Long-Term Toxicities of Selective Estrogen-Receptor Modulators and Antiaromatase Agents

Published literature indicates that the selective estrogen-receptor modulators (SERMs) tamoxifen and raloxifene (Evista) have favorable effects on bone density, lipid profiles, and the incidence of second breast cancers, and unfavorable effects on the incidence of venous thrombosis and hot flushes. Tamoxifen increases the risk of endometrial cancer, but raloxifene does not. The effects of SERMs on sexual function and cognition are unclear. Because the selective antiaromatase agents are relatively new, the long-term effects of these agents on normal tissues are less well established. It appears that the nonsteroidal agents (anastrozole [Arimidex], letrozole [Femara]) and steroidal (exemestane [Aromasin]) antiaromatase agents may have different effects on normal tissues. Preliminary data demonstrate that anastrozole increases the risk of arthralgias and produces a decrease in bone density. In contrast, exemestane appears to favorably affect bone density and lipid profile, similar to tamoxifen and raloxifene. The incidence of contralateral breast cancer is decreased in women on adjuvant anastrozole, but data for the other antiaromatase agents are not yet available. Hot flushes have been reported with the use of selective aromatase inhibitors, but their incidence seems to be comparable to what is reported with SERMs. Antiaromatase agents do not appear to cause venous thrombosis. More information about the effects of the antiaromatase agents on normal tissue will become available as data from ongoing adjuvant and chemoprevention trials are reported. Clinically, we should be conscious of the differences between antiaromatase agents and SERMs and their impact on women’s health.

The dominant role of tamoxifen in the treatment of estrogen-receptor positive breast cancer for the past 40 years is being challenged by a new class of agents—the third-generation aromatase inhibitors. These agents are selective in their action, suppressing the formation of estrogen by interfering with the aromatase enzyme. They are categorized according to two different mechanisms of action: (1) The nonsteroidal inhibitors letrozole (Femara) and anastrozole (Arimidex) bind reversibly to the cytochrome P450 moiety, exposing the enzyme-binding site. Because androstenedione can attach to the binding site and displace the drug, their action is reversible and may ultimately lead to an increase in aromatase activity. (2) The steroidal inactivator exemestane (Aromasin) binds irreversibly to the enzyme, thereby reducing aromatase activity. Despite these subtle differences in mechanisms of action, the third-generation aromatase inhibitors and inactivators are equally effective in decreasing serum concentrations of estradiol and estrone and are superior to tamoxifen in postmenopausal women, both as initial hormonal therapy for advanced disease and possibly as adjuvant therapy as well. [1] Conclusions about the clinical effectiveness of the selective estrogenreceptor modulators (SERMs) and antiaromatase agents are derived from independent studies and different cohorts of patients. Most of the available toxicity data on antiaromatase...
agents come from studies in postmenopausal women with advanced breast cancer. Patients were treated for less than 6 months and were followed for a short period of time- 6 to 18 months. In contrast, the toxicity data for the SERMs are derived from trials in women without cancer. Treatment was administered for 3 to 8 years, and follow-up ranged from 3 to 6 years. Four double-blind placebo-controlled trials of raloxifene (Evista) and tamoxifen have provided us with these important data. The National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT), the Royal Marsden Tamoxifen or Placebo (TAMOPLAC) trial, and the Italian Tamoxifen Prevention Trial (ITPT) evaluated the role of tamoxifen as chemoprevention for breast cancer; the Multiple Outcomes of Raloxifene Evaluation (MORE) trial tested raloxifene for the treatment of osteoporosis.[2] Although these are not the only trials that have addressed the effect of SERMs on normal tissue, they provide the broadest information on the long-term effects of these agents. The designs of these trials are summarized in Table 1. The goal of this paper is to present a comprehensive review of the literature and identify citations reporting the long-term toxicities of the SERMs tamoxifen and raloxifene and the third-generation antiaromatase agents anastrozole, exemestane, and letrozole, and to compare what is known about the clinical action of these compounds. Our findings are summarized in Table 2, and the accompanying text describes the actions of the drugs according to their effects on the end organ or organ physiology.

### Bone Densities and Fractures SERMs

The incidence of osteoporosis and bone fractures increases in postmenopausal women as a result of declining estrogen levels. An early placebo-controlled trial of adjuvant tamoxifen in node-negative postmenopausal breast cancer patients that prospectively assessed bone mineral density demonstrated an increase in this parameter in the hip and spine for women receiving tamoxifen. Fracture rates were not reported. Women receiving tamoxifen in the BCPT experienced a 31% decrease in fractures of the hip, wrist, and spine. The 7,705 postmenopausal women with documented osteoporosis in the MORE trial were randomized to receive either raloxifene or placebo as well as supplemental calcium and cholecalciferol. After 40 months of follow-up, women randomized to raloxifene had a 2% increase in bone mineral density of the hip compared with the control group, and a 30% decrease in vertebral fractures.[2] Based on such data, it is generally accepted that both tamoxifen and raloxifene have favorable effects on bone, although probably not to the same extent as estrogen.

### Antiaromatase Agents

The available data suggest that the effect of the nonsteroidal inhibitors is more in line with the effects of a lack of estrogen while the steroidal inactivator, exemestane, may have more favorable effects. With a median follow-up of 33 months, women in the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial who had been randomized to anastrozole experienced significantly more bone fractures than women randomized to tamoxifen.[1] Longer follow-up will be needed before the increased fracture rate can be attributed to osteopenia. Serial bone densitometry was performed in premenopausal women enrolled in an adjuvant trial initiated by the Austrian Breast Cancer Study Group.[3] All the women received goserelin (Zoladex) and either anastrozole or tamoxifen. In a second randomization, patients were assigned to receive 4 mg of zoledronate (Zabel, Zometa) every
6 months or no additional therapy. A significant decrease in the bone mineral density of the hip and spine was observed among patients receiving anastrozole alone compared with tamoxifen alone. The follow-up in both of these adjuvant trials is relatively short, but the data suggest that anastrozole may decrease bone density. The data for letrozole are somewhat sparse. A 3-month course of letrozole in 32 women with benign breast disease produced changes in serum markers of bone metabolism consistent with those of bone loss. A second controlled trial of letrozole in 43 postmenopausal women also demonstrated an increased rate of bone resorption and a compensatory decrease in serum parathyroid concentrations. Goss and colleagues have studied the effects of exemestane on ovariectomized Sprague-Dawley rats. After 16 weeks, the bone mineral density of the femur and spine in rats treated with exemestane was significantly higher than that in vehicle-treated ovariectomized rats and was similar to that of intact cycling rats. The principal metabolite, 17-hydroexemestane, prevented bone loss to a similar degree and may account for the favorable effects of exemestane on bone. In this same model, letrozole did not protect against bone loss.[4] Anecdotally, we have documented an increase in the bone mineral density of the hip (53%) and spine (57%) within 12 months of initiating single-agent exemestane as treatment of advanced disease. These data suggest that exemestane may protect bone from the loss associated with oophorectomy, and this effect is being confirmed in ongoing clinical and preclinical studies.

The SERMs tamoxifen and raloxifene produce an increase in bone density and a decrease in the incidence of bone fractures. The preclinical and clinical data suggest that the nonsteroidal inhibitors letrozole and anastrozole decrease bone mineral density, whereas exemestane protects against bone loss or may increase bone mineral density. The increased bone fracture rate seen in the ATAC trial with anastrozole is a matter for concern. However, because tamoxifen is known to increase bone density, one cannot exclude the possibility that the difference in fracture rates reflects tamoxifen-lack more than an adverse effect of anastrozole. More data will be needed to determine the long-term effects of the individual antiaromatase agents on bone. Lipid Profile/Thromboembolic Events SERMs Serial measurement of plasma lipids in individual patients indicates that tamoxifen produces a favorable, less atherogenic profile than placebo in postmenopausal women. Total cholesterol, low-density lipoprotein (LDL) cholesterol, lipoprotein(a), apolipoprotein A1, and apolipoprotein B are consistently decreased, whereas highdensity lipoprotein (HDL) cholesterol and triglycerides may be increased or decreased. These changes are consistent with estrogen-agonist effects. However,
tamoxifen does not produce the same magnitude of change in these parameters as seen with conventional hormone-replacement therapy.[5] The effect of raloxifene is similar to that of tamoxifen. Serial lipid profiles in women treated with raloxifene demonstrate consistent decreases in total cholesterol, lipoprotein (a), and LDL cholesterol. HDL cholesterol and triglyceride levels may be increased, decreased, or unchanged over baseline. Increases in apolipoprotein A1 concentrations and decreases in apolipoprotein B concentrations are consistent with a decrease in atherogenic potential.[6] Homocysteine, also a predictor of cardiovascular disease, is decreased in women treated with raloxifene. Data from early controlled adjuvant therapy trials suggest that women treated with tamoxifen are less likely to experience heart disease. These findings were not supported by the BCPT, which demonstrated after a mean follow-up of 49 months that tamoxifen had no impact on the incidence of cardiovascular deaths, even among patients with prior cardiac disease.[7] The Early Breast Cancer Trialsists’ Collaborative Group (EBCTCG) has consistently demonstrated an improvement in overall survival among women treated with tamoxifen but has been unable to identify a decreased death rate from cardiovascular causes. In the MORE trial, participants were not stratified according to cardiovascular risk factors, and the results show that the incidence of cardiovascular events was comparable between groups. However, a subset analysis of 135 women determined to be at highrisk on the basis of recognized factors such as prior myocardial infarction, coronary artery bypass surgery, percutaneous coronary intervention, diabetes, age, smoking, hypertension, and lipid profile, found that those assigned to raloxifene had a significantly lower incidence of cardiovascular events. The Raloxifene Use for the Heart (RUTH) study is an ongoing controlled multinational trial designed to address the cardiovascular effects of raloxifene in over 10,000 women ≥ 55 years old, or at risk for, coronary artery disease. **Antiaromatase Agents**

In Sprague-Dawley rats, both tamoxifen and toremifene (Fareston) decreased serum cholesterol and triglyceride levels, whereas anastrozole did not produce a change in either. Alterations in lipid profile have not been observed in women treated with anastrozole. Goss demonstrated an adverse effect of letrozole on the lipid profile of rats.[4] In healthy women treated with letrozole, a significant increase in total cholesterol, LDL cholesterol, and apolipoprotein B levels as well as total to HDL cholesterol and LDL to HDL cholesterol ratios was reported after 3 months. Goss used the same ovariectomized rat model described in his bone studies to assess the effects of the steroidal inactivator exemestane on lipids. Exemestane completely protected against adverse lipid changes induced by ovariectomy, whereas letrozole did not.[4] Women treated with exemestane often experience a decrease in total cholesterol and triglyceride levels, suggesting that the drug has no effect on atherogenic risk. The available information suggests that the effects of exemestane on plasma lipid profiles may differ from those of the nonsteroidal inhibitors. **Thromboembolic Complications SERMs**

The risk of venous thromboembolism (VTE) in women with early-stage breast cancer who are being treated with tamoxifen is 1% to 6.8%. This risk is higher than the increased risk conferred by the cancer or its therapy. Although participants in the BCPT were healthy women without a known predisposition to VTE, the risk for VTE increased threefold among women randomized to tamoxifen. The risk was greater for women over age 50 and appears to be comparable to what has been reported with conventional use of estrogen.[8] As with tamoxifen, the incidence of VTE is increased among women treated with raloxifene.[8] Similar to women in the BCPT, women participating in the MORE trial did not have cancer or any known predisposition to thrombosis. The relative risk for VTE among women in the MORE trial was 3.1, which is identical to the increased risk for VTE associated with the use of either tamoxifen or estrogen.[2] **Antiaromatase Agents**

Fewer thromboembolic events were seen with anastrozole than with tamoxifen in the ATAC trial.[1] Because tamoxifen is known to increase the incidence of VTE, it is not clear if anastrozole confers any increased risk for clotting or merely causes fewer VTEs than tamoxifen. In women with advanced disease randomized to either tamoxifen or an antiaromatase agent, the incidence of VTEs was 23/506 (4.5%) for those treated with anastrozole compared with 39/511 (7.6%) for those receiving tamoxifen. No VTEs were reported in 946 women with advanced disease treated with letrozole or in 527 treated with exemestane. None of the antiaromatase agents appear to increase the risk of VTE.

**Breast Cancer as a Second Malignancy SERMs**

The recognition that women treated with adjuvant tamoxifen are less likely to develop contralateral breast cancers led to the design of the BCPT. This trial demonstrated that women receiving tamoxifen are less likely to develop estrogen-receptor-positive breast cancer than women receiving a placebo. Results of a meta-analysis of the chemoprevention trials with tamoxifen support the BCPT finding that tamoxifen decreases the incidence of breast cancer. The MORE trial was primarily designed to assess the efficacy of raloxifene in the treatment of osteoporosis, but the incidence of breast cancer was also considered. Women diagnosed with breast cancer tend to have an increase,
not decrease, in bone mineral density. Nonetheless, women receiving raloxifene in the MORE trial were less likely to develop breast malignancies. Breast cancers were diagnosed in 13 of 5,129 women treated with raloxifene compared with 27 of 2,576 in the placebo arm (P Antiaromatase Agents
Our first glimpse of the effect of the antiaromatase agents on the incidence of breast cancer comes from the ATAC trial. With a median follow-up of 47 months, the incidence of contralateral breast cancer was lower in the anastrozole arm-25 of 3,125 compared with 40 of 3,116 women randomized to tamoxifen. Until the adjuvant and chemoprevention trials of letrozole and exemestane have matured, it is not possible to assess the efficacy of these agents in the prevention of breast cancer.

Endometrial Cancer as a Second Malignancy SERMs
The association between tamoxifen use and an increased risk of endometrial cancer was first appreciated in the adjuvant therapy trials and was recently confirmed by the BCPT. Endometrial hyperplasia, endometrial polyps, and possibly uterine sarcomas are also more common among women treated with tamoxifen. A meta-analysis of data on women with early breast cancer estimates that tamoxifen increases the risk for endometrial cancer 2.58-fold, which is comparable to what has been reported for women taking unopposed estrogen. Death from tamoxifen-related uterine cancer is uncommon. In the BCPT, 36 cases of endometrial cancer were diagnosed among tamoxifen-treated patients and 15 in the placebo arm; 50 of the 51 total cases were stage I disease. The preclinical studies suggesting that raloxifene has neither an agonist nor antagonist effect on the uterus were supported by the MORE trial. The incidence of endometrial abnormalities in the MORE trial was identical in the raloxifene and control arms.[2] A placebo-controlled trial of raloxifene in healthy women indicated no greater risk for vaginal bleeding, spotting, or discharge in the treatment arm, and ultrasonography of the uterus indicated no obvious structural differences between the placebo and drug-treated groups.[2] Unlike tamoxifen, raloxifene does not cause endometrial cancer. Antiaromatase Agents
Numerous studies have examined the effects of antiaromatase agents in animal models. One true indicator of estrogenic activity is the measurement of changes in uterine development or weight. Uterine weights were significantly lower in nude mice treated with anastrozole or letrozole compared with vehicle-treated (control) mice, indicating that nonsteroidal inhibitors have no effect on the endometrium. In rats with DMBA-induced mammary tumors, there was no evidence of intrinsic estrogenic activity—either uterotrophic or antiuterotropic-following exemestane therapy. To date, no cases of endometrial cancer have been reported with the use of antiaromatase agents in women with advanced breast cancer. In the ATAC trial, the incidence of endometrial cancer was lower among women treated with anastrozole than among those treated with tamoxifen. Because tamoxifen increases the incidence of uterine cancer, the trial cannot determine whether anastrozole has any effect on the uterus.[9] Longer follow-up in this trial and additional data from ongoing trials will be needed before an adverse effect from the antiaromatase agents can be discounted. Quality of Life SERMs
Many of the controlled trials of SERMs have addressed side effects that could affect quality of life; however, few have conducted systematic quality-of-life assessments. Those that did generally report no differences for SERMs vs placebo or SERMS vs other adjuvant therapy.[10] Antiaromatase Agents
Quality of life has not been extensively studied in women receiving antiaromatase agents. In large phase III studies comparing quality-of-life measures in patients receiving antiaromatase agents or megestrol acetate, no significant differences emerged among women with advanced disease in the anastrozole, letrozole, or megestrol arms. In contrast, quality of life was superior in postmenopausal women with advanced disease who received exemestane vs megestrol. In the ATAC trial, the primary quality-of-life end point was the Treatment Outcome Index (TOI). Preliminary analysis of data after 2 years on study identified no significant differences in index scores for anastrozole vs tamoxifen, or for the combination therapy vs tamoxifen groups. Sexuality SERMs
One-third of women treated with tamoxifen report vaginal discharge, which may be consistent with normal vaginal moisture or may be irritating. Vaginal smears obtained from these women demonstrate an estrogenic effect. The incidence of dyspareunia is higher than expected among these women, especially because tamoxifen has estrogen-agonist effects on the vaginal mucosa.[10] Measures of sexual functioning were serially assessed in the BCPT, TAMOPLAC, and ITPT chemoprevention trials. The combined information obtained from the self-report questionnaires completed by 488 women enrolled in the TAMOPLAC and ITPT trials did not identify any abnormalities in libido or functioning in tamoxifen-treated participants. In contrast, the larger BCPT found that women treated with tamoxifen had significant compromise in libido, ability to become
aroused, and ability to achieve orgasm.[10] These data suggest that SERMs may have effects on sexual functioning that have not previously been appreciated. Sexual functioning was not addressed in the MORE trial, but is being assessed in the ongoing STAR trial. **Antiaromatase Agents**

In the phase III trials in advanced disease, women on tamoxifen reported a vaginal discharge more often than women on anastrozole, who were more likely to complain of vaginal dryness. There are no data that address sexual functioning in women treated with the other antiaromatase agents.

**Cognitive Functioning** **SERMs**

In ovariectomized rat models, both tamoxifen and raloxifene have demonstrated favorable effects on functional measures of brain function, producing estrogentic effects on choline acetyl transferase in hippocampal and NMDA receptors. The effect of tamoxifen on the brain has been assessed through functional imaging and clinical studies in breast cancer survivors. In one population-based case-control study, questionnaires were used to determine cognitive function in women treated for breast cancer. Although objective changes in cognition could not be documented, women who received tamoxifen were significantly more likely to complain about memory loss. Using serial functional magnetic resonance imaging and positron-emission tomography, nonspecific changes in activity have been documented in women treated with tamoxifen. Some of the changes were similar to those observed with estrogen.[11] Measures to assess memory and cognitive function were performed in a subset of women enrolled in the MORE trial. After 3 years on study, raloxifene produced neither favorable nor unfavorable effects compared with baseline. However, in subset analyses, women > 70 years old who received raloxifene had significantly better scores on tests evaluating memory and attention than comparable women in the control arm. As a rule, women who experienced hot flushes were most likely to complain of memory problems. Therefore, it is of interest that women in the raloxifene arm who also experienced hot flushes demonstrated significantly better attention scores.[12] Compared to women assigned to placebo, women in the raloxifene arm (120 mg daily for 3 months) had improvements in some measures of memory. These data are intriguing, but inconclusive. **Antiaromatase Agents**

Clinical measures of brain function in women treated with specific antiaromatase agents are lacking. Preliminary data on 94 women in the ATAC trial identified a decreased verbal memory compared to the control group. Until the therapy is unblinded, it is unclear whether these effects occur more commonly with tamoxifen, anastrozole, or both drugs. **Depression** **SERMs**

Depression, anxiety, and distress were assessed by questionnaire in three of the chemoprevention trials: BCPT, TAMOPLAC, and ITPT. None identified any differences between the treatment and control arms. Data on the incidence of affective disorders with the use of raloxifene are not available. **Antiaromatase Agents**

Data addressing mood alterations are lacking for antiaromatase agents. **Hot Flushes** **SERMs**

Hot flushes are a recognized side effect of both tamoxifen and raloxifene. In the BCPT, severe hot flushes were more common with tamoxifen (17.6% vs 10.1%). A similar increase was also found in women in the raloxifene arm of the MORE trial (10.7% vs 6.4%).[2] The STAR trial will establish whether there is any difference in the incidence of hot flushes between the two SERMs. **Antiaromatase Agents**

It has been difficult to discern if the hot flushes reported during clinical trials of antiaromatase agents are attributable to the drugs or to other causes. In the initial phase II and III trials in advanced breast cancer, hot flushes were reported in 134 (25.9%) of 516 women treated with anastrozole, 107 (11.3%) of 946 treated with letrozole, 79 (14.9%) of 527 treated with exemestane, 138 (14.3%) of 966 treated with tamoxifen, and 45 (7.9%) of 601 treated with megestrol. Although the difference was small (34.3% vs 39.7%), women in the ATAC trial who had been randomized to single-agent anastrozole were less likely to complain of hot flushes than those in the tamoxifen arm.[1] Hot flushes are reported with the use of the antiaromatase agents, but the incidence appears to be less than that observed with the SERMs. **Weight Gain** **SERMs**

Although weight gain has often been considered a side effect of tamoxifen, neither the BCPT nor the TAMOPLAC trials identified any difference in weight in the treatment arm. **Antiaromatase Agents**

In phase III trials comparing antiaromatase agents with tamoxifen or megestrol, the antiaromatase agents did not produce weight gain. Weight gain in the ATAC trial was slightly less with anastrozole than with tamoxifen, but the difference was not statistically significant.[1] It has been suggested that weight gain may be more common with exemestane than with either letrozole or anastrozole. However, the number of women gaining > 10% baseline weight was too small to draw any definitive conclusions. More information is needed to determine the effect of antiaromatase agents on weight. **Joint Discomfort** **SERMs**

Neither tamoxifen nor raloxifene have been reported to produce musculoskeletal problems.
**Antiaromatase Agents**

In the ATAC trial, "musculoskeletal disorders" were significantly more common among women treated with anastrozole than among those treated with tamoxifen.[1] A phase III trial of letrozole in 454 women with advanced breast cancer reported a 14% incidence of arthralgia among letrozole-treated patients. However, 13% of tamoxifen-treated patients in this trial also complained of arthralgia. The ATAC trial results suggest that musculoskeletal discomfort is associated with the use of anastrozole. The information for letrozole and exemestane was derived from trials in advanced disease, and there are no data to suggest that either drug produces musculoskeletal disorders. **Discussion** Advances in diagnosis and medical management are credited with improving the survival of women with early-stage breast cancer. Tamoxifen has been and continues to be important in the treatment and prevention of breast cancer. It has been in use in this country since 1977, and its effects on estrogen-sensitive tissues are widely recognized. Survival data from a meta-analysis of tamoxifen for early-stage breast cancer continues to intrigue us, as the overall survival advantage for women treated with adjuvant tamoxifen exceeds the survival benefit expected from the decrease in breast cancer recurrences alone. It has been assumed that the beneficial effects are related to favorable estrogen-agonist effects on normal tissues, especially relative to the risk of cardiovascular disease. However, the chemoprevention trials have yet to demonstrate a decrease in cardiovascular events. It is possible that the hormonal environment of women who develop breast cancer differs from that of the high-risk women enrolled in chemoprevention trials. Perhaps with longer follow-up, the prevention trials will shed additional light on this issue. **Relative Risks and Benefits**

Based on the superiority of the antiaromatase agents in advanced disease, an improvement in disease-free survival with anastrozole might have been predicted in the ATAC trial. In advanced disease, the antiaromatase agents produce higher response rates and longer durations of benefit than tamoxifen. Although a survival advantage has not been consistently demonstrated when antiaromatase agents are used as initial therapy, subsets of patients may benefit more from an antiaromatase agent than from tamoxifen. The long-term effects of hormonal agents are of greater concern in women with early-stage breast cancer, as most will die of causes other than breast cancer. Because breast cancer survivors represent the largest group of cancer survivors, understanding the long-term toxicities of treatment needs to be a priority. In the adjuvant setting, anastrozole appears to be superior to tamoxifen in regard to disease-free survival and the incidence of contralateral breast cancer. Despite the American Society of Clinical Oncology guidelines supporting the continued use of tamoxifen except where it is contraindicated, antiaromatase agents are increasingly being used in the adjuvant setting. Both tamoxifen and raloxifene increase bone density[2] and have favorable effects on lipid profiles,[5,6] although it is uncertain whether these effects reduce cardiovascular complications. It is troubling that the nonsteroidal inhibitors may have adverse effects on bone density and lipid profiles.[1] Although no data suggest a difference in side effects between the two nonsteroidal inhibitors, it is intriguing that the steroidal inactivator exemestane may have different effects on normal tissues than the nonsteroidal inhibitors. Exemestane appears to have favorable effects on bone and lipids.[4] **Conclusions**

As new therapies are developed for the treatment of advanced or incurable disease, we are quick to incorporate them into our practices. Long-term toxicities are generally not a concern in this population. However, estrogenreceptor- positive breast cancer is an indolent disease, and the 47-month follow-up in the ATAC trial is too short to justify changes in practice standards, especially given the largely favorable 20-year experience with tamoxifen. Longer follow-up in the ATAC trial and a better understanding of the longterm toxicities of the individual classes of antiaromatase agents is needed before tamoxifen is summarily replaced by antiaromatase agents in the adjuvant setting.

**References:**


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