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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 Cau thorn, 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 after 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 after 7 years was 5·6% in the placebo group and 2·8% in the anastrozole group. 18 deaths were reported in the anastrozole group and 17 in the placebo group, and no specific causes were more common in one group than the other (p=0.836).

Interpretation Anastrozole effectively reduces incidence of breast cancer in high-risk postmenopausal women. This finding, along with the fact that most of the side-effects associated with oestrogen deprivation were not attributable to treatment, provides support for the use of anastrozole in postmenopausal women at high risk of breast cancer.

Funding Cancer Research UK, the National Health and Medical Research Council Australia, Sanofi-Aventis, and AstraZeneca.

Introduction Breast cancer is the most common form of cancer in women, with 1·4 million new cases reported worldwide in 2008.1 Its incidence is rapidly increasing, largely because of an ageing population, rising socioeconomic status, increases in obesity, and several lifestyle changes, such as decreases in physical activity, later age at first childbirth, and reductions in breastfeeding. Although improvements in lifestyle are an important part of breast cancer prevention, as they are for cardiovascular disease, prophylactic treatment is also likely to have an important role, especially for women at high risk (ie, 10-year risk of 5% or more).

Oestrogen is a key factor in breast cancer carcinogenesis, and reductions in its synthesis can decrease 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 recurrence24 and also development of new contralateral tumours25 in postmenopausal women than does tamoxifen. In a meta-analysis,3 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 tamoxifen27 and has been confirmed in a trial of the aromatase inhibitor exemestane,4 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,4 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.4 No serious side-effects of exemestane were recorded, but median follow-up was fairly short for detection of any serious adverse events.5 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 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).

**Anastrozole group (n=1920)**

- Age (years)
  - 59.5 (55.0–63.5)
  - 59.4 (55.1–63.3)
- Age at menarche (years)
  - 13.0 (12.1–14.0)
  - 13.0 (12.0–14.0)
- Parous
  - 640 (33%)
  - 644 (33%)
- Age at first child birth (years)
  - 25.0 (21.0–27.0)
  - 24.0 (21.0–27.0)
- Age at menopause (years)
  - 50.0 (45.0–52.0)
  - 49.0 (45.0–52.0)
- Height (cm)
  - 162.0 (158.0–166.0)
  - 162.2 (158.0–167.0)
- Weight (kg)
  - 70.8 (64.0–82.2)
  - 72.1 (64.0–83.5)
- Body-mass index (kg/m²)
  - <25
    - 581 (30%)
    - 568 (29%)
  - 25–30
    - 609 (36%)
    - 732 (38%)
  - >30
    - 640 (33%)
    - 644 (33%)
- Previous use of hormone replacement therapy
  - 893 (47%)
  - 910 (47%)
- Use of hormone replacement therapy within previous 12 months
  - 128 (7%)
  - 152 (8%)
- Hysterectomy
  - 631 (33%)
  - 656 (34%)
- Two or more first-degree or second-degree relatives with breast or ovarian cancer
  - 956 (50%)
  - 938 (48%)
- One first-degree relative with breast cancer at age 50 years or younger
  - 675 (35%)
  - 653 (34%)
- One first-degree relative with bilateral breast cancer
  - 164 (9%)
  - 141 (7%)
- Lobular carcinoma in situ or atypical hyperplasia
  - 154 (8%)
  - 190 (10%)
- Oestrogen-receptor-positive ductal carcinoma in situ treated by mastectomy within 6 months
  - 160 (8%)
  - 166 (9%)
- 10-year Tyrer-Cuzick risk (%)
  - 7.6% (5.8–9.9)
  - 7.8% (5.1–10.2)

**Placebo group (n=1944)**

- Age (years)
  - 59.4 (55.1–63.3)
  - 59.3 (55.0–63.5)
- Age at menarche (years)
  - 13.0 (12.0–14.0)
  - 13.0 (12.1–14.0)
- Parous
  - 631 (33%)
  - 656 (34%)
- Age at first child birth (years)
  - 25.0 (21.0–27.0)
  - 25.0 (21.0–27.0)
- Age at menopause (years)
  - 50.0 (45.0–52.0)
  - 49.0 (45.0–52.0)
- Height (cm)
  - 162.0 (158.0–166.0)
  - 162.2 (158.0–167.0)
- Weight (kg)
  - 70.8 (64.0–82.2)
  - 72.1 (64.0–83.5)
- Body-mass index (kg/m²)
  - <25
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  - 160 (8%)
  - 166 (9%)
- 10-year Tyrer-Cuzick risk (%)
  - 7.6% (5.8–9.9)
  - 7.8% (5.1–10.2)

**Data are median (IQR) or n (%).**
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, which, with 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 P value of 0.05). 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.

### Results
3864 women underwent randomisation (figure 1). Median age at entry was 59.5 years (IQR 55.0–63.5) and 695 (18%) were older than 65 years. 1803 women (47%) had previously used hormone replacement therapy, and 1287 (33%) had had a hysterectomy (table 1).

### Figure 2: Analyses by type of breast cancer
Numbers in subgroups do not match totals because of missing data. ER=oestrogen receptor.

### Figure 3: Cumulative incidence of all breast cancers and of invasive ER-positive breast cancers
ER=oestrogen receptor.

### Role of the funding source
The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. IS had full access to all the data in the study, and JC, JFF, and AH had final responsibility for the decision to submit for publication.
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 (9727 in the anastrozole group vs 9672 in the placebo group). At the time of data
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 (figure 4). When analyses (data not shown). Further details for ductal 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%).

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 the 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). Vasomotor 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>Cancer Type</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>0.53 (0.28–0.99)</td>
</tr>
<tr>
<td>Other cancer</td>
<td>7 (&lt;1%)</td>
<td>10 (1%)</td>
<td>0.51 (0.24–1.08)</td>
</tr>
<tr>
<td>Cerebrovascular accident or stroke</td>
<td>2 (&lt;1%)</td>
<td>2 (&lt;1%)</td>
<td>0.58 (0.17–1.97)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>3 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>0.41 (0.08–2.08)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (&lt;1%)</td>
<td>4 (&lt;1%)</td>
<td>0.58 (0.17–1.97)</td>
</tr>
<tr>
<td>Total</td>
<td>18 (1%)</td>
<td>17 (1%)</td>
<td>0.58 (0.39–0.85)</td>
</tr>
</tbody>
</table>

Table 2: Causes of death

<table>
<thead>
<tr>
<th>Cancer Type</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 (&lt;1%)</td>
<td>7 (&lt;1%)</td>
<td>0.58 (0.17–1.97)</td>
</tr>
<tr>
<td>Gastrointestinal cancer</td>
<td>4 (&lt;1%)</td>
<td>12 (2%)</td>
<td>0.34 (0.11–1.04)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>3 (&lt;1%)</td>
<td>11 (2%)</td>
<td>0.28 (0.08–0.99)</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>3 (&lt;1%)</td>
<td>5 (&lt;1%)</td>
<td>0.61 (0.15–2.54)</td>
</tr>
<tr>
<td>Leukaemia, lymphoma, or myeloma</td>
<td>4 (&lt;1%)</td>
<td>7 (&lt;1%)</td>
<td>0.58 (0.17–1.97)</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>0</td>
<td>2 (&lt;1%)</td>
<td>0.58 (0.17–1.97)</td>
</tr>
<tr>
<td>Cancer of the urinary tract</td>
<td>2 (&lt;1%)</td>
<td>5 (&lt;1%)</td>
<td>0.41 (0.08–2.08)</td>
</tr>
<tr>
<td>Cancer of the nervous system</td>
<td>3 (&lt;1%)</td>
<td>0</td>
<td>0.58 (0.17–1.97)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>4 (&lt;1%)</td>
<td>4 (&lt;1%)</td>
<td>1.01 (0.25–4.04)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>4 (&lt;1%)</td>
<td>7 (&lt;1%)</td>
<td>0.58 (0.17–1.97)</td>
</tr>
<tr>
<td>Vaginal cancer</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>0.58 (0.17–1.97)</td>
</tr>
<tr>
<td>Carcinomatosis</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;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>

Table 3: Frequency of cancers other than breast cancer
prolapse and vaginal pruritus were also significantly reduced with anastrozole (table 4). Hypertension was significantly increased with anastrozole, but we recorded no significant differences in frequencies of thrombo-embolic events, cerebrovascular events, or myocardial infarction (table 4).

**Discussion**

We have shown that anastrozole substantially reduces incidence of breast cancer in the first 7 years of follow-up in women at high risk. Our results are similar to those recorded with exemestane in the MAP.3 trial.8 The reduction in incidence that we have reported is greater than that recorded for selective oestrogen receptor modulators such as tamoxifen.6 The effect of tamoxifen has been shown to persist for at least 10 years, 6,13 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>
<thead>
<tr>
<th></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 (0.06–16.18)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>1226 (64%)</td>
<td>1124 (58%)</td>
<td>1.10 (1.05–1.16)</td>
</tr>
<tr>
<td>Arthralgia*</td>
<td>972 (51%)</td>
<td>894 (46%)</td>
<td>1.10 (1.03–1.18)</td>
</tr>
<tr>
<td>Mild</td>
<td>385 (20%)</td>
<td>386 (20%)</td>
<td>1.01 (0.89–1.15)</td>
</tr>
<tr>
<td>Moderate</td>
<td>422 (22%)</td>
<td>363 (19%)</td>
<td>1.18 (1.04–1.33)</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>Carpal 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 (1.00–1.22)</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>1.10 (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 (1.18–2.28)</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 (2%)</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 (0.86–6.88)</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 (1.06–4.19)</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.

Table 4: Adverse events of any severity reported at any time
was noted in the ATAC trial, 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. We have also confirmed an increase in frequency of hypertension with anastrozole, as was first reported in the ATAC trial.

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. Oestrogenic and androgenic receptors are located on corneal and conjunctival epithelia, but possible effects of aromatase inhibitors on vision have been previously linked with retinal changes. We know of only two uncontrolled reports in which dry eyes have previously been associated with aromatase inhibitors. In one, 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 and for which the ATAC trial suggested a non-significant increase with anastrozole compared with tamoxifen in the adjuvant setting. 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. It is also interesting that incidence of endometrial cancer did not reduce, because increased oestrogen concentrations are a strong risk factor for this disease. Additionally, a substantially decreased risk of endometrial cancer with anastrozole was recorded in the ATAC trial, although the comparator was tamoxifen which is known to increase risk of endometrial cancer.

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. 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. Therefore, anastrozole is an attractive option for 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. 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 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.

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