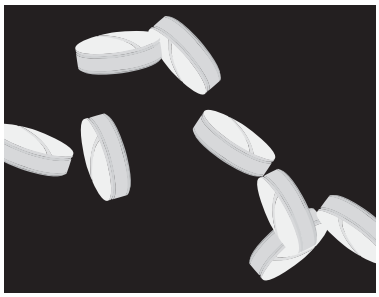
SIDE EFFECTS REVISITED:
Women's Experiences With Aromatase Inhibitors

A Report From Breast Cancer Action

JUNE 2008

BREAST CANCER ACTION



SIDE EFFECTS REVISITED:
Women's Experiences With Aromatase Inhibitors

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JUNE 2008

A Report From

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This report is dedicated to the 1,199 women who generously took the time to respond to Breast Cancer Action's Aromatase Inhibitor Side Effects Survey and to everyone who seeks to make informed decisions about the care they receive.

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INTRODUCTION

Aromatase inhibitors (AIs) have been incorporated into the standard of care for treating hormone-receptor-positive breast cancer in postmenopausal women. Three AIs have been approved by the U.S. Food and Drug Administration (FDA): anastrozole (Arimidex), exemestane (Aromasin), and letrozole (Femara).

> **"Thank you for the information you provide to patients. We often need to know what we are not being told about meds."**
>
> *—40- to 49-year old survey respondent*

Though some studies on AIs have pointed to some long-term side effects that are emerging, such as bone and joint effects and retinal hemorrhages (Dent et al., 2007; Eastell et al., 2007; Eisner et al., 2007; Renshaw et al., 2007), our knowledge of the long-term impact of these drugs is currently limited.

In 2005, Breast Cancer Action (BCA) launched an online survey to collect information about the side effects women were experiencing while taking AIs. The AI Side Effects Survey included questions about the women's ages, the AI prescribed to them, the reason they were prescribed the AI, their menopausal status at the time of prescription, and other treatments they received for breast cancer.

The questions are followed by a list of 38 side effects generated from the FDA's AI product information documents that were current in 2005. Women rated the side effects for severity (none, mild, moderate, or severe). Respondents were also asked to report any additional side effects not included in our list. Lastly, women were asked whether they had discontinued taking the AI, and if so, their reason for making that decision.

In January 2007, BCA published a preliminary report entitled *Side Effects Revealed: Women's Experiences With Aromatase Inhibitors.* It included general findings, such as the percentage of women who reported experiencing the side effects listed in the survey, additional side effects reported by the women, the number of women whose menopause had been induced or had occurred naturally, and the percentage of women who stopped taking their AI (which was most often due to the side effects they experienced). It also included general information about AIs, the development of the survey, and the methods used for analysis. It can be found online at www.bcaction.org/AIreport.

The findings in the report released in 2007 were based on the responses of the first 612 women who completed the AI Side Effects Survey. This second report is based on the initial 612 surveys as well as those completed by the next 587 women—a total of 1,199 surveys. The sample of women who responded was self-selected and may not be representative of the population of women taking AIs. Therefore, the overall results cannot be generalized to the larger population. However, it may be assumed that differences between subgroups of the women who responded (e.g., those whose menopause had been induced versus those whose menopause had occurred naturally) were not subject to a self-selection bias. Therefore, significant differences between the subgroups of women who responded to the survey may be generalized to larger groups of women in the same subgroups.

This report examines the relationship between the women's side effects and four other variables: their age, menopausal history, prior use of tamoxifen, and why the AI was prescribed for them—either to treat active disease or to reduce the risk of recurrence.

Age. Some side effects listed in the survey (e.g., mental fuzziness, weight gain, hair thinning, and osteoporosis) increase in frequency as women age, and thus the symptoms may be partially attributed to the effects of normal aging. However, it is possible that they are aggravated or made more severe with AI use. It is therefore difficult to separate whether side effects

women experience while on AIs occur naturally due to aging, occur as a result of taking the AI, or occur as a combination of the two. However, if the side effect occurs more often in younger than in older women, this suggests that the symptom is more clearly a side effect of AI use.

> **"This is quite a difficult choice to make between quality of life and fear of recurrence! Help us please find another way."**
>
> *—60- to 69-year old survey respondent*

Menopausal history. AIs are only approved for use in postmenopausal women. In the first report, over half of the women who responded to the survey reported they had a pharmaceutically or surgically induced menopause. We assume that for most of these women, menopause occurred prematurely and abruptly.

Two studies have discussed the possibility that premature and/or abrupt onset of menopause could exacerbate menopausal symptoms and joint pain. Jones et al. (2007) compared women's menopausal symptoms during the first year of adjuvant therapy with either exemestane or tamoxifen. The authors raised the possibility that younger women who received adjuvant chemotherapy could experience premature menopause, leading to an "increased and sometimes abrupt onset of (menopausal) symptoms."

Felson and Cummings (2005) reviewed data that linked pharmaceutically induced low estrogen levels to joint pain. They concluded, "The few data that do exist suggest a process of transient joint pain that, in the case of estrogen deprivation, is responsive to estrogen repletion [replacement]." The authors also noted that "another explanation for these findings would be that a rapid drop in estrogen levels enhances nociception," i.e., that a rapid drop in estrogen levels could cause an increase in pain sensitivity.

On the basis of these studies, we expected that relative to women who became menopausal naturally, women whose menopause was induced surgically or pharmaceutically would report an increased incidence and/or severity of menopausal and joint-related side effects.

Prior use of tamoxifen. All three AIs have been approved for use in postmenopausal women with hormone receptor positive breast cancer. Exemestane (Aromasin) has been approved by the FDA following treatment with tamoxifen. The two other AIs, letrozole (Femara) and anastrozole (Arimidex), have been approved either as first-line treatment without prior tamoxifen use, or for use following treatment with tamoxifen.

Studies show that AIs decrease bone mass density, while tamoxifen suppresses bone loss and is protective against osteoporosis in postmenopausal women. At least two studies have shown that taking tamoxifen prior to taking an AI may have beneficial effects on bone-related and joint-related side effects. Coombes et al. (2007), citing the results of a bone substudy, reported that "the rate of bone loss associated with exemestane seemed to be partly attenuated by previous treatment with tamoxifen." And Crew et al. (2006) found that the risk of joint symptoms in postmenopausal women on aromatase inhibitors was inversely associated with prior tamoxifen treatment.

Unlike tamoxifen, which either mimics or blocks estrogen selectively in different parts of the body, AIs do not mimic the effects of estrogen. In light of this and the studies noted, in this report we investigate the possibility that prior use of tamoxifen might reduce the incidence and/or severity of side effects in women taking an AI.

Reason for AI use: Active disease or to reduce the risk of recurrence. Twelve percent (144/1,199) of the women who responded to our survey were being treated for active disease. We investigated the possibility that these women might report a greater incidence and/or more severe side effects. We also assumed that women taking an AI for active disease may be less likely to stop taking an AI than women who were taking an AI to reduce their risk of a recurrence.

RESULTS*

The Women

The women who took the survey were asked a series of questions, including what their age was and whether they were postmenopausal at the time the AI was prescribed to them. If they responded that they were postmenopausal, they were also asked whether they entered menopause naturally or whether it was pharmaceutically or surgically induced. Women were also asked if they had used tamoxifen prior to taking an AI.

Table 1 includes the results for these questions, and below is a brief discussion for each characteristic.

Age. A total of 1,199 women responded to the survey, and their age distribution is shown in Table 1. The age categories in the survey ranged from 20- to 29-years-old to 80-plus-years-old. The majority of the women who responded to the survey were from 50- to 59-years-old. Two women were in the 20–29 age range and six women were in the 80-plus age range. Because there were so few women in these two age categories, their data were combined with those from women in the closest age groups for the data analyses.

The median age (age at which half the women were younger and half the women older) of the women who responded to our survey was estimated at 55 years. We compared the median age of our survey respondents with the median age of the women who participated in AI clinical trials. On average, the women who responded to our AI Side Effects Survey were significantly younger by

Table 1. Characteristics of Survey Respondents

AGE		
Age range	**Number**	**Percent**
20–39	37	3.1
40–49	244	20.3
50–59	632	52.7
60–69	249	20.8
70+	37	3.1
	Total 1,199	

MENOPAUSAL STATUS AT TIME PRESCRIPTION		
Reply	**Number**	**Percent**
Postmenopausal	1,118	94.8
Premenopausal	48	4.1
No answer	13	1.1
	Total 1,179[1]	

IF POSTMENOPAUSAL, HOW DID IT OCCUR?		
Reply	**Number**	**Percent**
Naturally occurring	460	39
Pharmaceutically	348	29.5
Surgically induced	230	19.5
No answer	141	12
	Total 1,118	

PRIOR TAMOXIFEN USE?		
Reply	**Number**	**Percent**
Yes	628	53.3
No	523	44.4
No Answer	28	2.3
	Total 1,179	

* The results have been written with the layperson in mind, so all significant tests have been omitted from the text and are listed as footnotes. Chi square (X^2) tests were done using the following web site: www.physics.csbsju.edu/stats/contingency_NROW_NCOLUMN_form.html, and Fisher's exact tests using www.matforsk.no/ola/fisher.htm. All other significance tests were done using SPSS 15.0 for Windows.

1 Though 1,199 women took the survey, 20 women did not provide sufficient information for further analysis. These women had taken more than one aromatase inhibitor and did not clearly indicate which of the three aromatase inhibitors they were referring to in their survey answers. Their responses were omitted from all subgroup analyses.

approximately 10 years.[2, 3, 4, 5]

Although a median age was not given for the women who took part in the exemestane trial (Coombes et al., 2007), the number of women who were younger than 60-years-old, between 60 and 69-years-old, or more than 70-years-old was provided. We used this information to establish the age distribution of the women who participated in the exemestane trial, and compared this to our age distribution. Again, the women who responded to BCA's survey were found to be significantly younger.[6] (See Table 2, and footnotes 2–6 for statistical significance values relating to these comparisons.)

Table 2. Median Ages From AI Clinical Trials

Aromatase Inhibitor	Median Age	Reference
Anastrozole	67 years[2]	Bonneterre et al., 2001
Anastrozole	68 years[3]	Nabholtz et al., 2000
Letrozole	62 years[4]	Goss et al., 2005
Letrozole	65 years[5]	Mouridsen et al., 2000

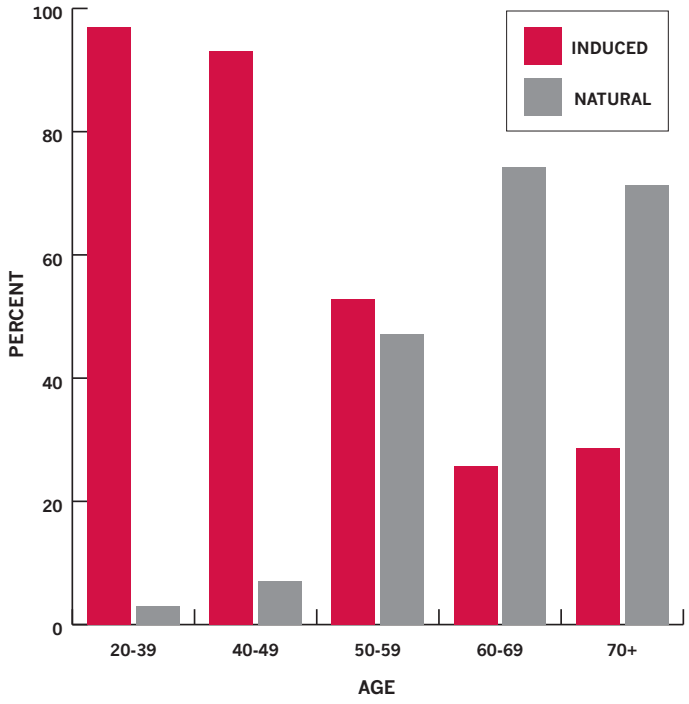
Menopausal history. Women were asked the following question: "Were you postmenopausal at the time that AIs were prescribed for you?" Overall, 94.8% of the women reported that they were postmenopausal, 4.1% that they were not postmenopausal, and 1.1% did not indicate whether or not they were postmenopausal (see Table 1).

As would be expected, the percentage of women who reported they were postmenopausal increased with age: 83.3% (30/36) of the 20- to 39-year-olds, 92.1% (222/241) of the 40- to 49-year-olds, 95.5% (590/680) of the 50- to 59-year-olds, 97.2% (240/247) of the 60- to 69-year-olds, and 100% (36/36) of the 70-plus-year-olds were postmenopausal.

Thirty-nine percent of the women reported that they had become menopausal naturally; 29.5% that they had become menopausal pharmaceutically, and 19.5% that they had become menopausal surgically (See Table 1).

Younger women (20- to 49-year-olds) were significantly more likely than older women (women 60-plus-years-old) to have become postmenopausal surgically or pharmaceutically.[7] As can be seen in Figure 1, the percentage of women in each age group who reported that their menopause was induced, pharmaceutically or surgically, decreased from 97% in the youngest age group to 28.6% in the oldest women, aged 70 years and older, whereas the percentage of women who reported becoming postmenopausal naturally increased from just over 3% in the youngest women to over 71.4% in the oldest women.

FIGURE 1. Percentage of women in each age group who reported their menopapuse was induced (pharmaceutically or surgically) or occurred naturally



2 $X^2(1) = 352.7$, p </= .001.

3 $X^2(1) = 249.6$, p </= .001.

4 $X^2(1) = 313.9$, p </= .001.

5 $X^2(1) = 243.7$, p </= .001.

6 $X^2(2) = 647.0$, p = .000.

7 $X^2(4) = 231.034$, p =.000.

Prior use of tamoxifen. The women were asked to report whether or not they had taken tamoxifen prior to taking an aromatase inhibitor. More women reported they had not taken tamoxifen prior to taking an AI (53.3%) than women who reported they did take tamoxifen prior to taking an AI (44.4%).[8] (See Table 1.) Figure 2 shows that the youngest women were significantly less likely to have taken tamoxifen before beginning an aromatase inhibitor, whereas the oldest women were significantly more likely to have taken tamoxifen prior to taking an aromatase inhibitor.[9] This difference may be influenced by changing protocols in breast cancer treatment as new treatments were approved.

Figure 3 shows the average number of years women took tamoxifen prior to taking an AI. The average number of years that the youngest women (20- to 39-year-olds) took tamoxifen prior to taking an AI was significantly lower than all the other age groups except for 40- to 49-year-old group, while the number of years the oldest women (70-plus-year-olds) took tamoxifen prior to an AI was significantly greater than all the other age groups.[10]

Reason for AI use: Active disease or to reduce the risk of recurrence. The women were asked whether they were taking an aromatase inhibitor to reduce the risk of recurrence, to treat active disease, or for some other reason. Overall, the majority of women (83.4%) reported that they were taking an aromatase inhibitor to reduce the risk of recurrence. Only 12% of the women reported that they were taking an aromatase inhibitor to treat active disease.[11] Figure 4 shows a breakdown of the reasons AI was prescribed, broken out by age group. It shows that the youngest women were significantly more likely to report taking an aromatase inhibitor to treat active disease than the women in the other four age groups.[12]

FIGURE 2. Percentage of women in each age group who reported that they had (Yes) or had not (No) taken tamoxifen prior to taking an aromatase inhibitor

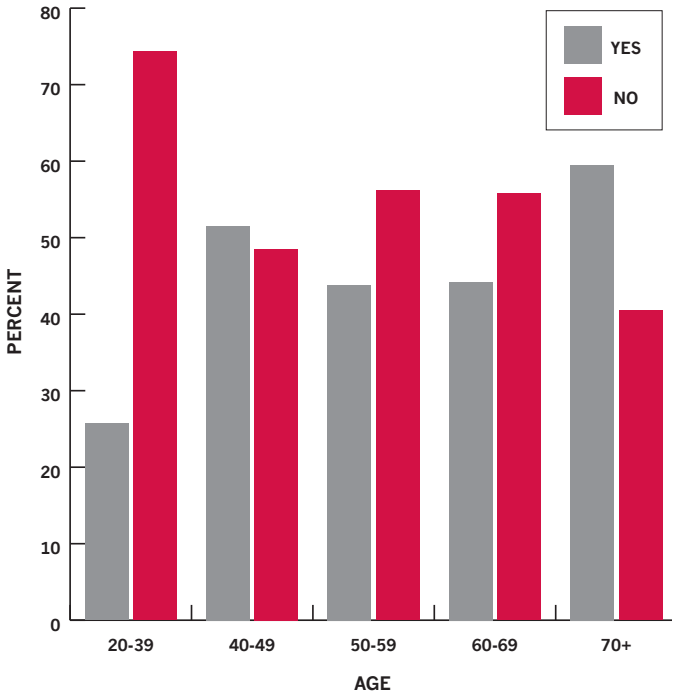
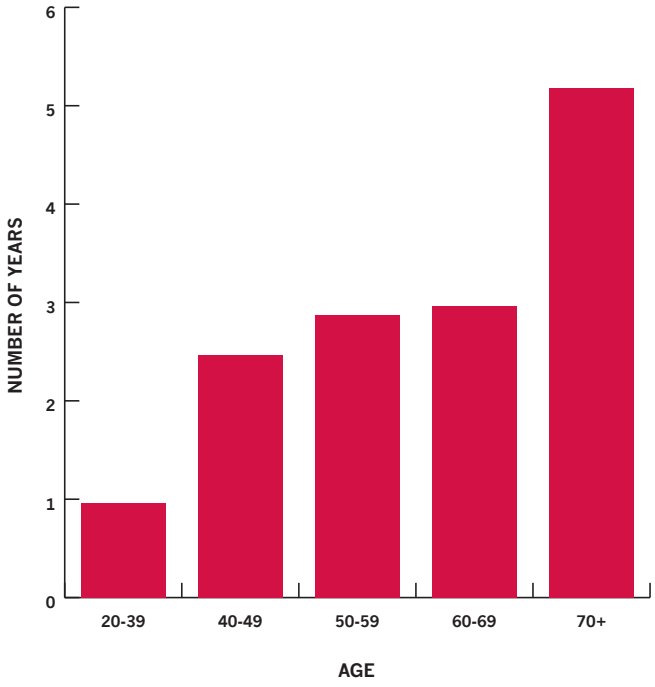


FIGURE 3. Average number of years women in each age group had taken tamoxifen before taking an AI



8 Twenty-eight women (2.3%) did not report whether or not they had taken tamoxifen prior to an aromatase inhibitor.

9 $X^2(4) = 12.7$, p =.013.

10 Univariate 5 x 3 (age group x AI) ANOVA, overall F(14) = 10.235, p < .000. Main effect for age was significant, F (4) = 10.357, p < .000. Pairwise comparisons between the youngest age group and the three oldest age groups, and pairwise comparisons between the oldest age group and the four younger age groups were significantly different at the p < .05 level.

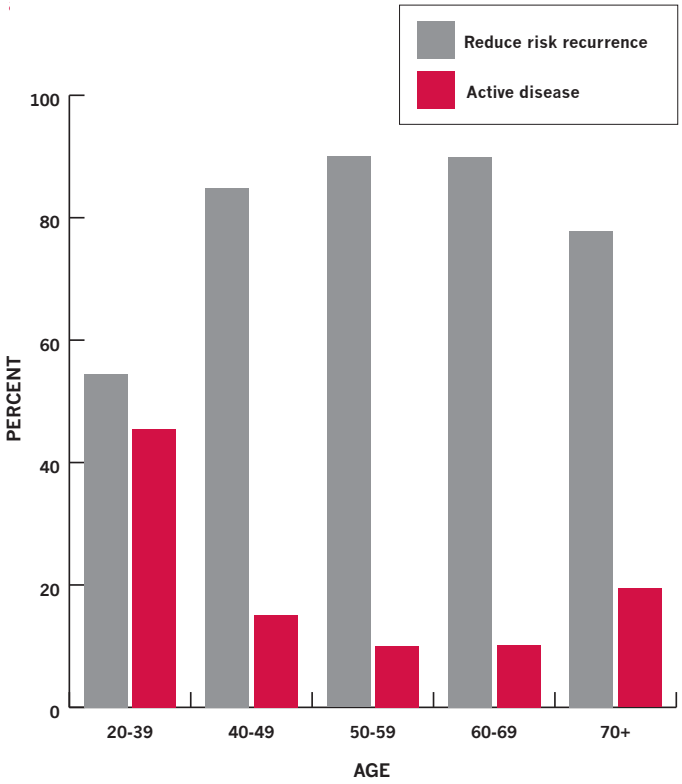
11 Thirty-six women cited another reason for taking an aromatase inhibitor. Twenty women did not respond.

12 $X^2(4) = 40.3$, p =.000.

In summary:

- The women who responded to the AI Side Effects Survey were, on average, about a decade younger than the women who participated in the clinical trials that led to the FDA approval of aromatase inhibitors for adjuvant treatment of postmenopausal women with hormone-receptor-positive breast cancer.
- Although almost all of the women who responded to the survey were postmenopausal, close to half of them reported that their menopause was induced, either pharmaceutically or surgically. Younger women were much more likely than older women to report that their menopause was induced.
- Slightly more than half of the women who responded to the survey had not taken tamoxifen prior to taking an aromatase inhibitor; however a much larger percentage (74%) of the youngest age group of women had not taken tamoxifen before starting an aromatase inhibitor.
- Most of the women who responded to the survey reported that they were taking an aromatase inhibitor to reduce the likelihood of a breast cancer recurrence. Twelve percent of the women were taking an aromatase inhibitor to treat active disease. However a larger percentage of the youngest women were taking an aromatase inhibitor to treat active disease.

FIGURE 4. Percentage of women in each age group who reported they were taking an aromatase inhibitor to reduce the risk of recurrence or to treat active disease



"I went from a very active sex life with my significant other to totally losing interest."

—50- to 59-year old survey respondent

"I felt like I was 95 years old. I stopped the AI. After being on tamoxifen for 8 months, I feel normal again".

—40- to 49-year old survey respondent

Side Effects

The AI Side Effects Survey included a list of 38 side effects generated from FDA product information documents for the three AIs. Women rated these side effects according to severity (none, mild, moderate, or severe). The vast majority (97.7%) of the women who responded to the survey reported experiencing one or more of the 38 side effects specifically listed in the survey. Only 27 women (2.3%) reported experiencing no side effects. Figure 5 displays the percentage (from highest to lowest) of women who reported experiencing each of the 38 side effects. Over 50% of the women reported experiencing hot flashes, bone pain, tiredness, muscle pain, and insomnia. Weight gain, mental fuzziness, increased sweating, anxiety, hair thinning and depression were reported by more than 30% of the women.

Table 3. Additional side effects reported by women

	Number of women	Percent of women[a]
JOINT / BONE / NERVE-RELATED SIDE EFFECTS		
Joint pain / arthritis / stiffness / pain	261	21.8
Trigger thumbs / fingers / toes	25	2.1
Numbness / tingling of hands / feet / toes / etc.	22	1.8
Osteopenia / bone loss	18	1.5
Carpal tunnel syndrome	15	1.3
Swelling of hands / feet / fingers / joints / etc.	14	1.2
Neuropathy in feet / hands / legs / arms	12	1.0
	367	30.6
OTHER SIDE EFFECTS		
Vaginal atrophy / dryness / discharge / etc.	61	5.1
Rise in cholesterol level	43	3.6
Loss of libido	32	2.7
Dryness of nails / eyes / mouth / skin / scalp	35	3.0
Cognitive impairment (memory loss, etc.)	23	1.9
Moodiness / irritability	18	1.5
Muscle weakness / loss of strength	14	1.2
Feeling aged	14	1.2

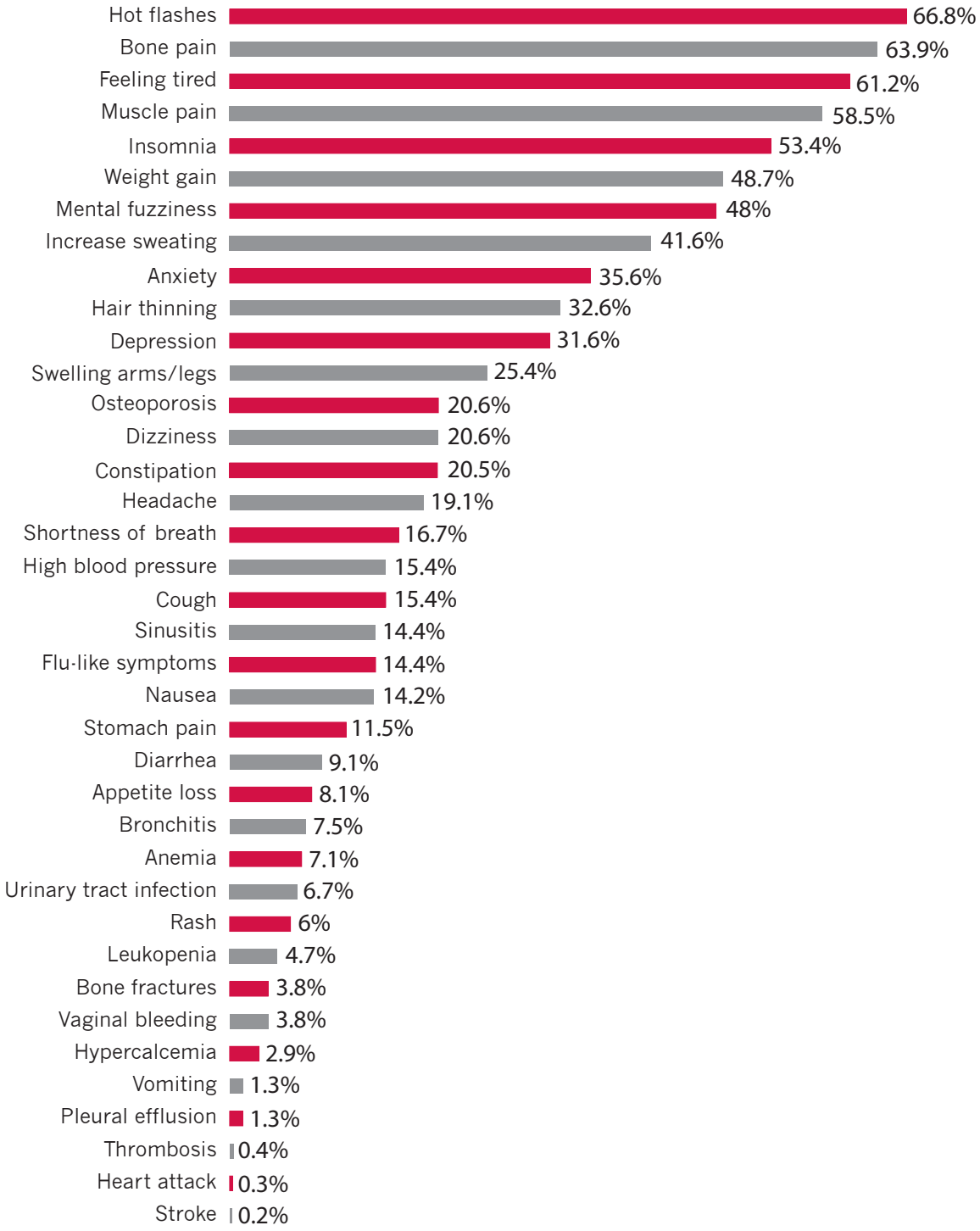
a When calculating the percentage of women in each category, the number of women was divided by the total number of women (1,199) who responded to our survey.

Many women reported side effects in addition to those specifically listed in the survey. Table 3 lists the additional side effects reported by at least 1% of the women and the number (and percentage) of women who reported each of these additional side effects.

In order to avoid misrepresenting or inflating the number of women reporting additional side effects, we counted an individual woman once in a category, regardless of whether she listed one or multiple effects under that specific category. For example, "joint pain/arthritis/stiffness/pain" is one category. If a woman listed both joint pain and joint stiffness, however, she would be counted only once in that category.

Because numerous joint-, bone-, and nerve-related side effects were reported as additional side effects by many women and are commonly reported in the literature, we decided to group these categories together to look at their frequency as a whole, which is reflected in the first portion of Table 3. Thirty percent of the women reported joint-related, bone-related, or nerve-related side effects. Other side effect categories were not grouped in this manner and are listed in the second portion of Table 3.

FIGURE 5. Percentage of women who reported experiencing each of the 38 side effects listed in the survey



"I ended up on three prescription drugs to counter effect the side effects."

—60- to 69-year old survey respondent

Noncompliance

Of the 1,199 women who responded to the survey, 27.8% (333 women) stopped taking their AI because of side effects. On average, each of these women reported experiencing two side effects when listing their reasons for discontinuing AI use.

Some women discontinued their AI for reasons not related to side effects. Reasons stated included: they had completed the prescribed period for their AI (nine women); they were not postmenopausal (five women); stopped for the duration of chemotherapy or radiation (six women); stopped prior to surgery (two women); they could not afford to continue the drug (two women); or due to disease progression (21 women). These women are not included in our analysis of the 333 women who discontinued use due to side effects.

Table 4 lists the side effects reported by at least 1% of the women who discontinued their AI due to side effects. Not all the women permanently stopped taking their AI. Nine women missed doses deliberately to get a break from the side effects, three women stopped for a mental break, and four women stopped for a short period before starting another AI.

As in Table 3, in order to avoid misrepresenting or inflating the number of women reporting a side effect, we counted an individual woman once in a category, regardless of whether she listed

Table 4. Side effects that led women to stop taking their AI

	Number of women	Percent of women[a]
Joint pain / inflammation / stiffness	168	50.4
Pain / bone pain / muscle pain	89	26.7
Intolerable side effects[b]	46	13.8
Fatigue / exhaustion / weakness / flu-like symptoms	43	12.9
Depression / mood swings / irritability	20	6.0
Vaginal bleeding / discharge / dryness / pain	19	5.7
Insomnia	17	5.1
Edema / swelling	17	5.1
Gastrointestinal pain / nausea / diarrhea	16	4.8
Migraines / headaches	15	4.5
Hot flashes	14	4.2
Neuropathy	14	4.2
Hair loss	12	3.6
Felt aged (80–100 years old)	12	3.6
Diminished mental processes	9	2.7
Bone loss / fractures	8	2.4
Bladder pain / spasms / infections	7	2.1
Elevated cholesterol	7	2.1
Allergic reactions	6	1.8
Anxiety	6	1.8
Weight gain	6	1.8
Dizziness	6	1.8
Chest pain / pressure	4	1.2
Dryness / skin / hair / mouth	4	1.2

a When calculating the percentage of women in each category, the number of women was divided by the number of women (333) who reported that they had stopped taking their AI because of one or more side effects.

b Women were only counted in this category if they reported stopping due to intolerable or unbearable side effects, and did not report the specific side effects they experienced. For example, if they listed intolerable side effects and joint pain, they were counted only under joint pain.

one or multiple effects under that specific category. As before, if a woman listed both joint pain and joint stiffness, she would be counted only once in the "joint pain/arthritis/stiffness/pain" category. However, if a woman responded that she had experienced joint pain and vaginal dryness, she was counted once in "joint pain/inflammation/stiffness" and once in "vaginal bleeding/discharge/dryness/pain."

The following additional reasons were given for discontinuing use, but were reported by fewer than 1% of women who stopped taking their AI because of side effects (number in parentheses indicates the number of women): elevated liver enzymes (3), elevated blood pressure (3), chest pain/pressure (3), tachycardia (2), atrial fibrillation (2), shortness of breath (2), high blood calcium (1), tendonitis (1), atypical complex hyperplasia (1), hormone-receptor-negative (1), tender nodules forming where breast removed (1), plantar fasciitis (1), breast pain (1), mild heart attack (1), transient ischemic attack (1), anemia (1), weight loss (1), nose blisters (1), Grave's disease (1).

Of the women who discontinued their AI due to side effects, over 50% cited joint pain or joint-related pain, over 25% cited other pain, including bone pain, muscle pain, vaginal pain, bladder pain, and chest pain, and over 10% cited fatigue or fatigue-related symptoms. Although two-thirds of the women (67%, see Figure 5) reported experiencing hot flashes as a side effect, less than 5% of the women who discontinued AI use cited hot flashes as their reason for stopping.

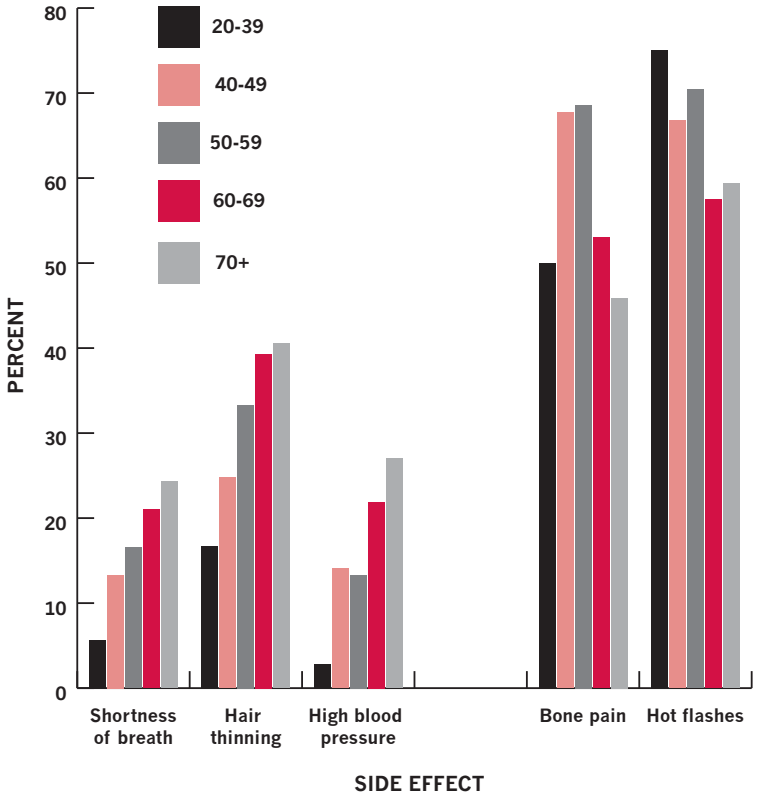
We expected that a higher percentage of women taking an AI to reduce the risk of recurrence would report stopping AI use compared to women being treated for active disease, and we did find a significant difference between the two groups.[13] Of the women who were taking an AI to reduce the risk of recurrence, 31.0% stopped taking an AI. Of the women who were taking an AI to treat active disease, 19.3% stopped taking their AI.

Side Effects and Age

Three of 38 side effects listed specifically in the survey—shortness of breath,[14] hair loss,[15] and high blood pressure[16]—could be related to increasing age. As seen in Figure 6, as the ages of the women increased from 20–39 years to 70 years and older, the percentage of women in each of the age groups who reported experiencing shortness of breath, hair thinning, and high blood pressure also increased.

However, the reverse appears to be true for the side effects of bone pain[17] and hot flashes.[18] These two side effects are also significantly related to age, but in contrast to the other side effects related to age, bone pain and hot flashes were cited by a higher percentage of the women in the

FIGURE 6. Percentage of women in each age group who reported shortness of breath, hair thinning, high blood pressure, bone pain, or hot flashes



13 Fisher's Exact Test (two-tailed, [305, 27, 679, 109]), p =.0007.

14 $X^2(12) = 26.3$, p = .010.

15 $X^2(12) = 31.1$ p = .002.

16 $X^2(12) = 33.8$, p = .001.

17 $X^2(12) = 38.5$, p = .000.

18 $X^2(12) = 21.3$, p = .046.

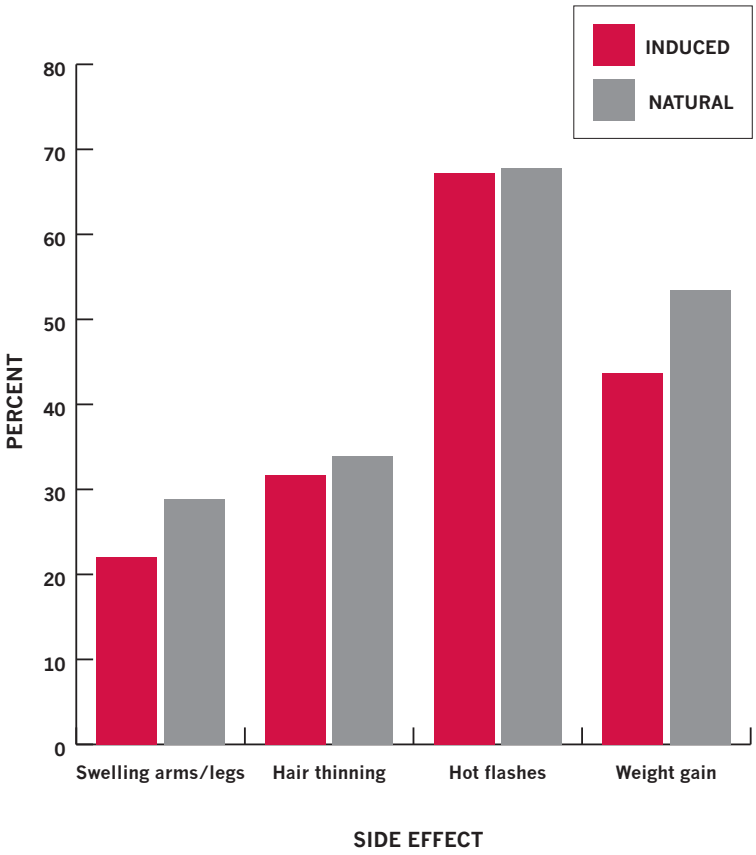
three youngest age groups. Bone pain and hot flashes, therefore, appear to be side effects associated with AI use.

Side Effects and Induced Menopause

Compared to women who entered menopause naturally, a significantly greater percentage of the women in whom menopause was induced (surgically or pharmaceutically) reported experiencing mild, moderate, or severe swelling of their arms and legs;[19] hair thinning;[20] hot flashes;[21] and weight gain.[22] (See Figure 7.) In some cases, the difference was on the order of 10% (weight gain) and 7% (swelling of arms and legs). In other cases the difference was small (2% hair thinning, less than 1% hot flashes).

We also further compared the groups of women whose menopause had been induced pharmaceutically versus surgically. Although a greater percentage of the women whose menopause had been surgically induced reported swelling of their arms and legs[23] and weight gain,[24] the differences were not statistically significant.

FIGURE 7. Percentage of women whose menopause occurred naturally or was induced who reported swelling of their arms or legs, hair thinning, hot flashes or weight gain



Side Effects and Prior Use of Tamoxifen

In contrast to women who had taken tamoxifen before switching to an AI, a significantly larger percentage of the women who had not taken tamoxifen experienced mild, moderate or severe vomiting,[25] diarrhea,[26] flu-like symptoms,[27] shortness of breath,[28] headaches,[29] mental fuzziness,[30] insomnia,[31] muscle pain,[32] and bone pain.[33] (See Figure 8.) These

19 $X^2(6) = 14.2$, p = .027.
20 $X^2(6) = 13.6$, p =.034.
21 $X^2(6) = 17.1$, p =.009.
22 $X^2(6) = 18.4$, p =.005.
23 $X^2(3) = 6.81$, p =.08.
24 $X^2(3) = 6.99$, p =.07.
25 $X^2(3) = 8.11$, p = .044.
26 $X^2(3) = 9.90$, p = .019.
27 $X^2(3) = 12.0$, p = .007.
28 $X^2(3) = 9.03$, p = .029.
29 $X^2(3) = 10.3$, p = .016.
30 $X^2(3) = 9.64$, p = .022.
31 $X^2(3) = 11.3$, p =.01.
32 $X^2(3) = 9.85$, p = .02.
33 $X^2(3) = 11.7$, p = .009.

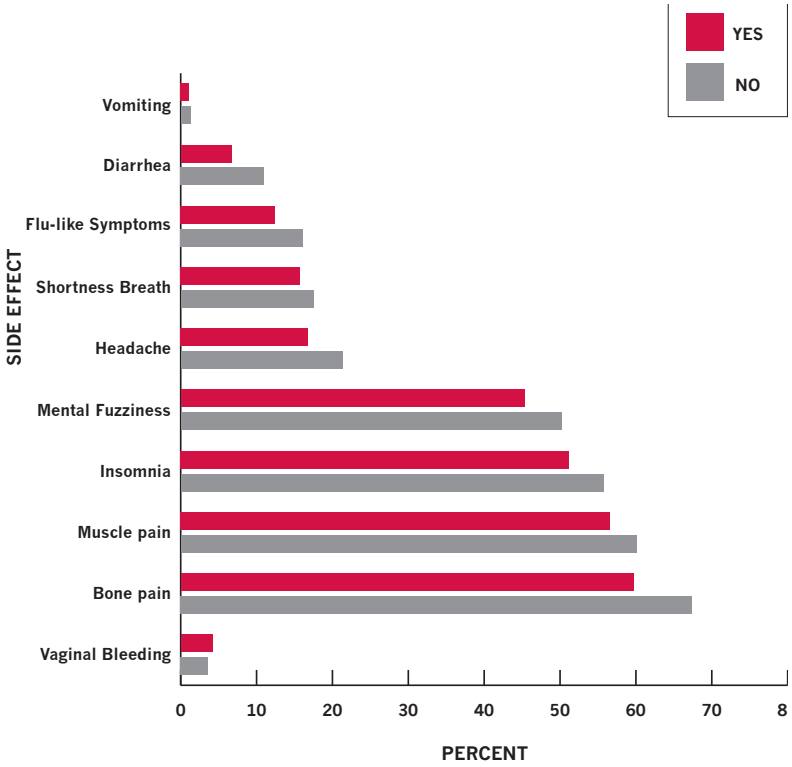
"They did tell me about side effects, but I felt they didn't tell me how severe the side effects might be. Also, I felt I wasn't given enough information about what the side effects are like for premenopausal women."

—40- to 49-year old survey respondent

results indicate that previous treatment with tamoxifen may attenuate not only bone loss (Coombes, et al., 2007) but also other common side effects associated with AI use.

Only one side effect, vaginal bleeding, was reported by a significantly greater percentage of women who had taken tamoxifen before taking an AI.[34] (See Figure 8.) Vaginal bleeding is a common side effect reported by women taking tamoxifen.

FIGURE 8. Percentage of women who had (Yes) or had not (No) taken tamoxifen prior to an AI who reported experiencing the following side effects



Side Effects and Active Disease

Bone fractures were the only side effect reported by a significantly larger percentage of the women taking an AI to treat active disease (4.3%) than by women taking an AI to reduce the risk of recurrence (3.9%).[35] Though statistically significant, the absolute difference seen between the two groups was small.

In summary:

- Hot flashes, bone pain, tiredness, muscle pain, and insomnia were reported by more than 50% of the women who responded to the survey. Weight gain, mental fuzziness, increased sweating, anxiety, hair thinning, depression, and joint/bone/nerve-related side effects were reported by more than 30% of the women.
- Close to 30% of the women who responded to the survey stopped taking their AI because of side effects, including some women who were taking an AI to treat active disease. Pain—joint pain or joint-related pain, bone pain, muscle pain, vaginal pain, bladder pain, and/or chest pain—was the major side effect that caused women to stop taking their AI.
- Many side effects appear to be exacerbated by the women's age and/or treatment. Women who were younger were more likely to suffer from bone pain and hot flashes, the two most commonly reported side effects. Women in whom menopause was induced were more likely to report swelling of their arms and legs, hair thinning, hot flashes, and weight gain. Women who had not taken tamoxifen prior to taking an AI were more likely to report insomnia, bone pain, mental fuzziness, muscle pain, diarrhea, shortness of breath, flu-like symptoms, headaches, and vomiting. Only one side effect, vaginal bleeding, was reported by a significantly greater percentage of women who had taken tamoxifen before taking an AI.
- Only one side effect, bone fractures, occurred in a significantly greater percentage of women being treated for active disease, compared to women taking an AI to reduce their risk of recurrence. The absolute difference observed was small.

34 $X^2(3) = 8.91$, p = .031.

35 $X^2(3) = 13.9$, p = .003.

DISCUSSION

Side Effects

The sample of respondents is self-selected and the results cannot be generalized to the larger population of women taking AIs. However, this self-selection provided us with subjects from a wider range of ages than women in clinical trials. The results from the younger women responding to our survey indicate that this population of women who are taking AIs should possibly be given AIs more cautiously and followed more closely.

> **"I wanted my life back. My family said I had lost my spirit."**
>
> *—50- to 59-year old survey respondent who quit AI*

The results on side effects presented in this report replicate the results from BCA's preliminary report in 2007. Almost all the women reported experiencing at least one of the 38 side effects listed in the survey, and more than half reported experiencing hot flashes, bone pain, tiredness, muscle pain, and insomnia.

In our preliminary report, the most common additional side effects women reported were joint pain, arthritis and stiffness, and other joint-related side effects. In the current report, over 30% of the 1,199 women who responded to the survey reported and joint/bone/nerve-related side effects. This is somewhat less than the 44% to 47% of women who reported joint stiffness and pain in a cross-sectional study of 200 patients attending the academic practice at Columbia University (Crew et al., 2006), but somewhat more than the 20% to 30% incidence of musculoskeletal disorders reported in several large adjuvant trials of AIs reported between 2000 and 2004 (Crew et al., 2006). In this respect, our population of women does not appear much different from the women in AI clinical trials.

The fact that many women taking AIs cite bone and joint (and/or joint-related) side effects is consistent with the literature documenting estrogen's effects on bones and joints. Aromatase is an enzyme that converts the hormone androgen into estrogen. Androgen is produced by the adrenal gland and is found throughout the body. It is the principle source of estrogen in postmenopausal women.

Over 20% of the women who responded to BCA's AI Side Effects Survey reported that they had osteoporosis (See Figure 5), and 1.5% listed osteopenia or bone loss as an additional side effect (see Table 3). The National Health and Nutrition Examination Survey (NHANES III, 1988-1994) reported that 56% of women 50 years old and older in the United States had some bone loss, that 16% of them (or 10.6% of the whole population) had osteoporosis, and that the prevalence of reduced bone density in American women increases dramatically with increasing age from 37% in 50- to 59-year-olds to 87% in women 80 years old or older (NHANES III, 1988-1994).

The women who responded to our survey ranged in age from 20- to 29-years-old to 80-plus-years-old. However, unlike the NHANES sample, we did not find a significant difference between the younger and older age groups and their reporting of osteoporosis, though we expected an even greater difference given the wider age range. One possible implication is that the younger women who responded to our survey were developing bone loss as frequently as the older women, perhaps because of AI use, and the fact that many of these women were experiencing menopause at a younger age and more abruptly than would normally be expected. In a paper on bone loss associated with cancer therapy, Guise (2006) proposed that, at the start of treatment with AIs, baseline bone density tests be done on all women and repeated thereafter at regular intervals.

Estrogen is also produced locally in women's (and men's) brains. Since AIs interfere with the catalytic activity of

aromatase, "in principle, they will inhibit estrogen biosynthesis in every tissue location of aromatase, leading to… bone loss and possibly loss of cognitive function" (Simpson & Dowsett, 2002). Forty-six percent of the women who responded to the survey reported that they were experiencing mental fuzziness (See Figure 5), and a further 1.9% listed some kind of cognitive impairment (e.g., poor memory, inability to plan, etc.) as an additional side effect (See Table 3).

It is unclear at this point whether these cognitive side effects are reversible or not. It is not known exactly what these women meant when they checked "mental fuzziness" as a side effect, but one plausible hypothesis is that they are experiencing and reporting the early signs of the loss of some cognitive functions. One woman who completed the survey wrote: "I'd be interested to see the 'mental fuzziness' broken down into more detail. In my experience, it's short-term memory and hence multitasking that took a hit. Fuzziness doesn't quite describe it. The cognitive side effects worry me more than any other—in part because they may not be reversible."

Noncompliance

In contrast to the 5% of patients in the large adjuvant trials of AIs who discontinued therapy because of toxic effects (Crew et al., 2006), a much greater percentage of women (27.8%) in this study report that they stopped taking their AI because of side effects. Given that women who participate in clinical trials tend to be compliant and reluctant to leave a trial early, it is to be expected that a greater percentage of women outside the clinical trial setting will stop taking their AI because of side effects. In addition, those who completed our survey came from a self-selected population. Still, it is interesting to note that the rate of noncompliance in a study conducted by the Ottawa Hospital Regional Cancer Center was also much greater (18.9%) than those seen in AI clinical trials, and the authors indicate that noncompliance in the clinical setting "merits serious attention" (Dent, 2007).

It is also interesting to note the reasons that women gave for discontinuing use. Although two-thirds of the women who responded to the survey reported experiencing hot flashes, this side effect was not the most cited as a reason for noncompliance. Only 14 women (4.2%) who discontinued use cited hot flashes as a reason for stopping. Also, 21% of women listed osteoporosis as a side effect they were experiencing, yet only 2.4% of those who discontinued AI use listed bone loss or fractures as a reason for stopping. Some side effects are more easily treated with medications or may not impact the quality of life as severely as others, so while they are more common, they may not be the side effects of most concern to patients when deciding whether or not to continue use.

The most commonly cited cause for discontinuing their therapy was pain—joint pain or joint-related pain, bone pain, muscle pain, vaginal pain, bladder pain and/or chest pain. Studying the side effects that women report on AIs is important, but additional studies must focus on the reasons women state for discontinuing AI use, as they are not necessarily the most common side effects. Despite a lower rate of noncompliance, the number of women being treated for active disease who stopped taking their AI due to side effects reflects the importance of addressing AI side effects and quality-of-life issues.

> **"Severe joint pain. Extreme fatigue. Hot flashes. Felt like I was 80 years old rather than 43."**
>
> *—40- to 49-year old survey respondent who quit AI*

Further research in this area could reveal important tradeoffs that women are facing when choosing whether or not to remain on AIs. Open lines of communication between medical professionals and breast cancer patients are essential for addressing these important quality-of-life issues and can facilitate doctors and patients jointly pressing for additional research on the side effects of AIs.

For many women the benefits of AI use outweigh the

associated side effects and risks. However, for a subset of women, the quality-of-life issues associated with AI use are serious enough to result in their discontinuation. Women must be given full information about the benefits and risks of taking AIs so that they can make the informed decision that is right for them.

The Women, Their Age, and Their Treatment

The women who responded to our survey differ in important ways from the women who participated in AI clinical trials that led to the FDA approval. The characteristics of women who responded also allowed us to investigate differences between subgroups of women being treated with an AI.

First, the women who responded to this survey were, on average, ten years younger the women who participated in the trials, and our results indicate that younger women were more likely to experience some side effects, such as bone pain and hot flashes, the two most common AI-related side effects.

Secondly, unlike the women in the trials, almost half of our survey respondents were premenopausal and had either a surgically or pharmaceutically induced menopause. Premature and abrupt beginning of menopause and cessation of estrogen may lead to exacerbation of menopausal symptoms (Jones et al, 2007; Felson & Cummings 2005), which may be additionally aggravated by the aromatase inhibiting activity of AIs. Younger women were much more likely than older women to have had their menopause induced.

From our survey data, it is not possible to ascertain the age at which the women's menopause occurred or whether cases of induced menopause were directly related to breast cancer medications (chemotherapy, tamoxifen use) or other medical reasons (use of LHRH agonists, surgical removal of ovaries). However, regardless of age or whether menopause was induced through medical treatment or occurred naturally, the resulting effect would still be lowered levels of circulating estrogen.

Compared to women who became menopausal naturally, a significantly greater percentage of the women whose menopause was induced reported swelling of their arms and legs, hair thinning, hot flashes, and weight gain. The incidence and severity of these side effects may be related to the sudden and premature onset of menopause in younger women.

Thirdly, our results indicate a larger percentage of women who had not previously taken tamoxifen experienced insomnia, bone pain, mental fuzziness, muscle pain, diarrhea, shortness of breath, flu-like symptoms, headaches, and vomiting, as compared to women who had taken tamoxifen prior to an AI. It may indeed be as Coombes et al. (2007) have suggested: "Early exposure to tamoxifen would… through its oestrogenic effects, ameliorate some of the adverse effects of aromatase inhibitors, such as excess calcium loss." The youngest women (20- to 39-year-olds) were significantly less likely to have taken tamoxifen prior to taking an AI, as compared to the older age groups.

Finally, unlike the women in early AI clinical trials, only 12% of the respondents to our survey were taking an AI to treat active disease. Over a third of the younger women (20- to 49-year-olds) were taking an aromatase inhibitor for active disease. Only one side effect, bone fractures, was reported by a significantly greater percentage of women who were being treated for active disease, though the absolute difference was small. The reason that bone fractures occur in a larger proportion of women being treated for active disease cannot be determined from the survey data. Whether the fractures were related to bone metastasis, osteoporosis, or a combination of the two also cannot be determined.

In summary, age—either alone or in conjunction with treatment (induced menopause or prior tamoxifen use)—appears to be related to the incidence and/or severity of the AI side effects the women experienced and reported.

CONCLUSIONS AND RECOMMENDATIONS

While the population of survey respondents is not necessarily representative of all women taking AIs, it is clear that aromatase inhibitors are being prescribed for a significant number of younger women, women much younger than those who have been studied in clinical trials. The younger women who responded to the survey were more likely to have reported experiencing hot flashes and bone pain. They were also more likely to have had their menopause induced, which was associated with an increased incidence and severity of hot flashes, weight gain, hair thinning, and swelling of their arms and legs.

At present no empirical data exist on the role or efficacy of ovarian function suppression or ablation with AI use in premenopausal women (Eisen, et al., 2007). Trials are underway that are studying the combination of ovarian suppression followed by AI use (IBCSG-2402, IBCSG-2502, FHCRC-6412) but it is not a currently FDA-approved use of AIs.

BCA has also learned anecdotally that some oncologists are prescribing AIs to patients with ductal carcinoma in situ (DCIS) or to women who have not had a diagnosis of breast cancer but are considered high risk, despite the absence of data or approval for these uses. These women—women diagnosed with DCIS, and high risk women with no breast cancer—should be fully informed that when a doctor prescribes an AI for them, that this is an off-label use of AIs in their situation. BCA is concerned about this off-label use because clinical trial data have not yet established safety or efficacy of AIs in this setting. These women should be monitored long-term for both side effects and efficacy.

The youngest women who responded to our survey (20- to 39-year-olds) were less likely to have taken tamoxifen prior to taking an AI and were more likely to have an increased incidence and severity of bone pain, muscle pain, insomnia, mental fuzziness, headaches, shortness of breath, flu-like symptoms, vomiting, and shortness of breath. Clearly, our findings indicate that this population of women who are taking AIs should be studied more closely.

Our findings also show that menopausal history and tamoxifen use are confounded with age. Unfortunately, our data do not allow the possibility of separating the effects of menopausal history or tamoxifen use from age. Additionally, we did not ask women to specify the time interval between tamoxifen use and AI use, which may relate to the potential for tamoxifen to mitigate the toxicities of AIs. Future research could further investigate AI side effects in women who switched directly from tamoxifen to an AI, and women who perhaps took tamoxifen when first diagnosed then took an AI years later with a diagnosis of a recurrence or metastasis.

Baseline measurements and regular bone mineral density testing are currently recommended for all patients taking AIs to monitor their bone loss. A similar follow-up testing protocol should be established for cognitive functioning in women who are taking AIs and ideally should be compared to a control group of women who are not taking an AI. This would make it possible to investigate whether the cognitive performance of women taking an AI was declining more or less rapidly than women who were not taking an AI, and would help address the concern about whether these side effects are reversible.

Pain (joint-pain, joint-related pain, bone pain, muscle pain, vaginal pain, bladder pain, and chest pain) was the side effect cited most often by the women who stop taking their AI. As previously stated, Felson and Cummings (2005) noted that a rapid drop in estrogen levels may cause an increase in pain sensitivity, and this warrants further investigation.

For many women the benefits of AIs outweigh the associated side effects. However, for some women the quality-of-life issues are serious enough to result in their discontinuation of AI use. Women must be given full information about the

benefits and risks of taking AIs, so that they can make an informed decision that is right for them.

The results of our data strongly suggest that new trials should be designed to examine:

- AI use and side effects in younger women.
- AI use and side effects in women who have had their menopause induced surgically or pharmaceutically.
- AI use with and without prior use of tamoxifen and associated side effects in women of all ages.
- Long-term side effects in women of all ages taking AIs, including systematic monitoring for bone, joint, and nerve side effects, with comparisons to control populations. We should also monitor patients for emerging side effects that may not be identified yet.
- Long-term cognitive side effects in women of all ages taking AIs, including systematic monitoring of cognitive changes, with comparisons to control populations.

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"I switched AI's because of the stiffness I was experiencing. The stiffness is still present but to a lesser extent."

—70- to 79-year old survey respondent

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—50- to 59-year old survey respondent

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