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

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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 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.

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*Listed in the appendix

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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 recurrence[2–4] and also development of new contralateral tumours[3,5] in postmenopausal women than does tamoxifen. In a meta-analysis,[6] 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[6,7] and has been confirmed in a trial of the aromatase inhibitor exemestane,[8] 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,[8] 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.[8] No serious side-effects of exemestane were recorded, but median follow-up was fairly short for detection of any serious adverse events.[8] 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

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See Online for appendix

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).

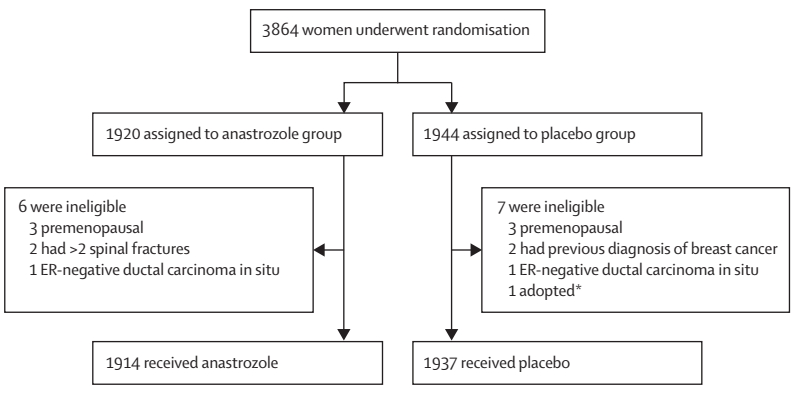

Figure 1: **Trial profile**
ER=oestrogen receptor. *Could not give family history to establish whether high risk.

	Anastrozole group (n=1920)	Placebo group (n=1944)
Age (years)	59·5 (55·0–63·5)	59·4 (55·1–63·3)
Age at menarche (years)	13·0 (12·2–14·0)	13·0 (12·0–14·0)
Parous	1601 (83%)	1637 (84%)
Age at first child birth (years)	24·0 (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)	71·8 (64·0–82·2)	72·1 (64·0–83·5)
Body-mass index (kg/m²)		
<25	581 (30%)	568 (29%)
25–30	699 (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)

Data are median (IQR) or n (%).

Table 1: **Baseline characteristics**

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 eligiblity 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%.[9]

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, which, with a 50% reduction in the anastrozole group, would translate to nine cases of breast cancer per 1000 women per year for placebo. 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[10,11] were used to derive HRs with 95% CIs. Survival curves were estimated with the Kaplan-Meier method.[12] 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 an 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.

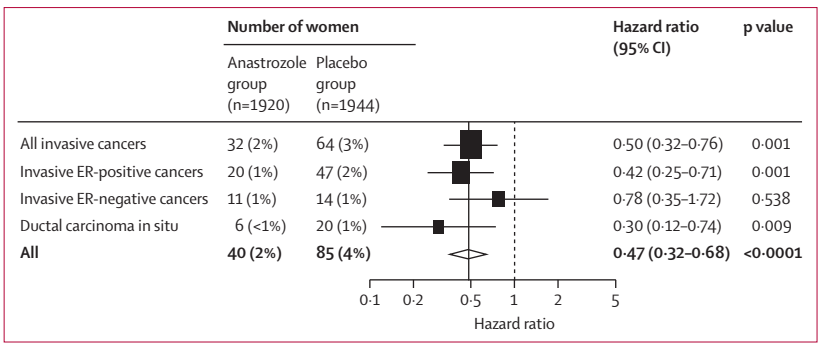

Figure 2: **Analyses by type of breast cancer**
Numbers in subgroups do not match totals because of missing data. ER=oestrogen receptor.

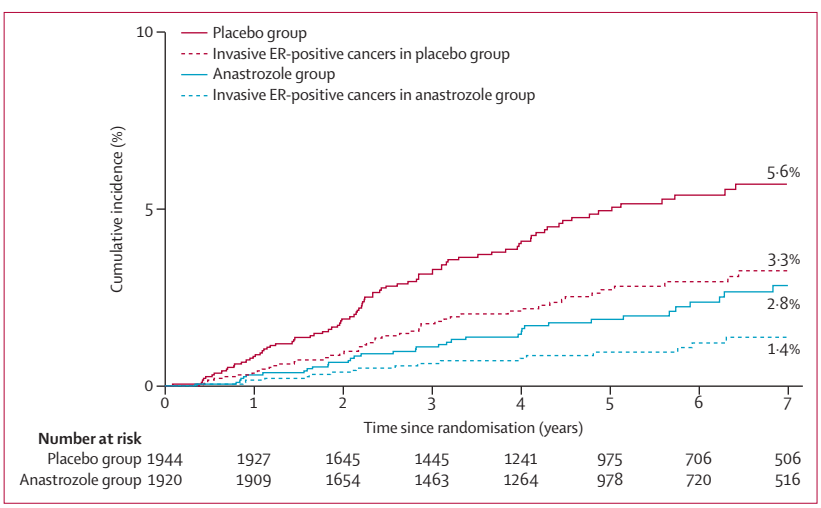

Figure 3: **Cumulative incidence of all breast cancers and of invasive ER-positive breast cancers**
ER=oestrogen receptor.

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.

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). 1894 (49%) had two or more first-degree relatives who had had breast or ovarian cancer, and 1328 (34%) had one first-degree relative who had had breast cancer when aged 50 years or younger (table 1, appendix). 326 women (8%) had been diagnosed with oestrogen-receptor-positive ductal carcinoma in situ within the previous 6 months and been treated by mastectomy, and 344 (9%) had a benign lesion with a diagnosis of lobular carcinoma in situ or atypical hyperplasia (table 1). 13 women were shown to be ineligible after

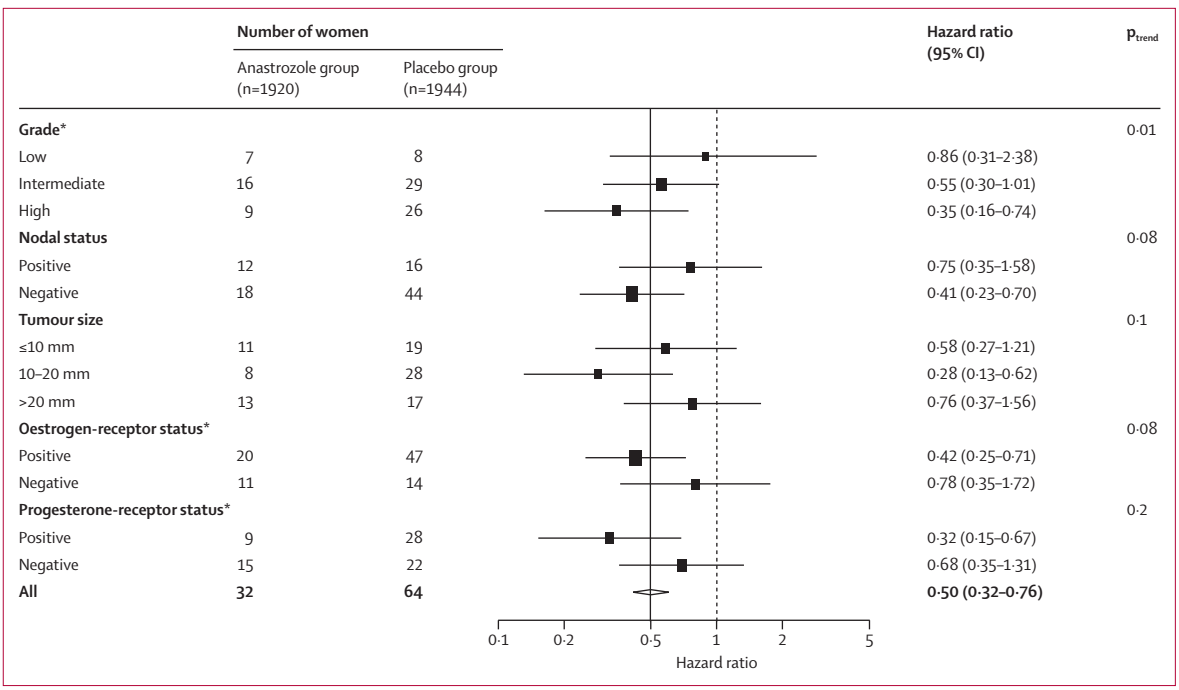

Figure 4: **Analyses by invasive breast cancer characteristics**
Numbers in subgroups do not match totals because of missing data. *Assessed at local laboratories.

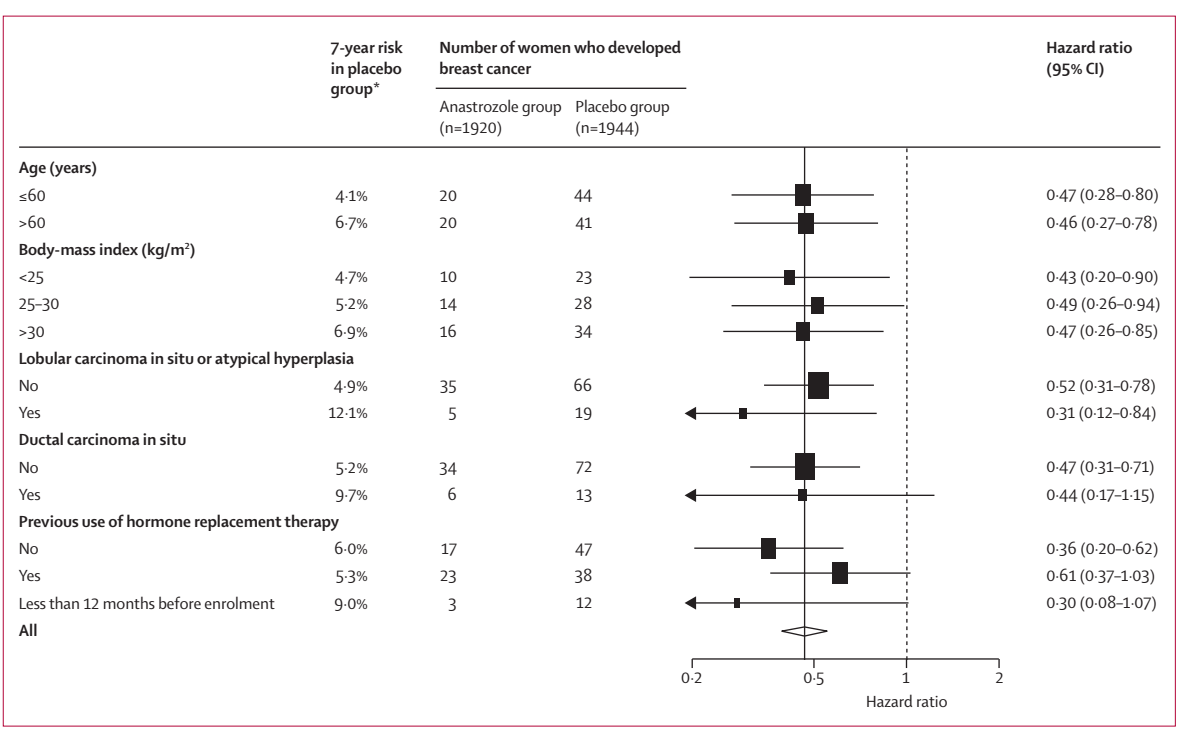

Figure 5: **Subgroup comparisons**
*Cumulative risk calculated with Cox proportional hazards model.

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

	Anastrozole group (n=1920)	Placebo group (n=1944)
Breast cancer	2 (<1%)	0
Other cancer	7 (<1%)	10 (1%)
Cerebrovascular accident or stroke	2 (<1%)	2 (<1%)
Cardiac arrest	3 (<1%)	1 (<1%)
Other	4 (<1%)	4 (<1%)
Total	18 (1%)	17 (1%)

Data are n (%).

Table 2: **Causes of death**

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

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

Table 3: **Frequency of cancers other than breast cancer**

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 0·32–68; 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 3), suggesting that 36 women (95% CI 33–44) would need to be treated with anastrozole to prevent one cancer in 7 years of follow-up. Invasive oestrogen-receptor-positive tumours were also significantly more common in the placebo group than in the anastrozole group (figures 2, 3), but no significant benefit was recorded for invasive oestrogen-receptor-negative tumours (figure 2). We noted no evidence of heterogeneity for invasive cancers (p=0·3).

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%).

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). 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

	Anastrozole group (n=1920)	Placebo group (n=1944)	Risk ratio (95% CI)
Any	1709 (89%)	1723 (89%)	1·00 (0·98–1·03)
Fractures	164 (9%)	149 (8%)	1·11 (0·90–1·38)
Arm	66 (3%)	61 (3%)	1·10 (0·78–1·54)
Leg	65 (3%)	57 (3%)	1·15 (0·81–1·64)
Rib, spine, or collarbone	23 (1%)	18 (1%)	1·29 (0·70–2·39)
Pelvic or hip	9 (<1%)	10 (1%)	0·91 (0·37–2·24)
Skull	1 (<1%)	1 (<1%)	1·01 (0·06–16·18)
Musculoskeletal	1226 (64%)	1124 (58%)	1·10 (1·05–1·16)
Arthralgia*	972 (51%)	894 (46%)	1·10 (1·03–1·18)
Mild	385 (20%)	386 (20%)	1·01 (0·89–1·15)
Moderate	422 (22%)	363 (19%)	1·18 (1·04–1·33)
Severe	151 (8%)	123 (6%)	1·24 (0·99–1·56)
Joint stiffness	143 (7%)	96 (5%)	1·51 (1·17–1·94)
Pain in hand or foot	178 (9%)	147 (8%)	1·23 (0·99–1·51)
Carpal tunnel syndrome or nerve compression	67 (3%)	43 (2%)	1·58 (1·08–2·30)
Vasomotor*†	1090 (57%)	961 (49%)	1·15 (1·08–1·22)
Mild	550 (29%)	504 (26%)	1·10 (1·00–1·22)
Moderate	390 (20%)	330 (17%)	1·20 (1·05–1·37)
Severe	150 (8%)	127 (7%)	1·20 (0·95–1·50)
Gynaecological	460 (24%)	423 (22%)	1·10 (0·98–1·24)
Vaginal dryness	357 (19%)	304 (16%)	1·19 (1·03–1·37)
Haemorrhage or bleeding	65 (3%)	81 (4%)	0·82 (0·60–1·13)
Vaginal or uterine prolapse	13 (1%)	31 (2%)	0·42 (0·22–0·81)
Vulvovaginal pruritus	40 (2%)	60 (3%)	0·68 (0·45–1·00)
Vascular	152 (8%)	127 (7%)	1·27 (0·97–1·52)
Hypertension	89 (5%)	55 (3%)	1·64 (1·18–2·28)
Myocardial infarction or cardiac failure	8 (<1%)	9 (<1%)	0·90 (0·35–2·32)
Thrombosis or embolism	19 (1%)	17 (1%)	1·13 (0·59–2·17)
Phlebitis	9 (<1%)	8 (<1%)	1·14 (0·44–2·95)
Cerebrovascular accident	3 (<1%)	6 (<1%)	0·51 (0·13–2·02)
Eye	348 (18%)	335 (17%)	1·05 (0·92–1·21)
Dry eyes	83 (4%)	58 (2%)	1·45 (1·04–2·01)
Conjunctivitis	12 (1%)	5 (<1%)	2·43 (0·86–6·88)
Glaucoma	12 (1%)	24 (1%)	0·51 (0·25–1·00)
Cataract	90 (5%)	95 (5%)	0·96 (0·72–1·27)
Infections	230 (12%)	217 (11%)	1·07 (0·90–1·28)
Influenza	25 (1%)	12 (1%)	2·11 (1·06–4·19)
Otitis media	18 (1%)	6 (<1%)	3·04 (1·21–7·64)

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**

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 thromboembolic 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

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.[14,15] 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,[8] 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,[16] 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.[17] We have also confirmed an increase in frequency of hypertension with anastrozole, as was first reported in the ATAC trial.[18]

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.[19] Oestrogenic and androgenic receptors are located on corneal and conjunctival epithelia,[19,20] 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.[21,23] 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[24] and for which the ATAC trial suggested a non-significant increase with anastrozole compared with tamoxifen in the adjuvant setting.[3] 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.[25] It is also interesting that incidence of endometrial cancer did not reduce, because increased oestrogen concentrations are a strong risk factor for this disease.[26] Additionally, a substantially decreased risk of endometrial cancer with anastrozole was recorded in the ATAC trial,[3] 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.[5] 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,[3] 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,[8] which had 85% overall adherence at 35 months. Adherence in our study was slightly better than for tamoxifen in IBIS-I,[14] 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.[5] 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.[6] 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,[31] 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.[32] 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. JK 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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