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Acceptability and Adherence in a Chemoprevention Trial among Women at Increased Risk for Breast Cancer Attending the Modena Familial Breast and Ovarian Cancer Center (Italy)

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■ **Abstract:** Chemoprevention for women at risk for breast cancer has been shown to be effective, but in actual practice, women's uptake of chemoprevention has been poor. We explored factors that influence acceptability, adherence, and drop-out in the International Breast (Prevention) Intervention Study during our first 3 years of activity at the Modena Familial Breast and Ovarian Cancer Center. We evaluated socio-demographic characteristics, health status, adherence, and side effect intensity. Semi-structured interviews analyzed reasons for accepting/refusing/stopping the trial. A total of 471 post-menopausal women were invited to participate, of which 319 declined to participate (68%), 137 accepted to participate (29%), and 15 participants did not make a final decision (3%). Breast cancer-related worries and trust in our preventive and surveillance programs were the most frequent reasons for accepting. Side effect-related worry was the most frequent reason for refusing. General practitioners' and family members' opinions played an important role in the decision-making process. Adherence significantly decreased after a 12-month follow-up, but it remained unchanged after 24- and 36-month follow-ups. Mild/moderate side effects reported by women did not change after 12 months of treatment. Forty percent of women withdrew from the study due to complaints of side effects. We concluded that chemoprevention trials are difficult medical experiments and that the process of deciding about whether or not to participate is based mainly on beliefs and values. This study has important clinical implications. During counselling with prospective participants, it is important to emphasize the potential benefits and to promote an informed choice. How participants make decisions, their belief systems, and their perception of risk are all factors that should be investigated in future research. ■

Key Words: acceptability, breast cancer risk, chemoprevention, compliance

Breast cancer (BC) is the most frequent malignancy among women in western countries. Although mortality is declining, incidence continues to increase and, therefore, prevention is an important aim in health care management (1). A number of factors are associated with an increased risk of BC. Some of them are important and well-established BC risk factors such as gender, age, residence, family history, hereditary breast-ovarian cancer syndrome, and presence of deleterious mutations into BRCA1 and BRCA2 genes, breast density, and previous BC. Other factors take into account: menstrual and reproductive history, endogenous and exogenous hormones, body size, and lifestyle behaviors, medical history, and environmental exposures. A correct evaluation of combination of these risk factors is the best approach to estimate a woman's risk of developing BC, and chemoprevention should be considered for those found to be at high risk. Among preventive actions, chemoprevention for cancer is a worthy goal, and there is tremendous effort underway to expand the development of new chemoprevention agents for breast and other cancers (2). Results of large randomized trials using such agents as

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tamoxifen and raloxifene for prevention among high-risk women have shown relative reductions in BC risk from 38% to 50% (3–10). Particularly, STAR study showed that with a median follow-up of 81 months (5) raloxifene retained the same effectiveness of tamoxifen in preventing invasive disease and grew closer over time to tamoxifen in preventing noninvasive disease, with far less toxicity. In 2009, the American Society of Clinical Oncology published the last update of the guidelines on pharmacologic interventions for BC risk reduction emphasizing and specifying the role of tamoxifen, raloxifene, aromatase inhibitors, and Retinoids as preventive agents (11). Recently, The NCIC Clinical Trials Group MAP.3 (exemestane versus placebo) has shown that exemestane significantly reduced invasive BC in postmenopausal women reduction who were at moderately increased risk for BC; at a median follow-up of 35 months they found a 65% relative reduction in the exemestane group (12).

Chemoprevention of BC is a worthy goal, which needs to be achieved with as little iatrogenic harm as possible to be acceptable. Cancer chemoprevention trials have proven to be a difficult medical experiment because they are conducted on people who, albeit at increased risk for a given neoplasm, are unaffected (13,14). Concerning tamoxifen, some studies reveal high levels of interest and acceptability among high-risk women (15) whereas other studies suggest that high-risk women are likely to opt against it for reasons such as side effect-related worry, bias against taking medication, and difficulty in understanding information about the drug (16,17).

Dropout rates in studies with tamoxifen to date have been variable, between 25% and 35%, and may well account for some of the conflicting results (18). Studies about adherence in BC prevention trials are few, although it is a major issue that can distort results and increase costs.

In the present work, we explore socio-demographic and other factors that influence acceptability, adherence, and drop out in Italian women eligible for International Breast Intervention (Prevention) Study (IBIS II), which compares 5 years of anastrozole treatment (1 mg/day) with placebo in postmenopausal women at increased risk for BC (19) during our first 3 years of activity. Specifically, we want to assess dropout rates, level of adherence, the motivation that influences the decision-making process, explore the hopes, expectations, perceived incentives for, and barriers to participating in the IBIS II prevention trial.

MATERIALS AND METHODS

IBIS II (Prevention) Study

The IBIS II prevention study is a multi-centered, double-blind, placebo-controlled, randomized trial which compares 5 years of anastrozole treatment (1 mg/day) with placebo in 6,000 postmenopausal women who are at increased risk of BC (19,20). To be eligible, women had to be postmenopausal, aged between 40 and 70 years, and at increased risk of BC. Increased risk was determined from family history (first-degree relatives with BC under 50 years of age or two or more second-degree relatives with BC), previous benign disease with evidence of proliferation or atypia; mammographic dysplasia; or nulliparity plus any first degree family history.

The protocol was approved by the NorthWest Multi-Centre Research Ethics Committee and by the Ethics Committee of Modena General Hospital.

Procedure and Participants

From June 2007 to November 2010, 471 healthy, postmenopausal women aged between 40 and 70 years (mean age: 58.91 ± 5.72) at increased risk of developing BC, who had met the inclusion criteria of the IBIS II prevention study and were attending our surveillance program at Modena Familial Breast and Ovarian Cancer Centre, received information about the trial. All of these women periodically attend the surveillance program at our center. In particular, mammography (oblique and craniocaudal views and, if necessary, compression views and magnifications), ultrasonography and clinical breast examination for BC prevention, and transvaginal ultrasound plus Ca125 serum levels for early diagnosis of ovarian cancer are proposed at different intervals based on the assessed risk (21). A breast MRI annual screening is proposed to BRCA carriers or, in the case of 30% or greater probability of developing BC, evaluated by BRCAPro model.

Women were invited to participate in an educational and informational interview, where oncologists from the center, together with a psychologist, provided information about the study. A 1-hour session was organized to allow women to ask questions and have their concerns about the study clarified. Leaflets describing the study were also given to the women at the end of the session. The leaflets included

information about the time-line of the study, the study's main objective, management of data, a definition of placebo, information about the side effects of anastrozole, and dosage of pills.

Study Design

The study was designed and carried out in a series of steps (Fig. 1):

1. "Informative Step": informative counselling was given to all women eligible for the IBIS II prevention study. In this step, women were interviewed about their reasons for participating or refusing to participate in the trial and provided socio-demographic data.
2. "Acceptance Step": women who accepted to participate gave their signed consent, completed a health- and lifestyle-related schedule, and planned the above-mentioned investigations.
3. "Randomization Step": randomization is double-blinded and occurs automatically via the Cancer Research UK system through the use of dedicated software for the trial. Successfully randomized women each received a numbered light-proof container which had a 6-month supply. Each container also had extra pills to allow for some delay until the next appointment (routine follow-up steps).
4. "Routine Follow-up Steps": 6-, 12-, 24-, and 36-month follow-up appointments were scheduled for the study participants.
5. "Dropout Step": this step occurred when the women wanted or needed to stop the treatment. These women met with the researchers to complete the final form schedule and were interviewed about their reasons for leaving the study.

Measures

The women participating in this research filled out the following questionnaire:

1. Socio-demographic schedule asking for the following: their age, their marital status, their educational level, and their occupational status.
2. Health- and lifestyle-related schedule asking about the following: their offspring, their body mass index (kg/m^2), whether they smoked (never, former, or current), any previous or current health diseases, and their use of medications.
3. Follow-up schedule assessing: their objective adherence by counting the number of pills returned, their reported side effects using a four-point scale (1 = none, 2 = mild, 3 = moderate, 4 = severe), any serious adverse events, and other symptoms.

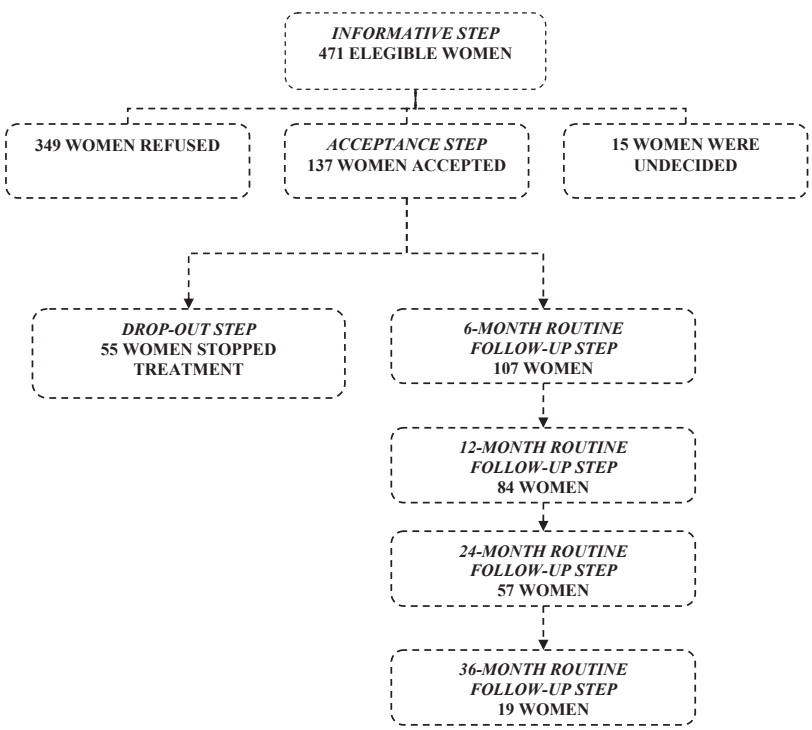

Figure 1. A flowchart illustrating the process and number of women who attended the initial visit and the eventual outcome.

4. Final Form schedule evaluating: their objective adherence by counting the number of pills returned, their reported side effects using a four-point scale (1 = none, 2 = mild, 3 = moderate, 4 = severe), any serious adverse events, and other symptoms.

Semi-structured interviews were conducted during both the informative and dropout steps. The researchers asked open-ended question about the women's willingness to take part in this study and recorded their answers on a designated form. These answers where then analyzed and sorted into different categories.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS/PC, release 15.0) was used for all of the analyses. Continuous variables are presented as a mean and standard deviation while other data are presented as a number (percentage) of women. To test age and educational level differences between women who accepted and those who refused to participate in the IBIS II, a between-subjects *t*-test was used. To test the other socio-demographic data, a Chi-squared test was used. To explore health habits, reasons for participating or refusing to participate in the trials, and the reason for stopping the treatment, frequency tables were constructed. Finally, for women who completed 12, 24, and 36 months of treatment, we explored adherence (mean number of pills taken) using a *t*-test for repeated measures and ANOVA for repeated measures. Moreover, differences in side effects were examined using Wilcoxon and Friedman tests for repeated measures.

RESULTS

Socio-Demographic Characteristics, Acceptability, and Dropout Rates of the Sample

The main socio-demographic characteristics of the women participating in this study appear in Table 1.

Of the 471 eligible women who took part in the informative step, 319 (68%) declined to participate in the trial, 137 (29%) agreed to participate in the trial, and 15 (3%) did not make a final decision. Statistical analysis reveals that participation in the trial is not affected by age, marital status, educational level, or number of family members diagnosed with BC.

At the end of November 2010, of the 137 participating women, 107 (78%) completed 6 months of treatment, 84 (61%) completed 12 months of treatment, 57 (42%) completed 24 months of treatment, 19 (14%) completed 36 months of treatment, and 55 (40%) withdrew from the study. Among the members of the dropout subgroup, 25 women stopped the trial before the 6-month follow-up, 16 stopped between the 6- and 12-month follow-up, and 14 stopped between the 12- and 24-month follow-up.

In terms of the socio-demographic features for the 137 participating women, 118 (86%) have children, 72 (53%) have never smoked, 53 (46%) are of normal weight and 65 (48%) are overweight. In addition, 43% of these women were retired at the time of recruitment.

With regard to their medical history, 42 (31%) suffered from cardiovascular diseases (mostly hypertension), 3 (2%) had diabetes mellitus, 4 (3%) had a history of thrombo-embolic episodes, 13 (9%) previously had fractures, 53 (39%) had a gynecological disease, and 13 (9%) previously had cancer.

Reasons for Participating or Refusing to Participate in the Trial

A semi-structured interview was conducted during the initial session/meeting that aimed to evaluate the reasons for participating or refusing to participate in the IBIS II study. Table 2 summarizes all of the reasons given for participating or refusing to participate in the trial. After the informational interviews, 15 (22.8%) women remained undecided for three main reasons: 7 needed more time to think about their participation; 3 were waiting for the results of a medical examination; 2 needed more information about the study and/or wished to talk with their General Practitioner (GP) about their potential participation.

We divided our sample into two categories (women who participated and women who refused to participate), and we analyzed their personal reasons by grouping them into different categories.

Among the 137 women who agreed to participate, the reasons reported were as follows: 68 women (50%) said that they were worried about the risk of getting BC and, thus, they wanted to participate; 51 women (37%) felt confident about our work and agreed to participate because they trusted our expertise in preventive activities; 12 women (9%) expressed their desire to improve BC research; six women (4%) decided to participate after receiving the support from their GP.

Table 1. Socio-Demographic Characteristics of the Sample (*N* = Number of Women)

	Total sample *N* = 471	Women who participated *N* = 137 (29%)	Women who refused to participate *N* = 319 (68%)	Women who were undecided *N* = 15 (3%)	Women who participated versus women who refused
Age					
Mean age (years ± SD)	59 ± 6	59 ± 6	59 ± 6	59 ± 5	$t = 0.46$ p = 0.50*
Range (years)	40–70	44–70	40–70	50–69	
Marital status					
Married	376	102	260	14	$\chi^2 = 3.99$
Not married	64	20	42	2	p = 0.14†
Widow	31	14	17	0	
Educational level					
University	39	7	1	1	$\chi^2 = 3.40$
High school	149	42	102	5	p = 0.49†
Less than high school	283	87	186	10	
Number of family members diagnosed with breast cancer					
≤3	423	127	314	12	$\chi^2 = 5.17$
>3	48	9	35	4	p = 0.64†

*t-test between women who accepted and women who refused to participate.
†Chi-squared-test between women who accepted and women who refused to participate.

Table 2. Reasons for Participating or Refusing to Participate in the Trial

	N (%)
Women who accepted to participate (*N* = 137)	
They were worried about the risk of getting breast cancer	68 (50)
They felt confident about our surveillance and preventive program	51 (37)
They followed their General Practitioner's advice	12 (9)
They wanted to contribute to research	6 (4)
Women who refused to participate (*N* = 319)	
They were worried about the side effects of anastrozole	163 (51)
Their General Practitioner and/or family members advised them against participating in the trial	61 (19)
They currently had a disease	41 (13)
They did not want to take any kind of drugs	30 (9)
Personal or psychological problems	13 (4)
They disagreed with the study design	5 (2)
They wanted to take hormonal replacement therapy	3 (1)
They had recently moved away	2 (0.7)
She was considering having a prophylactic mastectomy	1 (0.3)
Women who were undecided (N = 15)	
They needed to have more time to make a decision	7 (47)
They were waiting for some medical examination results	3 (20)
They needed more information about the study and wanted to speak with their GP	2 (13)

Among the 319 women who refused to participate, the reasons reported were as follows: 163 women (50%) refused because of concerns about the side effects of anastrozole, explaining that they were healthy, but that they did not want future health problems; 61 women (19%) refused to participate after consulting family members who disagreed with the study, and/or asking their GP who advised them against participating in the trial; 41 women (13%) did not agree to participate due to their current diseases and concern that their health could deteriorate; 30 women (9%) reported that they did not want to take any kind of drugs; 13 women (4%) reported that they were having family problems (the recent death and/or the serious illness of a family member) or psychological problems (anxiety or depression mostly), so they did not feel comfortable in participating in the trial; five women (2%) disagreed with the study design, particularly the long period for the study and the fact that participants may be taking a placebo; 3 women (1%) wanted to take hormonal replacement therapy; two women (0.7%) refused because they had recently moved away and had difficulty getting to our center; one women (0.3%) refused because she was considering having a prophylactic mastectomy.

Evaluation of the Perceived Side Effects After 6, 12, 24, and 36 Months of Treatment

Because the IBIS II involves a double-blind protocol, we could have generally measured the side effects for all members of the participating group only,

without knowing who was actually taking the anastrozole. Therefore, we devoted our attention both to the well-known side effects of anastrozole and to all other kinds of symptoms arising during the period of treatment. During the follow-up interview we verified that the symptoms reported were not present when the participating women were randomized.

In keeping with the IBIS II protocol, we evaluated the side effects of treatment for all randomized women at 6, 12, 24, and 36 months of follow-up using a four-point scale for each common side effect (1 = none, 2 = mild, 3 = moderate, 4 = severe). Women were asked to evaluate the side effects that appeared during the period of treatment by using this scale. We also analyzed all perceived symptoms and serious adverse events if they occurred.

As reported on Figure 1, 107 women completed 6 months of treatment, 84 women completed 12 months of treatment, 57 women completed 24 months of treatment, and 19 women completed 36 months of treatment. We analyzed the difference of perceived side effects among these four groups.

Table 3 shows the perceived side effects of 107 women who completed the 6-month follow-up.

Side effects were perceived as mild or moderate in the majority of cases and they were as follows: arthralgia in 36 women, vaginal charge in 14 women, eye disorders in 14 women, hot flushes and sweating at night in 11 women, and osteoporosis in three women. Other main symptoms reported by the participants included the following: headaches for 10 women, sleep disorders for 11 women, muscular disorders for eight women, fatigue for five women, weight gain for three women, alopecia for three women, hypercholesterolemia for three women, hypertension for three women, pruritus and dermatitis for three women, nausea for two women, and lack of concentration for two women.

We analyzed the differences between symptoms reported at the 6-month follow-up and those reported at the 12-month follow-up in 84 women who completed the 12-month follow-up. As shown in Table 4, perception of arthralgia and vaginal changes significantly varied whereas other symptoms remained unchanged. A Wilcoxon nonparametric test for repeated measures revealed that, at the 6-month follow-up, 21% of the women perceived mild arthralgia and 8% of them perceived moderate arthralgia, but at the 12-month follow-up, 23% of the women perceived this symptom as mild and 17% of them reported it as

Table 3. Evaluation of the Common Side Effects of Anastrozole on Women Who Completed the 6-Month Follow-up

Side effects	6-month follow-up (*N* = 107) (%)
Arthralgia	
None	71 (66)
Mild	23 (22)
Moderate	11 (10)
Severe	2 (2)
Hot flushes/sweating at night	
None	69 (64)
Mild	2 (27)
Moderate	6 (6)
Severe	3 (3)
Vaginal change	
None	93 (87)
Mild	11 (10)
Moderate	1 (1)
Severe	2 (2)
Irregular vaginal bleeding	
None	107 (100)
Eye disorder	
None	93 (87)
Mild	14 (13)
Osteoporosis/fractures	
None	104 (97)
Mild	3 (3)

Table 4. Evaluation of Differences in Common Side Effects of anastrozole Across 6 and 12 Months of Follow-up for Women Who Completed the 12-Month Follow-up

Side effects	6-month follow-up *N* = 84 (%)	12-month follow-up *N* = 84 (%)	p*
Arthralgia			
None	59 (71)	50 (60)	0.022
Mild	17 (21)	19 (23)	
Moderate	7 (8)	14 (17)	
Severe			
Hot flushes/sweating at night			
None	58 (69)	56 (66)	n.s.
Mild	21 (25)	19 (23)	
Moderate	4 (5)	9 (11)	
Severe	1 (1)		
Vaginal change			
None	76 (90)	67 (80)	0.012
Mild	8 (10)	14 (17)	
Moderate		2 (3)	
Severe			
Irregular vaginal bleeding			
None	84 (100)	84 (100)	n.s.
Eye disorder			
None	76 (90)	71 (84)	n.s.
Mild	8 (10)	12 (15)	
Moderate		1 (1)	
Osteoporosis/fractures			
None	84 (100)	83 (99)	n.s.
Mild		1 (1)	

*Wilcoxon nonparametric test for repeated measures.

moderate. In terms of vaginal changes, at the 6-month follow-up, only 10% of the women perceived it as mild, whereas at the 12-month follow-up, this side effect was perceived as mild for 17% of the women and as moderate for 3% of them.

No one had irregular vaginal bleeding both after 6 and 12 months. Mild osteoporosis was reported only at the 12-month follow-up by one woman. The majority of the group did not report hot flushes and sweating at night, one woman reported these symptoms as severe only after 6 months. Concerning eye disorders, after 12 months, 12 women reported this symptom as mild and one woman as moderate. Other symptoms reported were: muscular disorders in eight women, weight gain in five women, insomnia or sleep disorders in five women, pruritus and dermatitis in four women, fatigue and weakness in three women, alopecia in two women, hypercholesterolemia in two women, hypertension in two women, vascular disorders in two women, and headaches in two women.

For the 57 women who completed the 24-month follow-up and the 19 women who completed the 36-month follow-up, we did not find any significant changes in the intensity of side effects compared to after 12 months of treatment (Tables 5 and 6). The majority of the group did not complain about the side effects of anastrozole, and Wilcoxon and Friedman nonparametric tests for repeated measures did not show any significant differences.

In particular, we noticed that at the 6-month follow-up, headaches and sleep disorders were quite common whereas they rarely occurred in the group at the 12-month follow-up. Moreover, the number of women who experienced weight gain appeared to increase over the treatment.

In terms of serious adverse events, they occurred during the four controls. After 6 months, six women reported serious adverse events (cardiac arrhythmia, pruritic dermatitis, fractures, glottis edema, thyroid cancer, bunions). After 24 months, one woman got melanoma in situ. No serious adverse events occurred at the 12- and 36-month follow-ups. Thus far, no participant who was randomized into the trial has developed BC.

Adherence During the Trial

Adherence during the trial was evaluated by counting the number of pills returned in a specific pillbox with the number of days of treatment using the formula: [number

Table 5. Evaluation of Differences in Common Side Effects of Anastrozole Across 12 and 24 Months of Follow-up for Women Who Completed the 24-Month Follow-up

Side effects	12-month follow-up *N* = 57 (%)	24-month follow-up *N* = 57 (%)	p*
Arthralgia			
None	37 (65)	35 (62)	n.s
Mild	12 (21)	19 (33)	
Moderate	8 (14)	3 (5)	
Severe			
Hot flushes/sweating at night			
None	42 (74)	41 (72)	n.s.
Mild	10 (17)	16 (28)	
Moderate	5 (9)		
Vaginal change			
None	48 (84)	46 (81)	0.05
Mild	9 (16)	11 (19)	
Irregular vaginal bleeding			
None	57 (100)	54 (95)	0.05
Mild		3 (5)	
Eye disorder			
None	49 (86)	52 (91)	n.s
Mild	8 (14)	4 (7)	
Moderate		1 (2)	
Osteoporosis/fractures			
None	57 (100)	55 (96)	n.s.
Mild		1 (2)	
Moderate		1 (2)	

*Wilcoxon nonparametric test for repeated measures.

Table 6. Evaluation of Differences in Common Side Effects of Anastrozole Across 6, 12, 24, and 36 Months of Follow-up for Women Who Completed the 36-Month Follow-up

Side effects	12-month follow-up *N* = 19 (%)	24-month follow-up *N* = 19 (%)	36-month follow-up *N* = 19 (%)	p*
Arthralgia				
None	10 (53)	11 (58)	10 (53	n.s.
Mild	5 (26)	7 (37)	7 (37)	
Moderate	4 (21)	1 (5)	2 (11)	
Severe				
Hot flushes/sweating at night				
None	12 (63)	11 (58)	14 (74)	n.s.
Mild	5 (26)	8 (42)	5 (26)	
Moderate	2 (11)			
Vaginal change				
None	16 (84)	15 (79)	16 (84)	n.s.
Mild	3 (16)	4 (21)	2 (11)	
Moderate			1 (5)	
Irregular vaginal bleeding				
None	19 (100)	19 (100)	19 (100)	n.s.
Eye disorder				
None	16 (84)	17 (90)	18 (95)	n.s.
Mild	3 (16)	1 (5)	1 (5)	
Moderate		1 (5)		
Osteoporosis/fractures				
None	19 (100)	19 (100)	18 (95)	n.s.
Mild			1 (5)	

*Friedman nonparametric test for repeated measures.

Table 7. (a) Women Who Completed 12 Months of Treatment (*N* = 84): Evaluation of Differences Between Compliance at 6 Months of Treatment and 12 Months of Treatment (*t*-test for repeated measures). (b) Women who completed 24 months of treatment (*N* = 57): Evaluation of differences between compliance at 12 months of treatment and 24 months of treatment (*t*-test for repeated measures). (c) Women who completed 36 months of treatment (*N* = 19): Evaluation of differences among compliance at 12, 24, and 36 months of treatment (ANOVA for repeated measures)

(a)

	AFTER 6 months of treatment	AFTER 12 months of treatment	*t*	p
Mean of pills taken (±SD)	176 ± 21	165 ± 26	4,062	0.000

(b)

	AFTER 12 months of treatment	After 24 months of treatment	*t*	p
Mean of pills taken (±SD)	341 ± 44	344 ± 49	0.419	0.677

(c)

	After 12 months of treatment	AFTER 24 months of treatment	AFTER 36 months of treatment	*F*	p
Mean of pills taken (±SD)	353 ± 13	346 ± 49	340 ± 45	0.810	0.452

of days of treatment—pills returned = numbers of pills taken]. We evaluated adherence in the three groups: 84 women completed 12 months of treatment, 57 women completed 24 months of treatment, and 19 women completed 36 months of treatment. We analyzed differences in adherence with the trial across these three groups, as shown in Table 7.

Among the 84 women who completed 12 months of treatment, we evaluated the differences between mean number of pills taken at 6 months (176 ± 21) and mean number of pills taken at 12 months (165 ± 26) using a *t*-test for repeated measures, and we found a significant difference in adherence after 12 months ($p = 0.000$). Adherence significantly decreased after 1 year of follow-up. Among the 57 women who completed 24 months of treatment, a *t*-test for repeated measures found no significant difference between the mean number of pills taken at 12 months of treatments (341 ± 44) and the mean number of pills taken at 24 months of treatment (344 ± 49). Finally, for the 19 women who completed 36 months of treatment, we performed an ANOVA for repeated measures across the mean number of pills taken at 12 months (353 ± 13), the mean number of pills taken at 24 months (346 ± 49), and the mean number of pills taken at 36 months (340 ± 45). No significant differences were found.

Dropout

Fifty-five women (40%) decided to stop the treatment. Figure 2 shows the cumulative dropouts. As we can see, three women stopped the treatment during the first month. They did not take any pills and returned to our clinic with a full pillbox. These women reported that they did not start the trial because of several reasons: one said that her GP advised her against participating in the trial; one said that her family members strongly disagreed with the trial; one said that she had serious family problems and did not feel confident enough about starting the trial. There were no women who stopped the trial after less than 1 month of treatment. Moreover, 22 women dropped out of the study within the first 6 months of treatment, 16 women stopped within 12 months, 10 women stopped within 24 months, and four women stopped within 36 months.

Reasons for stopping the trial are summarized and shown in Table 8. The most frequent reason given for stopping the trial was the perceived side effects of anastrozole. Forty women (73%) ceased participation because they could not tolerate further side effects. They perceived that their condition was getting worse, and they wanted to stop the treatment. The other reasons given for ceasing treatment were as follows: seven women (13%) were worried about the perceived symptoms unrelated to anastrozole; four women (7%) stopped due to family or relational problems; two women (3%) said that their GP or other specialist advised them against continuing the trial; one woman (2%) stopped because family members disagreed with the trial; and one woman (2%) ceased treatment because a serious adverse event had occurred.

DISCUSSION

Chemoprevention trials among high-risk women have shown to effectively reduce BC risk from 38% to 65% (3,10,12), yet only a minority of high-risk

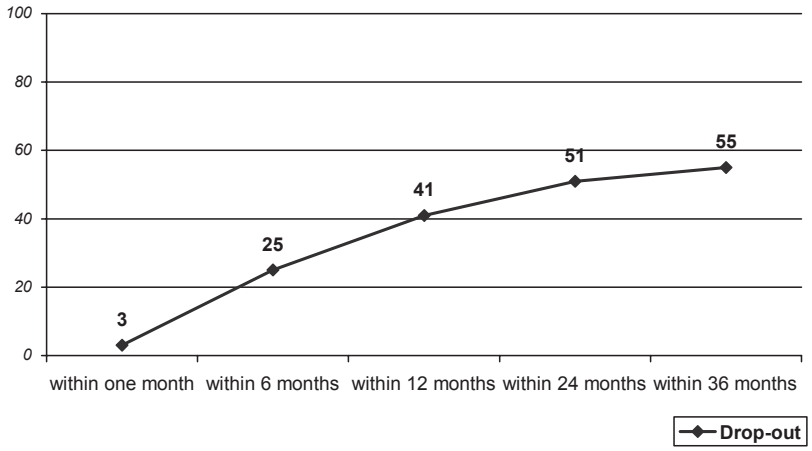

Figure 2. Cumulative dropouts during the first 3 years of treatment.

Table 8. Evaluation of the Reasons Given by Women Who Stopped the Trial (*N* = 55)

Reasons	Number of women (%)
Side effects of treatments	40 (73)
Worry about symptoms perceived but not related to anastrozole	6 (12)
Family or relational problems	4 (7)
General Practitioner or specialist advised against the study	2 (3)
Family members advised against the study	1 (2)
Occurrence of a serious adverse event	2 (3)

women participate in trials (15) compared, for example, to those in cardiovascular research. Few studies have attempted to measure women's interest in chemoprevention, but estimates vary widely (15,17) and influencing factors still remain unclear, even in cases where different factors were evaluated (22).

What we know is that physicians' recommendations, socio-cultural differences, concern about side effects, duration of the trial, psychological variables such as BC perceived risk, BC worry, and related distress strongly influence women's decision (23–25). Recently Rondanina and colleagues (14) found that participation in the chemoprevention trial of low-dose tamoxifen in hormone replacement therapy users was quite high, about a third of the eligible population, and was associated with participants' satisfaction of study personnel, lower BC worry, risk perception, and younger age. Maurice and colleagues (26) found that some factors can influence adherence, such as taking other drugs or having unhealthy habits (like smoking).

In this study, we focused our attention on evaluating acceptance rates and related reasons for participating in the IBIS II Study. Our results have shown that 29% of women who are eligible and invited to join the IBIS II study will participate, which is consistent with other preventive studies (13,15). Fear of developing BC and the perceived benefits of this study play an important role. As mentioned in previous studies, perceived risk is one of the most important factors that influence a woman's choice regarding cancer prevention strategies (14,15). Trust in our preventive activities demonstrates that the decision-making process is not only based on an objective evaluation of benefits and risks but also takes into account one's beliefs and values. In terms of the reasons why women refused to join the study, 51% declined due to concerns of possible side effects. These women felt that the harm (side effects) outweighed the benefits in terms of risk reduction, and this result demonstrated, once again, that chemoprevention trials are difficult medical experiments because they are mostly conducted on people who, although at increased risk for a type of cancer, are unaffected (14). It is likely that these women focused their attention on the potential negative side effects that would affect their present quality of life. This has important clinical implications. When communicating with prospective participants, it is important to emphasize to them the potential benefits of their involvement and clarify them that side effects are not certain, they are not permanent, and that there is wide variation in side effects across individuals. How participants make decisions, their belief systems and their perceptions of risk should be investigated to ensure that women come to an informed decision without misunderstanding, false beliefs or inaccurate information.

Consistent with other research (15,17), our results on participation indicated that not only was the GP's

opinion important but also that the opinion of family members played a critical role in determining the choice of 12% of women who participated and 19% of those who refused to participate. In addition, 13% of women who were undecided said that they needed to talk with their GP before making a decision. We also found that their GP's opinion not only influenced their decision to participate but could also influence their decision to withdraw from the study. In fact, in analyzing the reasons for withdrawing from the study, it was found that two women withdrew because their GP advised them against participating in the trial. Therefore, efforts to increase recruitment to a trial should also include enlisting the support of the GP.

Regarding the evaluation of side effects from this study, an evaluation of the differences between the placebo and anastrozole groups over time would be far more instructive that the simple longitudinal comparison in the anastrozole group alone. For women in this age group, in fact, there will be myriad symptoms among the women taking placebo as was seen in other studies (27,28).

However, we observed that intensity of common side effects tended to be stable over the 3 years and, in general, were mainly mild or moderate when they did occur. Arthralgia changed significantly only after the first year of treatment, but remained substantially unchanged over time, whereas vaginal change and irregular vaginal bleeding tended to grow worse over the 3 years of treatment. Furthermore, we found that after 24 months, sleep disorders, muscular disorders, and weight gain were quite common, whereas after 36 months, they disappeared altogether, but gastrointestinal problems arose.

It remains unclear as to how much the perceived utility of the drug taken influenced women's perception of pain. Future research should be directed toward evaluating the difference between women participating in a chemoprevention trial with anastrozole and women who need to take anastrozole because they have developed BC. It is likely that giving women the same medication, but for opposite reasons (prevention versus cure) influences their perception of the intensity of side effects.

Considering the dropout rate during the 3 years of activity, 55 participating women (40%) stopped the trial, and most of them left the study during the first year, whereas the dropout rate stabilized after 12 months. Reasons for withdrawing within the first months of treatment were mostly due to women rethinking their decision and discussing it with family members or their GP. It is likely that these women were not completely convinced of their decision when they began to participate. It is also possible that the first year of the study is the most challenging for sustaining women's motivation, and their perception of side effects could play a crucial role during this time. Indeed, 73% of these women ceased treatment because of the perceived intensity of side effects, and 12% ceased because they got worried about side effects not strictly related to anastrozole. Our dropout rate (40%) is consistent with results reported in other studies, ranging from 35% reported by Pritchard (18) to 50% reported by Goss et al. (12).

Regarding compliance with the trial, we found that compliance significantly decreased after 1 year of follow-up, but did not change after 24 and 36 months. We could hypothesize that, during the first year, women have some difficulty in getting used to taking pills, but after the first year, they have already developed the habit. However, we must be cautious in interpreting this result because there may be some bias. Each container had extra pills to allow for some delay in the routine follow-up appointment as it was not possible to schedule precisely the routine follow-up for all of the women. Thus, it may be that the time interval influenced our results.

Our findings have several important implications for clinical practice, despite several of the study's limitations, which should be mentioned. Sample size, not knowing who was taking the placebo and who was taking Anatrozole, not being able to set an exact time for the follow-up examinations, the high refusal rate to participate and the declining numbers of women in each follow-up period limited our interpretation and the extent to which we could record our results.

This study was a preliminary evaluation of participation, adherence and dropout rates of the IBIS II prevention study during our first 3 years of activity as a recruitment center, which still continues to recruit women.

Our study has offered us important suggestions about how to improve our recruitment strategy, and it has helped to clarify some aspects regarding adherence and dropout rate in chemoprevention trials using anastrozole.

In conclusion, we could say that lack of understanding during the first informational interviews compromises trial recruitment and gaining informed consent and, in turn, lack of informed consent influences

dropout rates. Providing appropriate information allows participants to clarify their values and to weigh the pros and cons of joining the trial before making a decision, so it is likely that an intervention which promotes informed decision-making would be useful in lowering the dropout rates, as well. Providing support materials, such as booklets containing evidence-based information presented in a clear, succinct form, could improve awareness, offer more realistic expectations, and facilitate informed, independent decision-making.

In other countries such as England (29), where there are higher rates of participation, publicity is an essential part of the recruitment strategy. Staff use leaflets, posters, and promotional videos, publish articles in local and regional newspapers, produce a participant newsletter, organize events such as medical conferences and Race for Life. Taken together, these efforts increase awareness of the trial and its importance among the general public and the media, encourage suitable women to come forward and find out more about the trial, foster an understanding of the eligibility criteria, and ultimately enhance overall recruitment. To sum up, then, it is likely that changing the Italian approach would increase the spread of the study which would, thus, help to increase participation and adherence in the study and to lower dropout rates.

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This study was carried out in accordance with current ethical regulations at the institution concerned. The authors maintain that there were no financial or personal conflicts between themselves and other interested parties that would have otherwise introduced bias into their work. As such, there are no potential conflicts of interest. The authors claim that this is an original, unpublished work that has not been submitted for publication elsewhere at this time.

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