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REVIEW ARTICLE

Aromatase Inhibitors for Breast Cancer Prevention

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BACKGROUND

Many lines of evidence point to sex hormones as the key factors in breast carcinogenesis. Classic risk factors include age at menarche, first child birth, and menopause. Estrogens, especially estradiol, appear to be the main factor. Hormone replacement therapy increases breast cancer risk,[1-4] especially when the combined pills using estrogen and progesterone are used. Weight is a risk factor for postmenopausal breast cancer, where aromatization of androgens in adipose tissue is the major source of estrogen. The variability of serum oestrogen levels in postmenopausal women from the lowest to highest quintile (about a six-fold difference) is associated with a two-fold variation in breast cancer risk (Fig 1).[5] Estrogen appears to be more closely linked with breast cancer than are the other steroid sex hormones, although they may also have an independent role.[5] Lastly, four major trials using the estrogen agonist, tamoxifen, to block the activity of estrogen at the receptor[6] have shown that about 50% of estrogen receptor (ER) -positive breast cancers (Fig 2A) can be prevented, although there appears to be little effect on ER-negative breast cancer (Fig 2B), leading to a 38% overall reduction in breast cancer.

Although the use of tamoxifen has been effective in reducing the incidence of breast cancer, both in the contralateral breast for women with early breast cancer, and for those at high risk who have not had the disease, it is not without side effects, especially thromboembolic events and gynecologic symptoms,[6] and this limits its utility in a prevention setting.

Recently, the third-generation aromatase inhibitors (AIs) have been introduced into the treatment of breast cancer, and their greater efficacy compared to tamoxifen, along with a more favorable side-effect profile, make them attractive agents for use in breast cancer prevention.

PREVIOUS AND CURRENTLY AVAILABLE AIs

The first-generation AI aminoglutethimide became available in the late 1970s, but despite proven efficacy, its widespread use was limited by its overall toxicity and lack of selectivity for the aromatase enzyme necessitating concomitant corticosteroid supplementation. This was improved in the so-called second-generation AIs (formestane, fadrozole, vorozole), but they still lacked selectivity. Anastrozole, letrozole, and exemestane are third-generation AIs, and have greater specificity with fewer side effects.

PHARMACOLOGY

AIs act via the inhibition of the cytochrome P450 enzyme aromatase, which catalyzes the conversion of androgens to estrogens. Their chemical structures are shown in Figure 3. Nonsteroidal AIs (anastrozole, letrozole, vorozole, fadrozole) bind reversibly to aromatase, whereas the steroidal AIs (formestane, exemestane) bind irreversibly, causing permanent inactivation of the complex, and are effective until new enzyme is synthesized.

EFFICACY

Advanced Disease

Several studies have shown that the AIs have benefits for metastatic cancers when

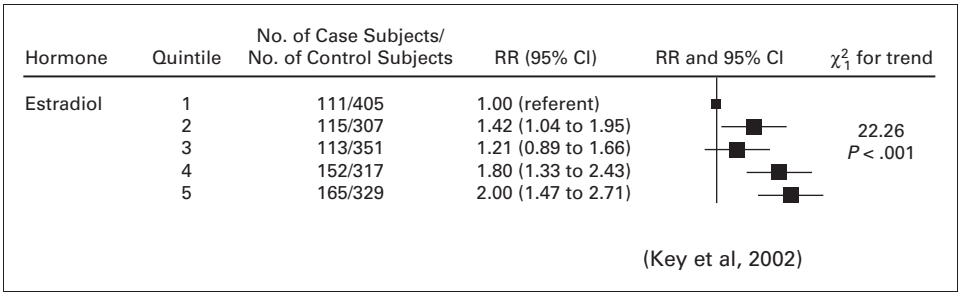

Fig 1. Risk of breast cancer according to quintile of serum estradiol in postmenopausal women from cohort studies. RR, relative risk; EHBCCG, Estrogen Hormones and Breast Cancer Collaborative Group. Reprinted from Key T, Appleby P, Barnes I, et al: Endogenous sex hormones and breast cancer in postmenopausal women: Reanalysis of nine prospective studies. J Natl Cancer Inst 94:606-616, 2002, by permission of Oxford University Press.

compared with megestrol acetate in terms of tolerability. Efficacy results have been somewhat mixed, but are most promising for the third-generation compounds.[7-12] In first-line treatment trials against tamoxifen, benefits have also been fairly marginal, but mortality benefits are seen with the newer compounds.[13-20]

Adjuvant Treatment and Contralateral Breast Cancer

Most of what we know about the potential use of AIs in prevention derives from adjuvant studies in women with early breast cancer, where the development of isolated contralateral tumors as a first event is a model for prevention of new tumors in healthy women. This has proved a reliable source for estimating the qualitative effects of tamoxifen in prevention, both in terms of major side effects and in terms of efficacy. This approach has generally been more reliable than animal models or observational epidemiologic studies, although randomized intervention studies in the prevention setting have been essential for fully quantifying effectiveness and balancing risks and benefits.

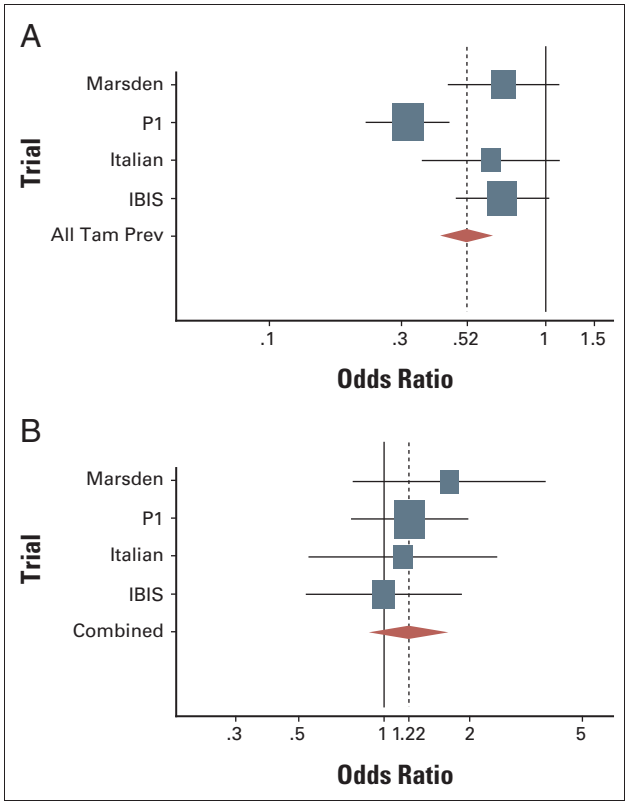

Fig 2. (A) Odds ratios for developing an estrogen receptor–positive invasive breast cancer among women involved in tamoxifen prevention trials; (B) odds ratios for developing an estrogen receptor–negative invasive breast cancer among women involved in tamoxifen prevention trials. IBIS, International Breast Cancer Intervention Study. Reprinted from Cuzick J, Powles T, Veronesi U, et al: Overview of the main outcomes in breast cancer prevention trials. Lancet 361:296-300, 2003, with permission from Elsevier.

To date, four different adjuvant trials have reported on the use of three different AIs for postmenopausal women with breast cancer (Table 1).[21-25] In these trials, adjuvant AIs have been found effective in three clinical settings. In the first setting, the AI was compared with tamoxifen as initial adjuvant hormonal therapy in patients with resected operable breast cancer. In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, 5 years of anastrozole significantly improved disease-free survival when compared with 5 years of tamoxifen.[21,22,26] In the second setting, the AI was compared with tamoxifen in patients who had already received 2 to 3 years of adjuvant tamoxifen. In the Intergroup Exemestane Study (IES) trial and the Italian Tamoxifen versus Anastrozole (ITA) trial, 2 to 3 years of exemestane or anastrozole, respectively, improved disease-free survival compared with 2 to 3 years of tamoxifen in patients who had already completed 2 to 3 years of tamoxifen therapy.[23,24] In the third setting, the AI was evaluated as extended adjuvant hormonal therapy following completion of 5 years of adjuvant tamoxifen. The National Cancer Institute of Canada (NCIC) MA.17 trial compared 5 years of letrozole with 5 years of placebo following completion of 5 years of adjuvant tamoxifen and demonstrated significant improvement in disease-free survival in favor of the group which received the AI.[25] Based on the results from the above trials, AIs are currently being increasingly utilized in all three of these clinical settings.

In all of the above trials evaluating adjuvant AIs, a consistent reduction in the rates of contralateral breast cancer has been observed in the group receiving the AI (Fig 4). In the ATAC trial, the number of contralateral breast cancers was reduced from 59 in the tamoxifen arm to 35 on

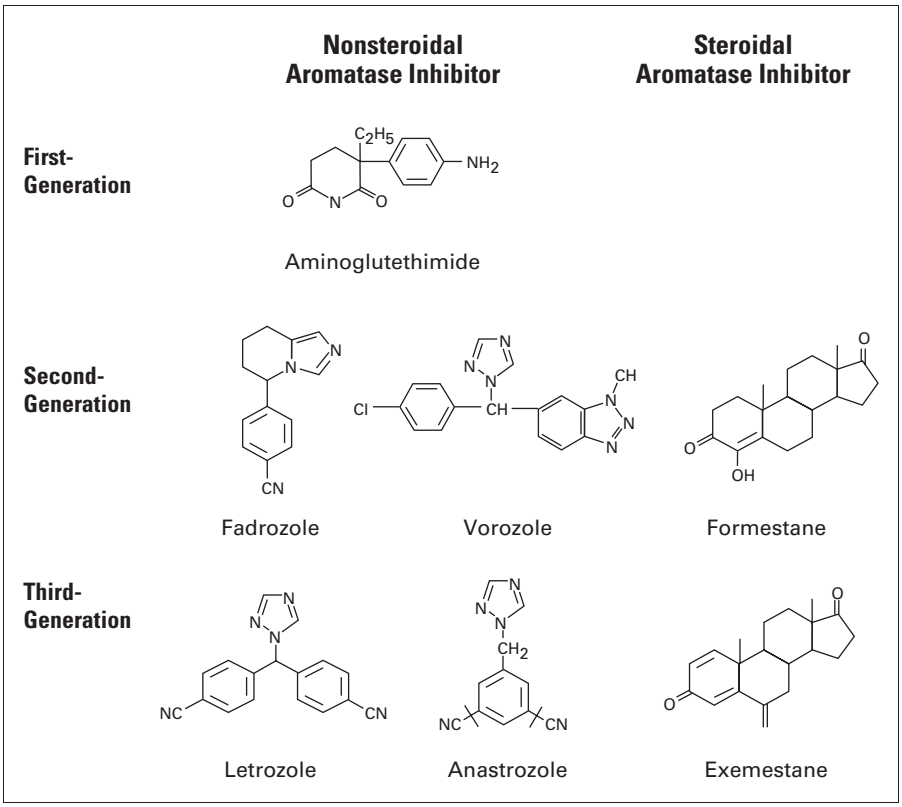

Fig 3. Structures of nonsteroidal and steroidal aromatase inhibitors.

anastrozole, a 42% reduction (95% CI, 12% to 62%; $P = .01$). A larger reduction of 53% (95% CI, 27% to 71%; $P = .001$) was seen in the hormone receptor–positive patients.[26] Tamoxifen is known to reduce the incidence of contralateral tumors by 46% in women with mostly ER-positive primary tumors, suggesting that the overall reduction of receptor-positive breast cancer associated with anastrozole may be around 70% to 80%. Information on the receptor status of the second cancers in this trial is not yet available, but one would expect the preventive effect to be restricted to ER-positive contralateral tumors, and to be greater for this group than for new breast tumors overall.

In the ITA trial, there were two cases of contralateral breast cancer in the tamoxifen group versus one in the tamoxifen/anastrozole group. The small number of patients included in that trial (n = 448), as well as the small number of events, precludes any meaningful comparison between the two groups. However, in the IES that employed a similar design to the ITA trial, women randomly assigned to 2 to 3 years of exemestane after 2 to 3 years of tamoxifen had a 56% reduction in contralateral breast cancer compared with those randomly assigned to continue tamoxifen for the remaining 2 to 3 years (nine *v* 20 cases; $P = .04$). A recent report of the combined ARNO95/ABCSG8 trial, which was of similar design to the ITA trial

Table 1. Trials of Aromatase Inhibitors in the Adjuvant Setting

Trial	Design	Sample Size	Median Follow-Up at Last Report (months)
ATAC[26]	Tamoxifen *v* anastrozole *v* combination for 5 years	9,366	68
Italian[24]	2-3 years of anastrozole *v* tamoxifen after 2-3 years of tamoxifen	426	30
MA-17[25]	Letrozole *v* placebo after 5 years of tamoxifen	5,187	29
IES[23]	2-3 years of exemestane *v* tamoxifen after 2-3 years of tamoxifen	4,742	31
BIG-1-98 (not yet published)	2 years of letrozole *v* tamoxifen randomized to continue or change for 3 more years	8,028	Not reported
ARNO/ABCSG[27]	Tamoxifen *v* anastrozole for 3 years after 2 years of tamoxifen	3,224	28

Abbreviations: ATAC, Arimidex, Tamoxifen, Alone or in Combination; IES, Intergroup Exemestane Study; BIG, Breast International Group; ARNO/ABCSG, Arimidex-Nolvadex/Austrian Breast Cancer Study Group.

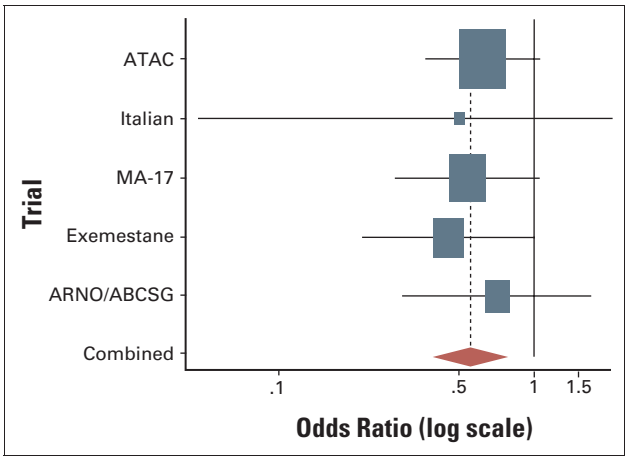

Fig 4. Contralateral tumors in aromatase inhibitor trials. ATAC, Arimidex, Tamoxifen, Alone or in Combination; ARNO/ABCSG, Arimidex-Nolvadex/ Austrian Breast Cancer Study Group.

but involved 3,224 patients, showed a smaller 26% reduction in contralateral breast tumors (12 *v* 16; $P = .4$).[27]

Finally, in the MA.17 trial, women who were randomly assigned to 5 years of letrozole after 5 years of tamoxifen had a 46% reduction in new contralateral tumors compared with women randomly assigned to placebo (14 *v* 26 cases; $P = < 0.01$).

Although the study designs of the above trials have been very different, all of the trials indicate that the impact of AIs on contralateral tumors has been greater than the impact on recurrences, which bodes well for prevention (Fig 4). When viewed cumulatively, the results are compatible with a 40% to 50% reduction in ER-positive contralateral breast cancer with the AI. Given that tamoxifen reduces ER-positive tumors by about 40% to 50%, a further 40% to 60% reduction by the AIs suggests that 70% to 80% of these tumors might be avoided by prophylactic treatment. However, no impact on ER-negative tumors is expected, and this remains a challenging area for breast cancer prevention. Possible agents for prevention of ER-negative tumors include cyclooxygenase-2 inhibitors, statins, low-dose tamoxifen, and vitamin D analogs, but none of these have randomized evidence for efficacy in humans, and their full evaluation presents major logistic challenges in terms of trial design. Undoubtedly, evidence from surrogate markers will be necessary to progress these compounds.

OTHER BENEFITS AND SIDE EFFECTS

The profound estrogen depletion associated with AIs produces a new state of human existence, and this is bound to have other effects beyond those related to breast carcinogenesis. These effects can only be reliably studied in prevention trials where a placebo is employed. There are suggestions from adjuvant trials that AIs may also reduce endometrial cancer and cerebrovascular events to below baseline rates, but full evaluation is difficult because there is no untreated comparison group. Bone loss and increased fracture rates appear to be the most serious side effects, and methods for combating them will be essential if these drugs are to be used prophylactically. Because of the importance of side effects in the prevention setting, details of the available toxicity data from current adjuvant AI trials are summarized in the following sections.

ATAC Trial

Data from this trial have been published for 36, 47, and 68 months of median follow-up. They are very similar and only the latest data are discussed here (Table 2).[26] Anastrozole was better tolerated than tamoxifen with about one-quarter fewer drop outs due to side effects and a surprising 20% relative reduction in hot flushes (at any time or

Table 2. Occurrence of Predefined Adverse Events in the Completed Treatment Analysis of the ATAC Trial

	Anastrozole (n = 3,092)		Tamoxifen (n = 3,093)		
Adverse Event	No. of Patients	%	No. of Patients	%	*P*
Drop-out due to side effects	344	11.1	442	14.3	.0002
Hot flushes	1,104	35.7	1,264	40.9	< .0001
Nausea and emesis	393	12.7	384	12.4	.7
Fatigue/tiredness (asthenia)	575	18.6	544	17.6	.3
Mood disturbances	597	19.3	554	17.9	.2
Musculoskeletal disorders	1,100	35.6	911	29.4	< .0001†
Vaginal bleeding	167	5.4	317	10.2	< .0001
Vaginal discharge	109	3.5	408	13.2	< .0001
Endometrial malignancies*	5	0.2	17	0.8	.02
Fractures	340	11.0	237	7.7	< .0001†
Ischemic cardiovascular disease	127	4.1	104	3.4	.1
Ischemic cerebrovascular events	62	2.0	88	2.8	.03
All venous thromboembolic events	87	2.8	140	4.5	.0004
Deep venous thromboembolic events	47	1.6	74	2.4	.02
Cataracts	182	5.9	213	6.9	.1

Abbreviation: ATAC, Arimidex, Tamoxifen, Alone or in Combination.
*Excluding patients with hysterectomy at baseline.
†In favor of tamoxifen.

severity). Tamoxifen-induced side effects such as venous thromboembolic events, vaginal bleeding and discharge, other gynecologic symptoms, and endometrial cancer did not occur with anastrozole. However, further follow-up is needed to be certain about this. Cerebrovascular events, including strokes and transient ischemic attacks, were reduced by 30%.

There were two side effects that were clearly increased by anastrozole. One was the occurrence of musculoskeletal events—primarily arthralgias, which were increased by about one third, from 30% to 36%. Most of these were mild and did not lead to a discontinuation of treatment. They are probably best explained at being due to a "second menopause" induced by lower levels of estrogen, and appear to be similar to the aches and pains associated with the normal menopause.

More important is the bone loss associated with estrogen deprivation. In a subset of 308 patients in the bone substudy, there was a median bone mineral loss over 2 years of 4.1% in the lumber spine and 3.9% in the hip on anastrozole compared with small increases on tamoxifen.[28] With a median follow-up of 68 months, this has translated into an increase of fractures from 7.7% to 11.0%, or a 50% relative increase.

MA-17 Trial

The side-effect profile was qualitatively similar to that seen for anastrozole, albeit the control arm in this trial was placebo (Table 3).[25] Arthritis, arthralgia, and myalgia were all significantly increased. Hot flushes were also increased compared with placebo, and vaginal bleeding was decreased. There was a marginal increase in osteoporosis (5.8% *v* 4.5%), but this was not significant ($P = .07$). Fracture rates were also slightly (3.6% *v* 2.9%), but not significantly, increased ($P = .24$). Follow-up time was short for this trial, and it seems likely that significant increases in bone loss and fracture will occur with longer treatment. At this stage it is not possible to compare the absolute effects on bone of letrozole with anastrozole, but it is clear that both will lead to bone loss and increased fracture rates. Further data on the issue will be important for use in prevention studies.

No other side effects have emerged and treatment was well tolerated in this trial, with a treatment-related drop-out rate of 4.5% on letrozole and 3.6% on placebo ($P = .11$).

IES Trial

Data on general side effects of exemestane compared with tamoxifen in the IES trial are shown in Table 4.[23] Again, similarities with other AIs emerge. There were fewer thromboembolic events, gynecologic symptoms, and cramps with exemestane, but more cases of arthralgia and osteoporosis (7.4% *v* 5.7%; $P = .05$). Curiously, diarrhea was reported more often (4.3% *v* 2.3%; $P < .001$), which has not been seen with the other AIs.

Early studies in animals[29] suggested that the steroidal structure of exemestane might lead to bone preservation and even enhancement. Preliminary data from the IES trial do not support this possibility and suggest a picture similar to the other AIs. Again, further data are needed to be able to compare the effect on bone of exemestane with that of the other AIs.

PREVENTION TRIALS WITH AIs

International Breast Cancer Intervention-II Trial

The International Breast Cancer Intervention (IBIS) -II prevention trial began in February 2003 and is comparing anastrozole to placebo in 6,000 postmenopausal women at increased risk of breast cancer. This study is still open to recruitment. Entry criteria are similar to IBIS-I, except that women with mammographic density covering at least 50% of the breast are also eligible. Mammographic density has emerged belatedly as an important risk factor for breast cancer, despite copious evidence being available

Table 3. Adverse Events During an Adjuvant Study of Letrozole Versus Placebo After 5 years of Tamoxifen

	Letrozole (n = 2,154)		Placebo (n = 2,145)		
Adverse Event	No. of Patients	%	No. of Patients	%	*P*
Drop-out due to treatment	97	4.5	77	3.6	.11
Edema	370	17.2	335	15.6	.17
Hot flushes	1,016	47.2	869	40.5	< .001
Fatigue	643	29.9	607	28.3	.26
Sweating	476	22.1	445	20.7	.28
Constipation	224	10.4	216	10.1	.72
Vaginal bleeding	92	4.3	128	6.0	.01
Arthritis	120	5.6	75	3.5	< .001
Hypercholesterolemia	257	11.9	247	11.5	.67
Clinical fractures	77	3.6	63	2.9	.24
Cardiovascular events	88	4.1	77	3.6	.40
Osteoporosis	124	5.8	97	4.5	.07
Dizziness	259	12.0	245	11.4	.54
Headache	389	18.1	399	18.6	.65
Arthralgia	459	21.3	355	16.6	< .001
Myalgia	254	11.8	204	9.5	.02

Table 4. Adverse Events in the IES Study of Exemestane Versus Tamoxifen After 2 to 3 years of Tamoxifen

Type of Event	Exemestane Group		Tamoxifen Group		
	No. of Patients	%	No. of Patients	%	*P*
Cardiovascular disease other than myocardial infarction	984	42.6	913	39.2	.11
Hot flushes	967	42.0	923	39.6	.28
Pain or aches	766	33.2	684	29.4	.17
Fatigue	545	23.6	547	23.5	.80
Insomnia	449	19.5	406	17.4	.30
Sweating	429	18.6	418	17.9	.95
Headaches	428	18.6	378	16.2	.09
Dizziness	288	12.5	279	12.0	.81
Nausea	248	10.8	258	11.1	.59
Visual disturbances	170	7.4	133	5.7	.04
Osteoporosis	171	7.4	134	5.7	.05
Gynecologic symptoms	135	5.8	211	9.0	< .001
Arthralgia	124	5.4	85	3.6	.01
Depression	120	5.2	93	4.0	.24
Diarrhea	100	4.3	54	2.3	< .001
Vaginal bleeding	93	4.0	129	5.5	.05
Cramps	64	2.8	102	4.4	< .001
Thromboembolic disease	30	1.3	55	2.4	.007

Abbreviation: IES, Intergroup Exemestane Study.

for some time.[30] In terms of population-attributable risk, it accounts for more breast cancers than does family history, and screening programs offer an excellent opportunity for identifying high-risk women. This could ultimately be a more important function than their role in early detection.

Baseline measurements in IBIS-II include a dual-energy x-ray absorptiometry scan and spinal x-ray. Osteoporotic women will be required to take a bisphosphonate and have regular dual-energy x-ray absorptiometry scans if they wish to join the study, but women with a T score less than 4, or more than two fragility fractures, will be ineligible. In addition, 1,000 women will be recruited into the bone substudy, in which regular bone monitoring will take place (Fig 5). This study will comprise three strata. For women with T scores below −2.5 at either the hip or spine, or having a spinal fragility fracture, oral weekly risedronate will be required. For women with T scores in the range −1.5 to −2.5 (moderate to severe osteopenia), there will be an additional randomization to risedronate or placebo. Women with higher T scores will be monitored, and only offered residronate if they become osteoporotic.

A second complimentary study (IBIS II) will look at the role of anastrozole for postmenopausal women with locally excised hormone receptor–positive ductal carcinoma-in-situ (DCIS), which has clear margins. Based on the results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 trial, this study has been restricted to receptor-positive DCIS and the comparator is tamoxifen. Again, treatment is for 5 years. A similar trial for DCIS is currently being carried out by the NSABP (B-35).

MAP.3

Another prevention trial with AIs is currently underway using exemestane. This three-arm trial sponsored by the NCIC-Clinical Trials Group compares placebo with exemestane alone, or exemestane plus celecoxib in 5,100 postmenopausal women at increased risk. Risk factors needed for eligibility include a Gail Score > 1.66, age ≥ 60 years, prior atypical ductal or lobular hyperplasia,

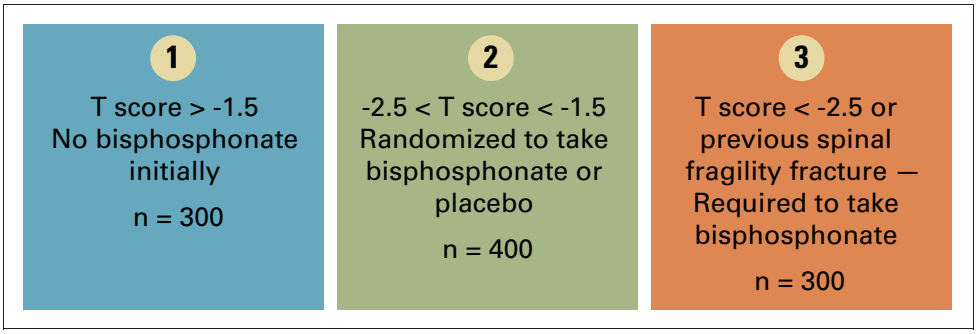

Fig 5. Three strata of the IBIS-II bone substudy of 1,000 high-risk postmenopausal women taking anastrozole or placebo. All women were monitored with dual-energy x-ray absorptiometry scans at baseline, 1, 3, 5, and 7 years. Blood samples were taken at baseline, 6, and 12 months for measurement of bone biomarkers. All women were recommended to take calcium and vitamin D supplements.

or DCIS treated with mastectomy. The sample size calculations are based on an expected risk reduction of 65% with exemestane versus placebo. Exemestane will be given for 5 years, although celecoxib will be given for 3 years.

CONCLUSION

Data from the adjuvant trials provide a compelling rationale for exploring the use of AIs in the prevention setting. Their efficiency is greater than that of tamoxifen, especially for new contralateral tumors, suggesting that 70% to 80% of ER-positive breast cancers can be prevented with these drugs. No impact is expected for receptor-negative cancers, however, and this remains a challenging area for future trials. The AIs also are better tolerated than tamoxifen, without the gynecologic and thrombotic complications, but do lead to bone mineral loss and increased fracture rates in the absence of additional bone-sparing therapy. An important question will be the effectiveness of bisphosphonates in arresting and/or reversing bone loss associated with the almost complete depletion of estrogen associated with AIs. Recent data from the Continuing Outcomes of Raloxifene Evaluation study[31] confirm earlier data from the Multiple Outcomes of Raloxifene Evaluation study that raloxifene is likely to be at least as effective as tamoxifen in preventing new tumors, but lacks the estrogen stimulus to the endometrium, thus avoiding excess cancers at that site. However, raloxifene still has thromboembolic complications and is not currently recommended for breast cancer prevention. Results of the direct comparison of raloxifene and tamoxifen in the Study of Tamoxifen and Raloxifene trial are awaited with great interest. If this trial is positive, the key issue will be a choice between raloxifene and an AI. The trial size needed to separate them is likely to be enormous ($\approx$ 50,000), and it is likely more indirect methods will be needed to choose between them.

Author's Disclosures of Potential Conflicts of Interest

The following author or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Consultant: Jack Cuzick, AstraZeneca, Pfizer, Lilly. For a detailed description of these categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section of Information for Contributors found in the front of every issue.

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