

Cigarette Smoking, Obesity, Physical Activity, and Alcohol Use As Predictors of Chemoprevention Adherence in the National Surgical Adjuvant Breast and Bowel Project P-1 Breast Cancer Prevention Trial

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Abstract

The double-blind, prospective, National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT) showed a 50% reduction in the risk of breast cancer for tamoxifen versus placebo, yet many women at risk of breast cancer do not adhere to the 5-year course. This first report of the rich BCPT drug adherence data examines predictors of adherence. Between June, 1992 and September, 1997 13,338 women at high risk of breast cancer were randomly assigned to 20 mg/d tamoxifen versus placebo; we analyzed the 11,064 enrolled more than 3 years before trial unblinding. Primary endpoint was full drug adherence (100% of assigned pills per staff report, excluding protocol-required discontinuation) at 1 and 36 months; secondary was adequate adherence (76%–100%). Protocol-specified multivariable logistic regression tested lifestyle factors, controlling for demographic and medical predictors. About 13% were current smokers; 60% were overweight/obese; 46% had moderate/heavy physical activity; 21%, 66%, 13% drank 0, 0–1, 1+ drinks per day, respectively; 91% were adequately adherent at 1 month; and 79% were at 3 years. Alcohol use was associated with reduced full adherence at 1 month ($P = 0.016$; OR = 0.79 1+ vs. 0), as was college education ($P < 0.001$; OR = 0.78 vs. high school); age ($P < 0.001$; OR = 1.4 age 60+) and per capita household annual income ($P < 0.001$; OR = 1.2 per \$30,000) with increased adherence. Current smoking ($P = 0.003$; OR = 0.75), age ($P = 0.024$, OR = 1.1), college education ($P = 0.037$; OR = 1.4), tamoxifen assignment ($P = 0.031$; OR = 0.84), and breast cancer risk ($P < .001$; OR = 1.5 high vs. low) predicted adequate adherence at 36 months. There were no significant associations with obesity or physical activity. Alcohol use and smoking might indicate a need for greater adherence support. *Cancer Prev Res*; 4(9); 1393–400. ©2011 AACR.

Introduction

Oral endocrine therapies, including tamoxifen, are an important option in the prevention, as well as treatment, of breast cancer (1). However, poor utilization of self-administered, oral endocrine therapies—that is, electing not to

adopt the regimen, to adhere or conform to the regimen, or to persist or continue through the planned duration—is a significant barrier to the efficacy of such therapies, and there have been calls for research to identify patients most at risk of poor utilization (2, 3). Studies using varying methodologies have, for example, reported tamoxifen non-persistence rates among women with breast cancer ranging from 22% at 1 year to 35% at 3.5 years (4–6). Evidence from tamoxifen treatment trials suggests that individuals with poor persistence probably benefited less than those who took the full course (7, 8).

In the prevention setting, rich drug utilization data are available from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT; also known as P-1), which tested whether a 5-year course of daily tamoxifen would reduce the rate of invasive breast cancer relative to a placebo in women at high risk but without a history of breast cancer. The BCPT was unblinded in 1998, following an interim analysis, and was soon approved by the Food and Drug Administration for primary reduction of breast cancer risk (9).

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In this first report of drug utilization in the BCPT, we focus on the lifestyle behavior factors at baseline of cigarette smoking, obesity, leisure-time physical activity, and alcohol use. We wished to examine whether these personal health behaviors, in a highly motivated clinical trial population, would be related to medication utilization. Our interest is motivated by the strong associations among unhealthy behaviors because together they may describe an individual who, we hypothesized, would be less likely to utilize chemoprevention as prescribed. Associations among smoking, obesity, physical activity, and alcohol use have been shown in numerous studies (10–18). There is also currently a great deal of attention to the biological pathways by which these lifestyle factors are associated with cancer. The understudied connection between lifestyle behaviors and chemoprevention utilization is another potential route by which people who engage in the behaviors may be more likely to develop cancer. In addition, the present analysis is important because few studies have addressed the associations of lifestyle behaviors and drug utilization in a healthy population. Identifying and understanding the factors that predict utilization is critical, if the long-term benefits of cancer chemopreventive therapies are to be realized.

Materials and Methods

Participants

This is a secondary analysis of the BCPT database. The BCPT, which was funded by the National Cancer Institute, was a double-blinded, placebo-controlled clinical trial that was open for accrual at several hundred clinical centers throughout North America from June 1, 1992, through September 30, 1997. During this interval, 13,338 women were randomly assigned to receive either 20 mg/d of tamoxifen or placebo for a duration of 5 years (9). The risk of breast cancer was estimated using the Gail model, which incorporates a woman's age at menarche, number of benign breast biopsies, histologic diagnosis of atypical hyperplasia, nulliparity or age at first live birth, and number of first-degree relatives with breast cancer (19–21). Women were required to have an estimated 5-year risk of at least 1.66% or a history of lobular carcinoma *in situ*. Exclusion criteria included a history of clinical depression or addictive disorder that would preclude obtaining informed consent or interfere with protocol compliance. As in our prior analyses of quality-of-life data from the BCPT (22, 23), we used data available on the 11,064 participants recruited as of May 31, 1994 (82.6% of total accrual), as they would have been expected to have at least 36 months of follow-up data when the study was unblinded in March, 1998. We included only 36 months of follow-up. All participants provided informed consent for the BCPT, which was approved by the Institutional Review Boards of all participating institutions. The present secondary analysis was approved by the University of Pittsburgh Institutional Review Board.

Measures

Participants' utilization of their assigned treatment (tamoxifen or placebo) was reported at 1, 3, 6, and every 6 months thereafter. The case report form included the staff assessment of the percentage of pills taken during the past 4 weeks (categorized as more than 100%, 100%, 76%–99%, 51%–75%, 26%–50%, 1%–25%, or 0%), pattern of utilization, and strategies used by the clinical staff to improve adherence. Adherence problems were recorded by the clinical staff using a checklist and an open-ended "other problem" response item. When participants went off therapy, their reasons were recorded. Until 1995, the staff also reported the number of pills remaining in the participant's medicine bottle. It was determined at that time that the qualitative pill use reporting was adequately reliable (unpublished analysis), and the physical counting of pills was no longer required. The adherence case report form was no longer required after January 19, 1996.

We use the term "adherence" for ease of expression, but noninitiation of study drug and nonpersistence (early discontinuation) were also included in the measure of utilization we have examined. Participants were not included in the denominator after they formally discontinued treatment for any of the following reasons: grade 4 adverse event, cardiovascular or stroke-related event, cancer, bone fracture, non-cataract eye toxicity, pregnancy, other medical problems related to the protocol, other diagnoses or procedures potentially related to protocol, or death. Participants who withdrew consent to be followed (in the absence of a major health event) or who were lost to follow-up were considered nonadherent after that time point.

A patient-reported instrument administered at enrollment collected cigarette smoking data (at least 100 cigarettes in lifetime, age of initiation, current smoking frequency and intensity, past intensity, and age at quitting if a former smoker). The instrument also provided descriptions of physical inactivity as well as light, moderate, or vigorous physical activity. Participants were asked to select 1 of these 4 levels to describe their activity during their leisure time in the previous 12 months. Frequency and quantity of consumed beer, wine, and alcohol were reported. Participant weight and height were recorded by clinic staff, from which body mass index (BMI) was calculated for the present study. Women with baseline BMI of at least 25 were defined as overweight or obese.

Statistical considerations

The significance of predictor variables was tested at 2-sided α -level of 0.05. Pill adherence was dichotomized using cutoff points of 100% ("full adherence") and 76% ("adequate adherence") of pills taken during the past 4 weeks, based on the staff assessment described under Measures. Full adherence was defined as the primary endpoint in the research proposal, but adequate adherence is an important secondary endpoint; tamoxifen is believed

to retain efficacy at this level because of the long half-life of tamoxifen after chronic use (24, 25). Mixed effects logistic regression analyses were conducted for the adherence outcomes at 1 month and at 3 years. Predictors of interest were cigarette smoking (current vs. other), unhealthy weight (overweight/obese), physical activity (inactive/light vs. moderate/heavy), and alcohol use. Alcohol use was classified for the present analysis as none, up to 1, or more than 1 drink per day, distinguishing healthy or unhealthy use based on the U.S. Department of Agriculture recommendation that women drink up to 1 drink per day [12 oz. (355 mL) beer, 5 oz. (148 mL) wine, or 1.5 oz. (44 mL) spirits; ref. 26]. Other predictors were assigned treatment group, age (>60), presence of comorbid conditions, estimated breast cancer risk (analyzed as a continuous variable), participant-reported race/ethnicity, education, marital status, family and personal history of life-threatening illness, employment status, occupation of self and spouse, per capita household income, and household inhabitants (living alone vs. with others). Pretreatment values were used for all predictors. Because of potential confounding of demographic and medical variables with the health behavior variables of interest (e.g., smoking and income), preliminary analyses included either medical/demographic variables or health behaviors. The full model then included all the lifestyle behaviors of interest and those medical/demographic factors that reached $P < 0.1$ significance in the preliminary model. A random effect for the institution where participants were treated accounted for correlation among participants from the same institution and for an institution-specific effect on adherence. Estimated adherence for levels of the lifestyle factors was based on back-transformed least squared means.

In preparation for the primary analyses, we conducted hierarchical clustering to identify profiles of women on the basis of the health behavior variables of interest (not including adherence). Cluster analysis revealed that the 2 major clusters were non-smokers versus smokers, with any combination of physical activity level, obesity, and alcohol use. Using the cluster variable in place of individual behavior variables did not improve model fit according to the Akaike Information Criterion (27), and we therefore used individual behavior variables in the reported analyses.

For 96 randomly selected participants who endorsed "other" problems with adherence (48 placebo, 48 tamoxifen; 6 from each of the 8 time points), an experienced data manager conducted content analysis of written responses to determine whether text responses fit into categories already in the checklist or constituted distinct problems.

The statistical power for a logistic regression of full adherence was estimated in the protocol to be 80% for odds ratios in the range of 1.1 to 1.8 for varying assumptions about the distribution of predictor variables. Computations were conducted in SAS 9.1 including PROC FASTCLUS, PROC CLUSTER, and PROC GLIMMIX.

Results

Of the 11,064 women enrolled in BCPT as of May 31, 1994, majorities were under the age of 60 and of White race. (Table 1) At baseline, 13% of participants were current cigarette smokers, 60% were overweight or obese, 54% were inactive or engaged in light leisure-time physical activity, and 13% consumed more than 1 alcoholic drink per day. Other demographic characteristics have been published elsewhere (9, 22, 23, 28, 29).

Short-term adherence to assigned treatment

About 75% of participants were fully adherent at 1 month. In the analyses of health behaviors and adherence, without adjusting for sociodemographic and medical factors, baseline alcohol use was associated with decreased 1 month full adherence ($P = 0.034$). Smoking, weight, and physical activity were not significantly associated with full adherence. In the analysis of 1-month full adherence adjusted for other factors, alcohol use remained significant ($P = 0.016$; OR = 0.87 for moderate drinkers, OR = 0.79 for heavy drinkers relative to non-drinkers). Significant sociodemographic variables were age, education, and per capita household income (Table 2). Figure 1 provides multivariable ORs and 95% CIs. At 1 month, 91% of participants were adequately adherent. One-month adherence was associated with race and living alone but was not significantly associated with the lifestyle behaviors of interest.

Long-term adherence to assigned treatment

At 36 months, full adherence was 41%. In the model for 36-month adherence, including demographic and medical factors, only age was associated with full adherence (Table 2 and Fig. 1). At 36 months, adequate adherence was 79%. Without adjusting for other factors, 36-month adequate adherence was associated with baseline smoking ($P < .001$). Figure 2 reveals the gradual decline in adherence over time for women in the study, according to smoking status. In the full model, smoking retained significance ($P = 0.003$; OR = 0.75). From that full model, estimated adequate adherence was 80.1% for women whose weight was low/normal, 78.9% for overweight/obese; 77.9%, 79.5%, or 80.9% for women whose alcohol consumption was none, moderate, or high; and 79.9% and 74.9% for non-smokers and smokers, respectively. In addition, women were less likely to adhere if they were younger than 60 years, less educated, or were assigned to tamoxifen (Table 2 and Fig. 1).

Reasons for nonadherence

Adverse reactions and illness were the most frequently reported problems that resulted in inadequate adherence at 36 months (Table 3). Forgetting was the primary reason given for less than full adherence at 36 months (62%). The same patterns appeared at 1 month (data not shown). In the content analysis of "other problems," 6 of 96 forms indicated cost issues and 8 indicated a loss of confidence in the study following negative publicity.

Table 1. Participant characteristics (11,064 NSABP BCPT participants randomly assigned on or before May 31, 1994)

Participant characteristic	N	Percent
Current smoker		
No	9,609	86.8
Yes	1,417	12.8
Unknown	38	0.3
Baseline BMI \geq 25	6,635	60.0
Leisure-time physical activity		
Moderate heavy	5,057	45.7
Inactive light	5,968	53.9
Unknown	39	0.4
Alcohol use		
None	2,268	20.5
1 drink/day	7,284	65.8
1+ drink/day	1,471	13.3
Unknown	41	0.4
Age \geq 60	3,308	29.9
Race		
White	10,572	95.6
Black	183	1.7
Hispanic	112	1.0
Other/unknown	197	1.8
Education		
Grade school/some high school/high school	2,617	23.7
Associate degree/some college/vocational training	4,291	38.8
College degree/some postcollege	2,466	22.3
Graduate degree	1,651	14.9
Unknown	39	0.4
Treatment assignment		
Placebo	5,537	50.0
Tamoxifen	5,527	50.0
Breast cancer risk		
\leq 2%	2,709	24.5
2%–5%	6,608	59.7
$>$ 5%	1,747	15.8
Comorbid conditions	8,701	78.6
Life-threatening illness	256	2.3
Living alone	1,717	15.5
Employment status		
Disabled/homemaker/medical leave/retired/unemployed	3,808	34.4
Full-time/part-time/student	7,216	65.2
Unknown	40	0.4
Occupation		
Operator/fabricator/laborer/other	842	7.6
Homemaker/managerial/service/technical, sales, administrative support	10,182	92.0
Unknown	40	0.4

Discussion

This examination of chemoprevention adherence in the NSABP BCPT revealed that heavy alcohol users were less likely to adhere fully in the short term and cigarette smokers were less likely to adhere adequately in the long term, whereas obesity and physical activity were not associated with adherence. A detailed pill adherence substudy of 100 participants in the International Breast Intervention Study (IBIS), a European study of tamoxifen for prevention of breast cancer, also reported lower adherence for women who smoked (30). In the second NSABP breast cancer prevention trial, the Study of Tamoxifen and Raloxifene (STAR; also known as P-2), women with a smoking history were less likely to persist in taking their assigned drug (31). Smoking has also been associated with poor adherence to breast cancer screening (32). For those women who do smoke and yet adhere to chemoprevention, it is unclear whether this inconsistent behavior is due to differing perceptions of personal risk of breast cancer versus diseases more commonly associated with smoking, or of the relative costs and challenges of smoking cessation versus chemoprevention adherence. It has been observed that a person's perceived risk tends to reflect underestimation or optimistic bias relative to objective risk (33).

The IBIS investigators did not examine the impact of alcohol, leisure-time physical activity, or obesity, and we found no other studies examining associations between these behaviors and chemoprevention adherence. Our results about other medical and demographic factors confirmed associations observed in IBIS including age and risk of breast cancer. STAR, as well as several studies about adjuvant tamoxifen therapy and other medications, found greater persistence or adherence for older patients (5, 6, 31, 34–37) although inverse or U-shaped associations have also been observed (3, 38). Veronesi reported that breast cancer patients taking tamoxifen in an adjuvant therapy trial were more likely to adhere than were women in a chemoprevention trial, which is consistent with our observation that higher perceived health risk increases adherence (39). Similarly in STAR, persistence was higher among those with higher predicted breast cancer risk (31). Although having higher income was positively associated with adherence, we found inconsistent associations with education: an inverse association in the short term and a positive association in the long term. Past literature in other settings has also not consistently reported a positive association with education (40, 41). Our finding that being Hispanic was associated with worse short-term adherence in our study was consistent with literature, but other studies have also reported associations with Black race as well as marital status (37, 38, 41). Some past studies have been observational, reflecting adherence in general clinical practice rather than in the clinical trial setting, which also might account for differences.

We considered both full and adequate adherence to be of interest because this study has implications for adherence to oral therapies in general, and in other settings, higher

Table 2. Significance tests in full multivariable models of adherence in the NSABP BCPT trial at 1 and 36 months

	1 month		36 months	
	Full	Adequate	Full	Adequate
Smoking	0.73	0.84	0.43	0.003
Overweight/obese	0.60	0.29	0.20	0.39
Low physical activity	0.33	0.21	0.55	0.42
Alcohol	0.016	0.13	0.19	0.38
Age (≥ 60)	<0.001	–	<0.001	0.024
Race	0.15	0.043	–	–
Education	<0.001	–	–	0.037
Treatment assignment	–	–	–	0.008
Breast cancer risk	–	–	–	<0.001
Comorbid conditions	–	–	–	0.059
Single habitation	0.091	0.015	–	0.074
Not employed	0.099	–	–	0.11
Per capita income	<0.001	–	–	–

NOTE: The 4 lifestyle variables of interest are included. Medical and demographic variables that were significant at $P < 0.1$ in preliminary models (models not including lifestyle factors) are included.

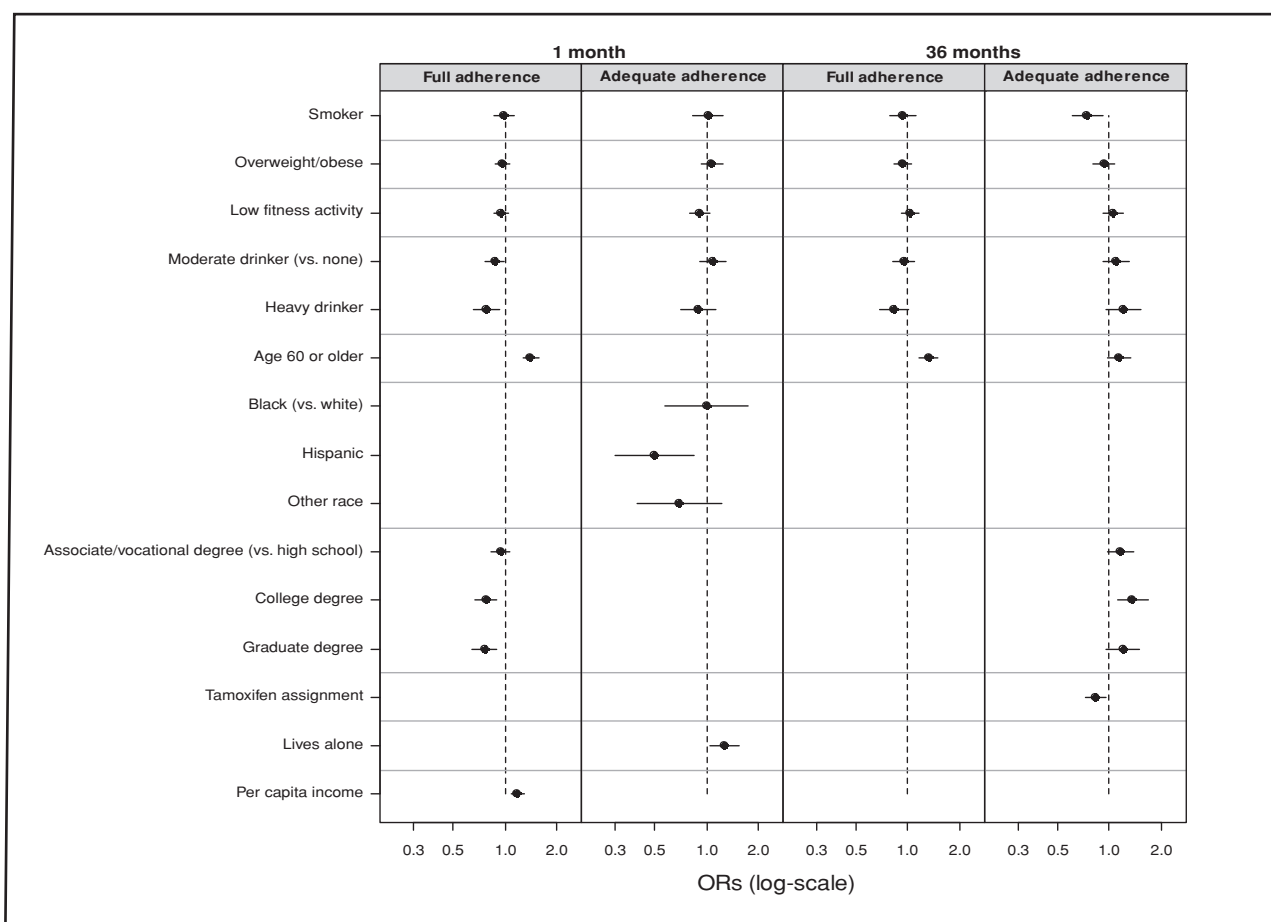
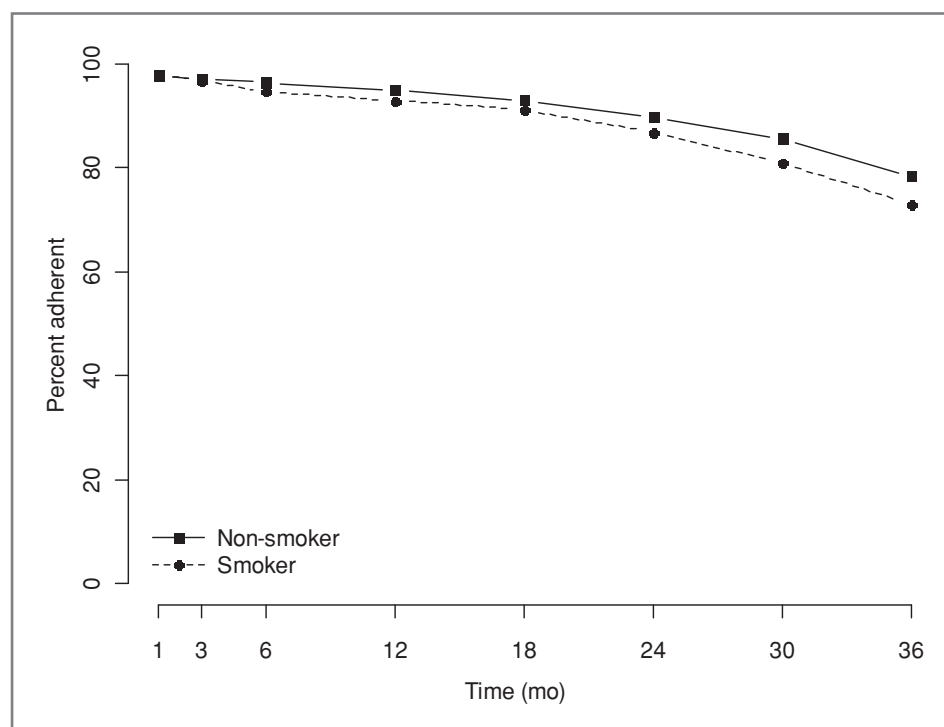


Figure 1. ORs with 95% CIs for full and adequate adherence based on full multivariable models. ORs are shown for variables that retained significance ($P < 0.05$) in the full models. ORs for income is per \$30,000 in annual per capita household income.

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Figure 2. Adequate adherence over time according to baseline smoking status.



levels of adherence may be necessary to achieve efficacy. Therefore, although 75% adherence might be the most clinically important endpoint for tamoxifen, we also provide results for full adherence.

The lack of strong associations with obesity and physical activity suggest that poor adherence is not simply based on a pattern of unhealthy behavior in general but could be related to common sociologic, psychological, biological, or genetic mechanisms that impact both substance use and medication adherence. The present report was limited to

baseline factors—those factors that would enable a care provider to predict poor adherence at the start of treatment. Separately, we will report associations of adherence with the participant's experience while on treatment including quality of life and symptoms. In that report, we will examine whether smoking and alcohol use were associated with worse symptoms and quality of life, mediating their effects on adherence. Past studies have examined how emotional factors influence decision making about taking tamoxifen (42, 43). Differences in emotional factors and symptoms might also help explain the higher adherence among older women. Older women had lower levels of emotional distress and fewer vasomotor symptoms (28).

The effectiveness of breast cancer chemoprevention for high-risk women has been shown (9, 44, 45) but that benefit will only be translated to the general population if women adopt and adhere to a chemopreventive agent. Although we are ultimately concerned with adherence to the 5-year regimen in clinical practice, our study examined adherence in the context of a placebo-controlled clinical trial. In clinical practice, adherence might be supported because all patients are receiving a proven therapy. However, given the active adherence promotion by BCPT headquarters and institutional clinical staff, and other factors noted in the literature, it is likely to have been higher in the BCPT (46). Our report does not address strategies to improve adherence in clinical practice and does not provide data beyond three years, after which adherence might continue to decline. It is worth noting that in our context, even women who were of healthy weight, nonsmoking, moderate alcohol users, white, older than 60 years, and college educated had some problems with adherence.

Table 3. Problems reported for inadequate adherence at 36 months

Reason	% Endorsed
Adverse reaction	22
Illness	17
Testing efficacy	12
Forgot (usual schedule)	10
Forgot (disrupted schedule)	11
No medication	3
Lacked information	1
Nonacceptance	2
Emotions	9
Other priorities	8
Social criticism	2
Decision to omit dose	2
Negative thoughts	4
Not yet known	2
Other problem	16

However, the need to better define the patient groups at risk for nonadherence has been noted in the literature (40, 47). Additional adherence interventions targeting women who smoke cigarettes and drink alcohol and addressing the underlying factors that lead to the unhealthy behaviors may be necessary to maximize the benefits of chemoprevention treatment.

Disclosure of Potential Conflicts of Interest

D.L. Wickerham disclosed being an Eli Lilly Consultant/Advisory Board member.

The authors retain the right to provide a copy of the final manuscript to the NIH upon acceptance for journal publication, for public archiving in PubMed Central as soon as possible but no later than 12 months after publication by the journal. None of the acknowledged people was compensated beyond normal salary for this work.

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