frequency of hypertension with anastrozole, as was first reported in the ATAC trial.\(^8\)

A new exploratory finding is the significant increase in frequency of dry eyes with anastrozole, although the total number of events was small. Mixed findings relating to dry eyes in the menopause and hormone replacement therapy have been reported.\(^9\) Oestrogenic and androgenic receptors are located on corneal and conjunctival epithelia,\(^9,20\) but possible effects of aromatase inhibitors on vision have been previously linked with retinal changes.\(^21,22\) We know of only two uncontrolled reports in which dry eyes have previously been associated with aromatase inhibitors.\(^23,24\) In one,\(^23\) sicca syndrome of the eyes and mouth was associated with anastrozole in patients with probable Sjögren’s syndrome. However, in our study, only four cases of Sjögren’s syndrome were reported—three with anastrozole and one with placebo. Further validation of the increased frequency of dry eyes in women taking an aromatase inhibitor is merited.

The reduced frequency of cancers other than breast cancer recorded in the anastrozole group is surprising, especially for colorectal cancers, in which hormone replacement therapy is known to be protective\(^9\) and for which the ATAC trial suggested a non-significant increase with anastrozole compared with tamoxifen in the adjuvant setting.\(^1\) Likewise, the reduction in non-melanoma skin cancer has not been reported previously with aromatase inhibitors, although the skin is known to be a site of aromatase activity.\(^9\) It is also interesting that incidence of endometrial cancer did not reduce, because increased oestrogen concentrations are a strong risk factor for this disease.\(^25\) Additionally, a substantially decreased risk of endometrial cancer with anastrozole was recorded in the ATAC trial,\(^1\) although the comparator was tamoxifen which is known to increase risk of endometrial cancer.\(^14,27,28\)

Strengths of this study are the large number of breast cancer events recorded and the median follow-up of 5 years, which is longer than for previous trials. Further follow-up is needed to fully assess the value of anastrozole in the prevention setting. Although a wide range of entry criteria were used in this trial, we recruited few women because of their breast density, which is a strong risk factor for the identification of high-risk women.\(^29,30\) Establishment of whether an aromatase inhibitor is effective in such a population is needed.

We have shown that anastrozole reduces the risk of invasive oestrogen-receptor-positive breast cancer and ductal carcinoma in situ by more than 50%, but that it has little effect on oestrogen-receptor-negative cancers. The reported reductions are larger than are those reported for tamoxifen or raloxifene.\(^1\) Therefore, anastrozole is an attractive option for postmenopausal women at increased risk of breast cancer. Although many side-effects recorded have been associated with oestrogen deprivation, they were only slightly more frequent in the anastrozole group than in the placebo group, indicating that most of these symptoms are not drug related. No additional side-effects have been recorded with anastrozole after treatment completion in the adjuvant setting,\(^1\) which is likely to be true in the preventive setting as well.

Full adherence for 5 years was 70% overall and only slightly lower in the anastrozole group than in the placebo group. Overall adherence at 3 years was 75%, which is similar to that in the MAP.3 trial,\(^3\) which had 85% overall adherence at 35 months. Adherence in our study was slightly better than for tamoxifen in IBIS-I,\(^1\) but our findings emphasise the need to understand and

Panel: Research in context

Systematic review

We searched PubMed before our study began for reports published in English between Jan 1, 1980, and Dec 31, 2001. We used the search terms “breast cancer”, “prevention”, and “aromatase inhibitor”. We identified no other trials of breast cancer prevention with an aromatase inhibitor. However, we identified several adjuvant trials in which contralateral tumours were reported.\(^1\) Before the planned analysis, we used the same criteria to search PubMed again for reports published before May 30, 2013. Only one other prevention trial with exemestane had been reported,\(^8\) and updated or new results for contralateral tumours had been reported for some of the adjuvant trials. We also identified an overview of selective oestrogen receptor modulators for breast cancer prevention.\(^8\) Finally, we identified two large trials in which aromatase inhibitors are being assessed for prevention of ductal carcinoma in situ (ISRCTN37546358 and NCT00053898), but results have not been reported.

Interpretation

Overall, our data suggest that aromatase inhibitors are the most effective agents available for breast cancer prevention. Follow-up in our trial was longer than that in the MAP.3 prevention trial\(^8\) and adjuvant trials, and we recorded substantially more events. Equally important is the finding that most side-effects associated with oestrogen deprivation were not attributable to the treatment; most were also increased in the placebo group.

Because anastrozole and exemestane have greater efficacies than do tamoxifen and raloxifene, and have a different but generally decreased side-effect profile, anastrozole or exemestane emerge as the treatments of choice for risk reduction in most postmenopausal women at high risk of breast cancer.
minimise dropout. Dissemination of the fact that most side-effects are not treatment related could help.

In the USA, the American Society of Clinical Oncology task force has recommended that exemestane be considered for prevention in addition to tamoxifen and raloxifene, and in the UK, the National Institute for Health and Care Excellence has recommended that tamoxifen and raloxifene be offered to women at high risk of breast cancer.12 Our results strongly support the use of anastrozole for preventive treatment of high-risk postmenopausal women (panel).

Contributors
JC, JFF, MD, SC, CS, NR, REM, GVm, BB, TP, and AH designed the study. JC, JFF, SC, CS, NR, REM, GVm, BB, TP, and AH collected data. JC and IS analysed data and wrote the report. JC, IS, JFF, MD, SC, CS, NR, REM, GVm, BB, TP, and AH interpreted data. JC managed the project.

Conflicts of interest
JC received funding for IBIS-II from Sanofi-Aventis and AstraZeneca, and is a paid member of a speaker’s bureau for AstraZeneca. JFF has received grant support from Novartis. MD has received grant support from and is a paid member of a speakers’ bureau for AstraZeneca. The other authors declare that they have no conflicts of interest.

Acknowledgments
This study was funded by Cancer Research UK (C569/A5032), the National Health and Medical Research Council Australia (GNT300755, GNT569213), Sanofi-Aventis, and AstraZeneca. Sanofi-Aventis and AstraZeneca provided anastrozole and matching placebo. The study sponsor was Queen Mary University of London.

References
23 Laroche M, Borg S, Lassoued S, De Lafontan B, Roche H. Joint pain and in the UK, the National Institute for Health and Care Excellence has recommended that tamoxifen and raloxifene be offered to women at high risk of breast cancer.12 Our results strongly support the use of anastrozole for preventive treatment of high-risk postmenopausal women (panel).
Supplementary appendix

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


This appendix has been corrected. The corrected version first appeared at thelancet.com on February 6, 2014.
Appendix

Steering Committee:

Bernardo Bonanni (Division of Chemoprevention and Genetics; Milano, Italy)
Mary Buchanan (London, United Kingdom)
Nigel Bundred (South Manchester University Hospital; Manchester, United Kingdom)
Simon Cawthorn (Southmead Hospital; Bristol, United Kingdom)
Robert E. Coleman (Weston Park Hospital; Sheffield, United Kingdom)
Jack Cuzick – Co-Chairman (Centre for Cancer Prevention, Queen Mary University; London, United Kingdom)
Mitch Dowsett (The Royal Marsden NHS Trust; London, United Kingdom)
Richard Eastell (Sheffield University; Sheffield, United Kingdom)
Bent Ejlersen (The Finsen Centre; Copenhagen, Denmark)
Ian Ellis (University of Nottingham; Nottingham, United Kingdom)
John F. Forbes – Co-Chairman (Australian New Zealand Breast Cancer Trials Group, Calvary Mater Hospital, University of Newcastle; Newcastle, Australia)
Anthony Howell – Co-Chairman (Genesis Breast Cancer Prevention Centre; Manchester, United Kingdom)
Zsuzsanna Kahan (University of Szeged; Szeged, Hungary)
Gerry Leonard (Queen Mary University; London United Kingdom)
Christine Levy (Centre Hospitalier Universitaire de Caen; Caen, France)
Robert E. Mansel (University of Wales College of Medicine; Cardiff, United Kingdom)
Jennifer Marshall (AstraZeneca UK Limited; Macclesfield, United Kingdom)
Patrick Neven (UZ Gasthuisberg Ziekenhuis; Leuven, Belgium)
Tiina Palva (Pirkanmaa Cancer Society; Tampere, Finland)
Yuri Rukazenkov (AstraZeneca UK Limited; Macclesfield, United Kingdom)
Lisa Rydén (Department of Surgery; Lund, Sweden)
Hans-Jorg Senn (Center for Tumordetection & Prevention; St. Gallen, Switzerland)
Ivana Sestak – Trial Statistician (Centre for Cancer Prevention, Queen Mary University; London, United Kingdom)
Michael Stierer (Univ. Prof. Dr. Michael Stierer; Wien, Austria)
Fatima Vaz (Instituto Portugues de Oncologia; Lisbon, Portugal)
Gunter von Minckwitz (German Breast Group; Frankfurt, Germany)

Principle Investigators:

Ehtesham Abdi (The Tweed Hospital; Tweed Heads, Australia)
Bahriye Aktas (Frauenklinik am Universitätsklinikum Essen; Essen, Germany)
Fabrizio Artioli (Ospedale B. Ramazzini; Carpi (MO), Italy)
Doris Augustin (Klinikum Deggendorf; Deggendorf, Germany)
Caroline Baker (Victorian Breast & Oncology Care; East Melbourne, Australia)
Matthias Beckmann (Friedrich-Alexander-Universität; Erlangen, Germany)
Ian Bennett (Princess Alexandra Hospital; Woolloongabba, Australia)
Gianfilippo Bertelli (Singleton Hospital; Swansea, United Kingdom)
Robert Blum (Peter MacCallum Cancer Centre; East Melbourne, Australia)
Barbara Bolliger (Center for Tumordetection & Prevention; St. Gallen, Switzerland)
Bernardo Bonanni (Istituto Europeo di Oncologia; Milano, Italy)
Adam Boyce (Lismore Base Hospital; Lismore, Australia)
Howard Bradpiece (St. Margaret's Hospital; Epping, United Kingdom)
Maria Bramley (The Royal Oldham Hospital; Oldham, United Kingdom)
Georg-Peter Breitbach (Krankenhaus Neunkirchen GmbH; Neunkirchen, Germany)
Stephen Brincat (Sir Paul Boffa Hospital; Floriana, Malta)
Karen Briscoe (Coffs Harbour Health Campus; Coffs Harbour, Australia)
Olaf Buchholz (Caritas-Krankenhaus St. Josef; Regensburg, Germany)
Katharina S. Buser (Oncocare Klinik Engeried ; Bern, Switzerland)
Susanne Bucher (Luzerner Kantons spitale, Luzern, Switzerland)
Ian Campbell (Waikato Hospital; Waikato, New Zealand)
Hugh Carmalt (Royal Prince Alfred Hospital; Camperdown, Australia)
Simon Cawthorn (Southmead Hospital; Bristol, United Kingdom)
James Bristol (Cheltenham General Hospital; Cheltenham, United Kingdom)
Pierre O. Chappuis (HUG Unite d'oncogénétique et de prévention; Genève, Switzerland)
David Clark (The Breast and Endocrine Centre; Gateshead, Australia)
Robert E. Coleman (Weston Park Hospital; Sheffield, United Kingdom)
John Collins (Royal Melbourne Hospital; Parkville, Australia)
Bettina Conrad (Elisabeth Krankenhaus; Kassel, Germany)
Serban-Dan Costa (Otto-von-Guericke-Universitaet; Magdeburg, Germany)
Raouf Daoud (Frimley Park Hospital NHS Trust; Frimley, United Kingdom)
Stephen Della-Fiorentina (Australia & Southern Highlands Cancer Centre; Bowral, Australia)
Mustafa Deryal (Caritasklinik St. Theresia; Saarbruecken, Germany)
Michael Donovan (Nambour Hospital; Nambour, Australia)
Philip Drew (Royal Cornwall Hospital; Truro, United Kingdom)
Siddharth Dubey (Derriford Hospital; Devon, United Kingdom)
Simon Ellenbogen (Tameside General Hospital; Ashton-Under-Lyne, United Kingdom)
Denis Evoy (ICORG, the all-Ireland Cooperative Oncology Research Group; Dublin, Ireland)
Massimo Federico (Azienda Ospedaliera Universitaria die Modena; Modena, Italy)
Douglas Ferguson (Royal Devon and Exeter Hospital; Exeter, United Kingdom)
John F. Forbes (Australia and New Zealand Breast Cancer Trials Group, Calvary Mater Hospital, University of Newcastle; Waratah, Australia)
John N. Fox (The Hull and East Yorkshire Breast Care Unit; Hull, United Kingdom)
Jorge Gamboa (Corporación Nacional del Cáncer; Santiago, Chile)
Jens Peter Garne (Aalborg Hospital; Aalborg, Denmark)
Val Gebski (ANZBCTG Statistical Centre, NHMRC Clinical Trials Centre; Sydney, Australia)
Raafat Gendy (Mid Staffordshire NHS Foundation Trust; Stafford, United Kingdom)
Claudio Graff (Azienda Sanitaria di Bolzano; Bolzano, Italy)
Peter Grantley Gill (Royal Adelaide Hospital; Adelaide, Australia)
Sabine Gross (Marienhospital; Stuttgart, Germany)
Rajnish Gupta (ICORG, the all-Ireland Cooperative Oncology Research Group; Limerick, Ireland)
Eleanor Gutteridge (Nottingham University Hospitals NHS Trust; Nottingham, United Kingdom)
Hisham Hamed (Academic Oncology Unit; London, United Kingdom)
Claus A. Hanusch (Frauenklinik vom Roten Kreuz; Munich, Germany)
Senn Hans-Jorg (Center for Tumordetection & Prevention; St. Gallen, Switzerland)
Claudia Harding-McKean (Countess of Chester Hospital; Chester, United Kingdom)
Georg Heinrich (Praxis Dr. Heinrich; Fuerstenwalde, Germany)
Jane Hill (Riverina Cancer Care Centre, Wagga Wagga, Australia)
Arnold Hill (ICORG, the all-Ireland Cooperative Oncology Research Group; Dublin, Ireland)
Gerald Hoffmann (St. Josefhospital; Wiesbaden, Germany)
Chris Holcombe (Royal Liverpool University Hospital; Liverpool, United Kingdom)
Anthony Howell (Genesis Breast Cancer Prevention Centre; Manchester, United Kingdom)
Jibril A. Jibril (United Lincolnshire Hospitals NHS Trust; Lincoln, United Kingdom)
Zsuzsanna Kahan (University of Szeged; Szeged, Hungary)
Karin Kast (Technische Universität Dresden; Dresden, Germany)
Manfred Kaufmann (Universitaetsklinikum Frankfurt; Frankfurt, Germany)
John Kennedy (ICORG, the all-Ireland Cooperative Oncology Research Group; Dublin, Ireland)
Michael Kerin (ICORG, the all-Ireland Cooperative Oncology Research Group; Galway, Ireland)
Hussein Khaled (National Cancer Institute; Cairo, Egypt)
Peter Klare (Praxisklinik Krebsheilkunde für Frauen; Berlin, Germany)
Jalal Kokan (Macclesfield District General Hospital; Macclesfield, United Kingdom)
Petr Krabisch (Klinikum Chemnitz; Chemnitz, Germany)
Charlotte Lanng (Herlev Hospital; Herlev, Denmark)
Alison Lannigan (Wishaw General Hospital; Wishaw, United Kingdom)
Mark Lansdown (St James's University Hospital; Leeds, United Kingdom)
Michael Law (Maroondah Breast Clinic; Ringwood East, Australia)
Sabine Lemster (Klinikum Schaumburg; Stadthagen, Germany)
Tom Lennard (University of Newcastle Upon Tyne; Newcastle Upon Tyne, United Kingdom)
Rick Linforth (Bradford Teaching Hospitals NHS Foundation Trust; Bradford, United Kingdom)
Robert E. Mansel (University of Wales College of Medicine; Cardiff, United Kingdom)
Frederik Marmé (Universitaetsklinikum Heidelberg; Heidelberg, Germany)
Franca Martignoni (Uniklinikum Dusseldorf; Dusseldorf, Germany)
Carlo Tondini (Ospedali Riuniti Di Bergamo; Bergamo, Italy)
Augustinus Tulusan (Klinikum Bayreuth; Bayreuth, Germany)
Christoph Uleer (Gemeinschaftspraxis Hildesheim; Hildesheim, Germany)
Jayant Vaidya (Royal Free and UCL Medical School; London, United Kingdom)
Fatima Vaz (Instituto Portugues de Oncologia; Lisbon, Portugal)
Janice Walshe (ICORG, the all-Ireland Cooperative Oncology Research Group; Dublin, Ireland)
Peter A. Wamberg (Vejle Hospital; Vejle, Denmark)
Wolfgang Wiest (Katholisches Klinikum Mainz/St. Vinzenz; Mainz, Germany)
Shane White (Austin Heath; Heidelberg, Australia)
Stephen Wilkinson (Royal Hobart Hospital; Hobart, Australia)
Virginia Wolstenholme (St Bartholomew's Hospital; London, United Kingdom)
Martin Wrigley (Peter MacCallum Cancer Centre; East Melbourne, Australia)
Christina A. Wynne (Canterbury Breast Care, Christchurch Hospital; Christchurch, New Zealand)
Khalil Zaman (Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland)
Charles Zammit (Royal Sussex County Hospital; Brighton, United Kingdom)

Local Coordinating Centres:

Rochelle Thornton (Australia & New Zealand Breast Cancer Trials Group, Newcastle, Australia)
Fionda Probert (Australia & New Zealand Breast Cancer Trials Group, Newcastle, Australia)
Anthony Morrison (Australia & New Zealand Breast Cancer Trials Group, Newcastle, Australia)
Akiko Fong (Australia & New Zealand Breast Cancer Trials Group, Newcastle, Australia)
Margaret Chamen (Armidale Hospital & Tamworth Rural Referral Hospital, Armidale, Australia)
Rebecca Griffiths (Armidale Hospital & Tamworth Rural Referral Hospital, Armidale, Australia)
Angela Benson (Austin Health, Heidelberg, Australia)
Janet Holland (The Bendigo Health, Bendigo, Australia)
Amanda Rundle (The Bendigo Health, Bendigo, Australia)
Amy Tang (Box Hill Hospital, Box Hill, Australia)
Judith Silcock (The Breast & Endocrine Centre, Gateshead, Australia)
Yvonne Harrower (Calvary Mater Newcastle, Waratah, Australia)
Victoria Sproule (Calvary Mater Newcastle, Waratah, Australia)
Clara Baldo (Coffs Harbour Health Campus, Coffs Harbour, Australia)
Annabel Pickett (Coffs Harbour Health Campus, Coffs Harbour, Australia)
Sonia Byrne (Lismore Base Hospital, Lismore, Australia)
Peta King (Lismore Base Hospital, Lismore, Australia)
Kessler Warburton (Lismore Base Hospital, Lismore, Australia)
Jennifer Aung (Liverpool Hospital, Liverpool, Australia)
Sheela Subramani (Liverpool Hospital, Liverpool, Australia)
Debra Vantine (Macarthur Cancer Therapy Centre, Campbelltown, Australia)
Anne Whatman (Macarthur Cancer Therapy Centre, Campbelltown, Australia)
Krystine Walsh (Maroondah Hospital, Ringwood East, Australia)
Cecelia Preston (Nambour Hospital, Nambour, Australia)
Shiwangi Sharma (Peter MacCallum Cancer Centre, East Melbourne, Australia)
Chuan Tan (Princess Alexandra Hospital, Wooloongabba, Australia)
Mari Lashbrook (Riverina Cancer Care Centre, Wagga Wagga, Australia)
Joanne Rossini (Royal Adelaide Hospital, Adelaide, Australia)
Debbie Quarmby (Royal Hobart Hospital, Hobart, Australia)
Linda Garrett (The Royal Melbourne Hospital, Parkville, Australia)
Marian Lieszke (The Royal Melbourne Hospital, Parkville, Australia)
Giuliana D'Aulerio (Sir Charles Gairdner Hospital, Nedlands, Australia)
Isabel Davis (Southern Highlands Cancer Centre, Bowral, Australia)
Nadia Ranieri (St Vincent's Hospital, Melbourne, Fitzroy, Australia)
Maree Uhe (St Vincent's Hospital, Melbourne, Fitzroy, Australia)
Lynne Jolly (St Vincent's Hospital, Sydney, Darlinghurst, Australia)
Sharon Clark (The Tweed Hospital, Tweed Heads, Australia)
Karin Dunne (The Tweed Hospital, Tweed Heads, Australia)
Caroline Howells (The Tweed Hospital, Tweed Heads, Australia)
Kaye Robinson (Victorian Breast & Oncology Care, East Melbourne, Australia)
Heather Flay (Waikato Hospital, Hamilton, New Zealand)
Jenni Scarlet (Waikato Hospital, Hamilton, New Zealand)
Jayne Bowers (Wellington Hospital, Newtown, New Zealand)
Debra Morriss (Wellington Hospital, Newtown, New Zealand)
Kathryn Neilson (Christchurch Hospital, Christchurch, New Zealand)
Nic Stevens (Christchurch Hospital, Christchurch, New Zealand)
Sherry Nisbet (North Shore Hospital, Auckland, New Zealand)
Janice Wood (North Shore Hospital, Auckland, New Zealand)
Inge Lefever (University Hospitals, Leuven, Belgium)
Daisy Supply (University Hospitals, Leuven, Belgium)
Zdenka Zlutar (Chilean Cooperative Group for Oncologic Research, Santiago, Chile)
Bettina Müller (Chilean Cooperative Group for Oncologic Research, Santiago, Chile)
Maiju Välimaa (Pirkkanmaa Cancer Society, Tampere, Finland)
Riitta Toivonen (Pirkkanmaa Cancer Society, Tampere, Finland)
Heike Beckel (GBG Forschungs GmbH, Frankfurt, Germany)
Petra Feer (GBG Forschungs GmbH, Frankfurt, Germany)
Szeko Judit (University of Szeged, Szeged, Hungary)
ZsuZsanna Kahan (University of Szeged, Szeged, Hungary)
Aliana Guerrieri-Gonzaga (Division of Cancer Prevention and Genetics, European Institute of Oncology, Milan, Italy)
Giorgia Bollani (Division of Cancer Prevention and Genetics, European Institute of Oncology, Milan, Italy)
Clara Varricchio (Division of Cancer Prevention and Genetics, European Institute of Oncology, Milan, Italy)
Paola Maggioni (Ospedali Riuniti, Bergamo, Italy)
Elisabetta Cretella (Azienda Sanitaria di Bolzano, Bolzano, Italy)
Roberta Guerzoni (Ospedali B. Ramazzini, Carpi (MO), Italy)
Isabella Marchi (Azienda Ospedaliera Universitaria di Modena, Modena, Italy)
Laura Cortesi (Azienda Ospedaliera Universitaria di Modena, Modena, Italy)
Elisa Picardo (Ospedale Ostetrico Ginecologico S.Anna, Torino, Italy)
Furio Maggiorotto (IRCC Candiolo, Candiolo (TO), Italy)
Ilaria Vallini (Ospedale di Circolo, Varese, Italy)
Nadia Cilia (Sir Paul Boffa Hospital, Floriana, Malta)
Conceição Costa (Instituto Portugues de Oncologia Francisco Gentil, Lisbon, Portugal)
Estelle Cassoly (SAKK, Swiss Group for Clinical Cancer Research, Bern, Switzerland)
Rose Beamish (ICORG, the all-Ireland Cooperative Oncology Research Group, Cork, Ireland)
Debra O’Hare (ICORG, the all-Ireland Cooperative Oncology Research Group, Cork, Ireland)
Anna Cole (ICORG, the all-Ireland Cooperative Oncology Research Group, Cork, Ireland)
Elizabeth Lenhan (ICORG, the all-Ireland Cooperative Oncology Research Group, Cork, Ireland)
Elaine Cronin (ICORG, the all-Ireland Cooperative Oncology Research Group, Cork, Ireland)
Rose Beamish (ICORG, the all-Ireland Cooperative Oncology Research Group, Cork, Ireland)
Trudi Roche (ICORG, the all-Ireland Cooperative Oncology Research Group, Dublin, Ireland)
Aisling Corcoran (ICORG, the all-Ireland Cooperative Oncology Research Group, Dublin, Ireland)
Ingrid Kiernan (ICORG, the all-Ireland Cooperative Oncology Research Group, Dublin, Ireland)
Michelle Maguire (ICORG, the all-Ireland Cooperative Oncology Research Group, Dublin, Ireland)
Liz Egan (ICORG, the all-Ireland Cooperative Oncology Research Group, Dublin, Ireland)
Eamon Boland (ICORG, the all-Ireland Cooperative Oncology Research Group, Galway, Ireland)
Niamh Killilea (ICORG, the all-Ireland Cooperative Oncology Research Group, Galway, Ireland)
Marian Jennings (ICORG, the all-Ireland Cooperative Oncology Research Group, Galway, Ireland)
Laura Lowry (ICORG, the all-Ireland Cooperative Oncology Research Group, Limerick, Ireland)
Maria Gillespie (ICORG, the all-Ireland Cooperative Oncology Research Group, Tallaght, Ireland)
Ashley Bazin (ICORG, the all-Ireland Cooperative Oncology Research Group, Tallaght, Ireland)
Mariella D’Alessandro (ICORG, the all-Ireland Cooperative Oncology Research Group, Aberdeen, Ireland)
Min Cheung (North East London National Cancer Research Network Barts Health NHS Trust, London, United Kingdom)
Ana Marie PenaRemorin (North East London National Cancer Research Network Barts Health NHS Trust, London, United Kingdom)
Sarah Scovell (North East London National Cancer Research Network Barts Health NHS Trust, London, United Kingdom)
Fiona McKirdy (North East London National Cancer Research Network Barts Health NHS Trust, London, United Kingdom)
Richard Benton (Bradford Royal Infirmary, Bradford, United Kingdom)
Helen Robertshaw (Bradford Royal Infirmary, Bradford, United Kingdom)
Linda Bamford (Bradford Royal Infirmary, Bradford, United Kingdom)
Hayley Inman (Bradford Royal Infirmary, Bradford, United Kingdom)
Qamar Akbar (Bradford Royal Infirmary, Bradford, United Kingdom)
Naomi Hill (Belfast City Hospital, Belfast, United Kingdom)
Emma Hanna (Belfast City Hospital, Belfast, United Kingdom)
Jonathan Thompson (Belfast City Hospital, Belfast, United Kingdom)
Bobbie Yoong (Royal Sussex County Hospital, Brighton, United Kingdom)
Helen Mitchell (Royal Sussex County Hospital, Brighton, United Kingdom)
Beverly Etherington (Royal Sussex County Hospital, Brighton, United Kingdom)
Imogen Batty (Royal Bournemouth Hospital, Bournemouth, United Kingdom)
Hemant Patel (Royal Bolton Hospital Foundation Trust, Bolton, United Kingdom)
Shirley Cocks (Royal Bolton Hospital Foundation Trust, Bolton, United Kingdom)
Jane Shackleton (University Hospitals Bristol NHS Foundation Trust, Bristol, United Kingdom)
Verity Henson (University Hospitals Bristol NHS Foundation Trust, Bristol, United Kingdom)
Helen Boal (University Hospitals Bristol NHS Foundation Trust, Bristol, United Kingdom)
Catharine Dawe (Southmead Hospital, Bristol, United Kingdom)
Katrina Kirby (Southmead Hospital, Bristol, United Kingdom)
Helen Garlicka (Southmead Hospital, Bristol, United Kingdom)
Ms Jackie Elliott (Queens Hospital Burton, Burton, United Kingdom)
Helen Cox (Queens Hospital Burton, Burton, United Kingdom)
Sarah Hathaway-Lees (Queens Hospital Burton, Burton, United Kingdom)
Kathy Rooke (Essex County Hospital, Colchester, United Kingdom)
Christine Morris (University Hospital Llandough, Cardiff, United Kingdom)
Sian Gibson (Broomfield Hospital, Chelmsfield, United Kingdom)
Yvonne Lester (Broomfield Hospital, Chelmsfield, United Kingdom)
Catherine Stuart-Grumbar (3 Counties Cancer Research Network, Cheltenham, United Kingdom)
Sue Anderson (3 Counties Cancer Research Network, Cheltenham, United Kingdom)
Jill Chittock (3 Counties Cancer Research Network, Cheltenham, United Kingdom)
Rehana Bakawala (3 Counties Cancer Research Network, Cheltenham, United Kingdom)
Kate Trigg-Hogarth (3 Counties Cancer Research Network, Cheltenham, United Kingdom)
Mary Aldous (Countess of Chester Hospital, Chester, United Kingdom)
Denise Archer (Countess of Chester Hospital, Chester, United Kingdom)
Helen Eccleson (Countess of Chester Hospital, Chester, United Kingdom)
Janet Spriggs (Countess of Chester Hospital, Chester, United Kingdom)
Helen Beveridge (Royal Derby Hospital, Derby, United Kingdom)
Sonya Bradshaw (Royal Derby Hospital, Derby, United Kingdom)
Helen Cumming (Ninewell Hospital, Dundee, United Kingdom)
Morag Carroll (Perth Royal Infirmary, Dundee, United Kingdom)
Rachel Reid (Ninewell Hospital, Dundee, United Kingdom)
Fiona Geddes (Western General Hospital, Edinburgh, United Kingdom)
Caroline Turner (St Margaret’s Hospital, Epping, United Kingdom)
Joanna Howard (Conquest Hospital, Hastings, United Kingdom)
Sarah Goodwin (Conquest Hospital, Hastings, United Kingdom)
Jo-Anne Taylor (Conquest Hospital, Hastings, United Kingdom)
Suzy Tasker (Royal Devon and Exeter Hospital, Exeter, United Kingdom)
Susan Downer (Royal Devon and Exeter Hospital, Exeter, United Kingdom)
Kizzy Baines (Royal Devon and Exeter Hospital, Exeter, United Kingdom)
Dawn Edwards (Royal Devon and Exeter Hospital, Exeter, United Kingdom)
Carole Fletcher-Foale (Frimley Park Hospital, Frimley, United Kingdom)
Jacqueline Brighton (Frimley Park Hospital, Frimley, United Kingdom)
Carrie Burgess (Frimley Park Hospital, Frimley, United Kingdom)
Lynn Osborne (Grantham & District Hospital, Grantham, United Kingdom)
Ashmi Patel (Oncology & Haematology Clinical Trials (OHCT), London, United Kingdom)
Claire Partridge (Oncology & Haematology Clinical Trials (OHCT), London, United Kingdom)
Mary Perrin (Huddersfield Royal Infirmary, Huddersfield, United Kingdom)
Denise Hancock (Huddersfield Royal Infirmary, Huddersfield, United Kingdom)
Simone Ryan (Huddersfield Royal Infirmary, Huddersfield, United Kingdom)
Deborah Melia (Huddersfield Royal Infirmary, Huddersfield, United Kingdom)
Elaine Gullaksen (Castle Hill Hospital, Hull, United Kingdom)
Abigail Alfard (Castle Hill Hospital, Hull, United Kingdom)
Ellie Waldron (Airedale NHS Foundation Trust, Keighley, United Kingdom)
Helen Hothersall (Airedale NHS Foundation Trust, Keighley, United Kingdom)
Alison Shaw (Airedale NHS Foundation Trust, Keighley, United Kingdom)
Carol Lockwood (Lincoln County Hospital, Lincoln, United Kingdom)
Suzanne Archer (Lincoln County Hospital, Lincoln, United Kingdom)
Olesya Francis (Lincoln County Hospital, Lincoln, United Kingdom)
Beverley Mashegede (Pilgrim Hospital, Boston, United Kingdom)
Issy Thomas (Pilgrim Hospital, Boston, United Kingdom)
Sue Hartup (St James's University Hospital, Leeds, United Kingdom)
Jane Gibb (St James's University Hospital, Leeds, United Kingdom)
Amy Henson (St James's University Hospital, Leeds, United Kingdom)
Karen Makinson (Royal Liverpool University Hospital, Liverpool, United Kingdom)
Laura Francis (Royal Liverpool University Hospital, Liverpool, United Kingdom)
Yukie Kano (The Royal Marsden NHS Foundation Trust, London, United Kingdom)
Karen Brooks (The Royal Marsden NHS Foundation Trust, London, United Kingdom)
Janet Self (The Royal Marsden NHS Foundation Trust, London, United Kingdom)
Barbara Townley (Macclesfield District General Hospital, Macclesfield, United Kingdom)
Victoria Adimkra (Macclesfield District General Hospital, Macclesfield, United Kingdom)
Marilyn McCurrie (Macclesfield District General Hospital, Macclesfield, United Kingdom)
Philippa Hill (Macclesfield District General Hospital, Macclesfield, United Kingdom)
Lisa Hardstaff (Macclesfield District General Hospital, Macclesfield, United Kingdom)
Rosemary Greenhalgh (Wythenshawe Hospital, Manchester, United Kingdom)
Jenny Affen (Wythenshawe Hospital, Manchester, United Kingdom)
Justine Bluett Bennett-Cowell (Royal Victoria Infirmary, Newcastle, United Kingdom)
Rebecca Puvanendran (Royal Victoria Infirmary, Newcastle, United Kingdom)
Hattie Murdoch (Royal Victoria Infirmary, Newcastle, United Kingdom)
Kathryn Walker (Royal Victoria Infirmary, Newcastle, United Kingdom)
Alison Sutherland (Royal Victoria Infirmary, Newcastle, United Kingdom)
Charlotte Gordon (Royal Victoria Infirmary, Newcastle, United Kingdom)
Hannah Stevenson (Royal Victoria Infirmary, Newcastle, United Kingdom)
Shameem Asif-Suleman (Nottingham City Hospital, Nottingham, United Kingdom)
Sandra Dennis (Nottingham City Hospital, Nottingham, United Kingdom)
Tracey Gibbins (Nottingham City Hospital, Nottingham, United Kingdom)
Colleen Rouse (Nottingham City Hospital, Nottingham, United Kingdom)
Reshma Kanani (Northwick Park Hospital, Harrow, United Kingdom)
Joanne Johnson (The Royal Oldham Hospital, Oldham, United Kingdom)
Richard Jones (The Royal Oldham Hospital, Oldham, United Kingdom)
Melinda Foster (Poole Hospital NHS Foundation Trust, Poole, United Kingdom)
Hilary Rowley (Derriford Hospital, Plymouth, United Kingdom)
Julie Pascoe (Derriford Hospital, Plymouth, United Kingdom)
Sian Whelan (South West Wales Cancer Institute, Swansea, United Kingdom)
Dawn Withers (South West Wales Cancer Institute, Swansea, United Kingdom)
Susie Pitcher (South West Wales Cancer Institute, Swansea, United Kingdom)
Mandy Cook (South West Wales Cancer Institute, Swansea, United Kingdom)
Elaine Brinkworth (South West Wales Cancer Institute, Swansea, United Kingdom)
John Beachill (Weston Park Hospital, Sheffield, United Kingdom)
Carol Crabtree (Weston Park Hospital, Sheffield, United Kingdom)
Alison Clarke (Weston Park Hospital, Sheffield, United Kingdom)
Kim Stevens (Southampton General Hospital, Southampton, United Kingdom)
Ms Jill Stacey (Staffordshire General Hospital, Stafford, United Kingdom)
Ms Carol Parton (Staffordshire General Hospital, Stafford, United Kingdom)
Sadie Mitchell (Royal Cornwall Hospital, Truro, United Kingdom)
Darren Beech (Royal Cornwall Hospital, Truro, United Kingdom)
Vivienne Maidens (The Whittington Hospital, Whittington, United Kingdom)
Veronica Conteh (The Whittington Hospital, Whittington, United Kingdom)
Mrs Paula Botham (Wishaw General Hospital, Wishaw, United Kingdom)
Michelle Kotze (Yeovil District NHS Foundation Trust, Yeovil, United Kingdom)
Kerry Rennie (Yeovil District NHS Foundation Trust, Yeovil, United Kingdom)

**IBIS-II Coordinating Centre:**

Jason Chattoo
Rob Edwards
Sheila Ferguson
Jane Hickman
Amalia Ndoutoumou
Lauren Rockliffe
Navdip Sahota
Peter Searles

**Cancer Research UK Cancer Prevention Trials Unit:**

Benoit Aigret
Chris Farrance
Jessica Gaviria
Joan Idris
Roseann Kealy
Richard Ostler
Peter Sasieni

We would also like to acknowledge the contribution from the National Cancer Research Network and the Wales Cancer Research Network.
Supplementary Table 1: Entry criteria and distribution by treatment allocation.

<table>
<thead>
<tr>
<th>Category</th>
<th>Anastrozole (N=1920)</th>
<th>Placebo (N=1944)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For women aged 45-70</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First degree relative who developed breast cancer at age 50 or less.</td>
<td>677 (35.3%)</td>
<td>655 (33.7%)</td>
</tr>
<tr>
<td>First degree relative who developed bilateral cancer.</td>
<td>164 (8.5%)</td>
<td>141 (7.3%)</td>
</tr>
<tr>
<td>Two or more first or second degree relatives who developed breast or ovarian cancer.</td>
<td>952 (49.6%)</td>
<td>933 (48.0%)</td>
</tr>
<tr>
<td>Nulliparous or age 30 or above at first birth, and first degree relative who developed breast cancer.</td>
<td>211 (11.0%)</td>
<td>207 (10.6%)</td>
</tr>
<tr>
<td>Benign biopsy with proliferative disease and first degree relative who developed breast cancer.</td>
<td>21 (1.1%)</td>
<td>33 (1.7%)</td>
</tr>
<tr>
<td>Mammographic opacity covering at least 50% of the breast</td>
<td>7 (0.4%)</td>
<td>10 (0.5%)</td>
</tr>
<tr>
<td>First degree relative with breast cancer at any age.</td>
<td>488 (25.4%)</td>
<td>499 (25.7%)</td>
</tr>
<tr>
<td>Age at menopause 55 years or more.</td>
<td>45 (2.3%)</td>
<td>38 (2.0%)</td>
</tr>
<tr>
<td>Nulliparous or age 30 or above at first birth.</td>
<td>86 (4.5%)</td>
<td>83 (4.3%)</td>
</tr>
<tr>
<td><strong>For women aged 40-44</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two or more first or second degree relatives who developed breast cancer or ovarian cancer at age 50 or less.</td>
<td>8 (4.2%)</td>
<td>8 (0.4%)</td>
</tr>
<tr>
<td>First degree relative with bilateral breast cancer who developed first breast cancer at age 50 or less.</td>
<td>2 (0.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Nulliparous or age 30 or above at first birth, and first degree relative who developed breast cancer at age 40 or less.</td>
<td>0</td>
<td>2 (0.1%)</td>
</tr>
<tr>
<td>Benign biopsy with proliferative disease and first degree relative who developed breast cancer at age 40 or less.</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>For women in all age groups</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobular carcinoma in situ (LCIS)</td>
<td>50 (2.6%)</td>
<td>55 (2.8%)</td>
</tr>
<tr>
<td>Atypical ductal or lobular hyperplasia in a benign lesion.</td>
<td>104 (5.4%)</td>
<td>135 (6.9%)</td>
</tr>
<tr>
<td>DCIS (ER-positive) diagnosed within last 6 months with completed adequate local treatment.</td>
<td>160 (8.3%)</td>
<td>166 (8.5%)</td>
</tr>
<tr>
<td>Women with a clearly apparent family history indicating appropriate increased risk</td>
<td>34 (1.8%)</td>
<td>38 (2.0%)</td>
</tr>
</tbody>
</table>

ER = Oestrogen Receptor, LCIS = Lobular Carcinoma In Situ, DCIS = Ductal Carcinoma In Situ
Supplementary Table 2: Characteristics of breast cancers occurring during the trial (N=125) according to treatment allocation.

<table>
<thead>
<tr>
<th></th>
<th>Anastrozole (N=1920)</th>
<th>Placebo (N=1944)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Invasive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>7</td>
<td>8</td>
<td>0·86 (0·31-2·38)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>16</td>
<td>29</td>
<td>0·55 (0·30-1·01)</td>
</tr>
<tr>
<td>High</td>
<td>9</td>
<td>26</td>
<td>0·35 (0·16-0·74)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>DCIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td>4</td>
<td>0·25 (0·03-2·23)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>7</td>
<td>0·29 (0·06-1·37)</td>
</tr>
<tr>
<td>High</td>
<td>3</td>
<td>9</td>
<td>0·33 (0·09-1·22)</td>
</tr>
<tr>
<td>Unknown</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Nodal status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Invasive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>18</td>
<td>44</td>
<td>0·41 (0·23-0·70)</td>
</tr>
<tr>
<td>Positive</td>
<td>12</td>
<td>16</td>
<td>0·75 (0·35-1·58)</td>
</tr>
<tr>
<td>Not done/Unknown</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>DCIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>4</td>
<td>12</td>
<td>0·33 (0·11-1·03)</td>
</tr>
<tr>
<td>Positive</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Not done/Unknown</td>
<td>2</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td><strong>Tumour size</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Invasive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10mm</td>
<td>11</td>
<td>19</td>
<td>0·58 (0·27-1·21)</td>
</tr>
<tr>
<td>10-20mm</td>
<td>8</td>
<td>28</td>
<td>0·28 (0·13-0·62)</td>
</tr>
<tr>
<td>&gt;20mm</td>
<td>13</td>
<td>17</td>
<td>0·76 (0·37-1·56)</td>
</tr>
<tr>
<td><strong>DCIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10mm</td>
<td>1</td>
<td>3</td>
<td>0·33 (0·03-3·20)</td>
</tr>
<tr>
<td>10-20mm</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>&gt;20mm</td>
<td>5</td>
<td>13</td>
<td>0·38 (0·14-1·07)</td>
</tr>
<tr>
<td><strong>ER status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Invasive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>11</td>
<td>14</td>
<td>0·78 (0·35-1·72)</td>
</tr>
<tr>
<td>Positive</td>
<td>20</td>
<td>47</td>
<td>0·42 (0·25-0·71)</td>
</tr>
<tr>
<td>Not done/Unknown</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>DCIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>2</td>
<td>5</td>
<td>0·40 (0·08-2·07)</td>
</tr>
<tr>
<td>Positive</td>
<td>3</td>
<td>11</td>
<td>0·27 (0·08-0·97)</td>
</tr>
<tr>
<td>Not done/Unknown</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>PR status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Invasive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>15</td>
<td>22</td>
<td>0·68 (0·35-1·31)</td>
</tr>
<tr>
<td>Positive</td>
<td>9</td>
<td>28</td>
<td>0·32 (0·15-0·67)</td>
</tr>
<tr>
<td>Not done/Unknown</td>
<td>8</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td><strong>DCIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>3</td>
<td>9</td>
<td>0·33 (0·09-1·23)</td>
</tr>
<tr>
<td>Positive</td>
<td>2</td>
<td>4</td>
<td>0·49 (0·09-2·70)</td>
</tr>
<tr>
<td>Not done/Unknown</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Detection method</td>
<td>24</td>
<td>54</td>
<td>0.44 (0.27-0.71)</td>
</tr>
<tr>
<td>------------------</td>
<td>----</td>
<td>----</td>
<td>------------------</td>
</tr>
<tr>
<td>Screen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>14</td>
<td>29</td>
<td>0.48 (0.25-0.91)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>

HR=Hazard Ratio, mm=millimetre, DCIS=Ductal Carcinoma In Situ, ER=Oestrogen Receptor, PR=Progesterone receptor
Supplementary Figure 1: Five year adherence according to treatment allocation.