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Symptoms and QOL as Predictors of Chemoprevention Adherence in NRG Oncology/ NSABP Trial P-1

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Abstract

Background: Tamoxifen provides a 50% reduction in the incidence of breast cancer (BC) among high-risk women, yet many do not adhere to the five-year course of therapy. Using the prospective double-blind National Surgical Adjuvant Breast and Bowel Project P-1 study, we evaluated whether participant-reported outcomes were associated with drug adherence and whether baseline behavioral risk factors modified those associations.

Methods: P-1 participants were randomly assigned to placebo vs tamoxifen (20 mg/day). Mixed effects logistic regression was used to evaluate whether baseline or three-month SF-36 quality of life (QOL) mental and physical component summaries (MCS, PCS), and participant-reported symptoms (gynecologic, vasomotor, sexual, and other) predicted 12-month drug adherence (76–100% of assigned medication). The evaluation accounted for age, treatment, estimated breast cancer risk, education, baseline smoking, alcohol consumption, and obesity. All statistical tests were two-sided.

Results: Participants enrolled at least three years before trial unblinding and without medically indicated discontinuation before 12 months were eligible for the present analyses (n = 10 576). At 12 months, 84.3% were adherent. Statistically significant predictors of adherence were: three-month MCS (odds ratio [OR] = 1.15 per 10 points, 95% confidence interval [CI] = 1.06 to 1.25); three-month gynecologic symptoms among moderate alcohol drinkers (OR = .79, 95% CI = 0.72 to 0.88); baseline vasomotor symptoms among participants assigned tamoxifen (OR = .88, 95% CI = 0.80 to 0.97); and three-month sexual symptoms among younger participants (OR = .89 at age 41 years, 95% CI = 0.80 to 0.99). The strongest association was with three-month other symptoms (OR = .77, 95% CI = 0.63 to 0.93). PCS was not associated with adherence. Symptom and QOL associations were not modified by smoking or obesity.

Conclusions: Promoting QOL and managing symptoms early in therapy may be important strategies to improve adherence.

The multicentered randomized placebo-controlled phase III National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 (Breast Cancer Prevention Trial [BCPT]) and other trials have demonstrated a statistically significant reduction in breast cancer incidence among women at high risk of the disease (1–4). Effective agents include tamoxifen, tested in P-1, and other selective estrogen receptor modulators and aromatase inhibitors that target developing hormone receptor–positive breast cancers. The US Preventive Services Task Force (USPSTF) and the American Society of Clinical Oncology have recommended

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broader adoption of chemoprevention (5,6). However, despite the evidence of benefit, adherence to the daily regimen (or persistence with the full course, usually five years) remains a challenge (7,8). The need to better define the patient groups at risk for nonadherence has been noted in the literature (11,12).

Symptoms and quality of life (QOL) difficulties experienced during therapy may color the patient's perception of benefit (if symptoms are interpreted as indicating that they are on the active drug) or of harm (intolerable adverse symptoms). If symptoms are severe, the patient might not be able to maintain adherence to either placebo or tamoxifen. In this report, we examine the role of symptoms and QOL for nonadherence in NSABP P-1. The present report builds on our previous examination of behavioral risk factors as predictors of adherence (13). We broaden our understanding by testing whether participants who reported poor QOL (in terms of mental, physical, or sexual functioning) or who experienced more severe symptoms (gynecological, vasomotor, sexual, or other) were less likely to adhere to assigned treatment. We also examined whether the associations of these participant-reported outcomes (PROs) with adherence differed according to a participant's age, treatment assignment, or behavioral risk factors (cigarette smoking, obesity, and alcohol consumption). We postulated that women who engaged in other unhealthy behavior might be more vulnerable to nonadherence as a response to poor QOL or symptoms. A profile of women who are less likely to adhere to tamoxifen has not been established, especially with respect to the outcomes we focus on in this report. Understanding factors that predict which patients are less likely to adhere and which modifiable factors might improve adherence will enable the health care system to provide additional adherence support where it is most needed.

Methods

Participants

This is a secondary analysis of the NSABP P-1 database. P-1, funded by the National Cancer Institute, was a double-blinded, placebo-controlled clinical trial that was open for accrual at clinical centers throughout North America from June 1, 1992 through September 30, 1997. During this interval, 13 388 women were randomly assigned to receive either 20 mg/day of either tamoxifen or placebo for a planned duration of five years (14). A participant's risk of breast cancer was estimated using the Gail model, which incorporates a woman's age, race, age at menarche, number of benign breast biopsies, histological diagnosis of atypical hyperplasia, nulliparity or age at first live birth, and number of first-degree relatives with breast cancer (15–17). Participants were required to have an estimated five-year risk of 1.66% or a history of lobular carcinoma in situ. Exclusion criteria included history of clinical depression or addictive disorder that would preclude obtaining informed consent or interfere with protocol compliance. We used data available on the 11 064 participants recruited as of May 31, 1994 (82.6% of total accrual). The cutoff based on accrual date was established in prior P-1 PRO analyses (18,19), in which longer-term measures were examined, because participants would have been expected to have had at least 36 months of follow-up data when the study was unblinded in March, 1998. The present study does not require participants to have had three years of follow-up data. Women who did not begin study treatment were excluded from these analyses because our analysis regards PROs experienced during treatment and their effects on adherence. All participants provided informed consent for P-1, which was approved by the institutional review boards of all participating institutions, in accord with assurances filed with and approved by the US Department of Health and Human Services. This secondary analysis was approved by the University of Pittsburgh Institutional Review Board.

Measures

Adherence

Participants' utilization of their assigned treatment (tamoxifen or placebo) was reported at one, three, and six months and every six months thereafter. The case report form (described in greater detail previously [13]) included the staff assessment of the percentage of pills taken during the past four weeks (categorized as more than 100%, 100%, 76%-99%, 51%-75%, 26%-50%, 1%-25%, or 0%), based on the number of pills dispensed, minus the number of unused pills in the medication bottles, which participants were required to bring to each visit. Adherence was dichotomized at 76%, selected a priori for our previously published analyses; tamoxifen is believed to retain efficacy at this level because of its long half-life after chronic use (20,21). 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, noncataract eye toxicity, pregnancy, other medical problems related to the protocol, other diagnoses or procedures potentially related to the 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. Women whose (staff-reported) adherence information was missing were excluded. A sensitivity analysis was also conducted, which considered women with missing adherence information as nonadherent.

Participant-Reported Outcomes

A questionnaire battery was administered upon enrollment and at one, three, and six months and every six months thereafter. For these analyses, we utilized the mental component summary (MCS) and physical component summary (PCS) scores of the SF-36 QOL instrument (normed to a population mean of 50 and an SD of 10) (22) and a modified Medical Outcomes Study sexual function instrument (23). The latter was categorical: not sexually active within 12 months; sexually active but with no 'definite' or 'very serious' problem with sexual interest, arousal, enjoyment, or orgasm; sexually active and with a 'definite' or 'very serious' problem. The other PROs were the BCPT symptom scales (described in detail previously [13,23-25]) for gynecological (3 items), vasomotor (3 items), and sexual symptoms (2 items). Scales were constructed following procedures in our previous psychometric validation (each ranges 0–5, with higher values indicating greater severity) (25). A fourth symptom measure in the present analysis is the sum of severity scores for the remaining 34 symptoms, included as a measure of "other" symptom burden that was not associated with tamoxifen (see the footnotes of Tables 2 and 3).

Behavioral Risk Factors

A baseline questionnaire collected cigarette smoking data and beer, wine, and liquor consumption. Alcohol consumption was classified, as in our previous work (13,26), as none, less than one, or more than one drink per day, based on the US Department of Agriculture recommendation that women who choose to drink alcohol do so in moderation, defined as one

ARTICLE

or fewer drinks per day (12 oz. [355 mL] beer, 5 oz. [148 mL] wine, or 1.5 oz. [44 mL] spirits) (27). Clinic staff recorded participant weight and height, from which body mass index (BMI) was calculated.

Statistical Considerations

The significance of predictor variables and interactions was tested at a two-sided alpha level of .05. Mixed effects logistic regression modelling was used to estimate associations of PROs with adherence at 12 months. A random effect was included to account for correlation among participants treated at the same institution and for an institution-specific effect on adherence. Preliminary analyses included a single PRO, behavioral risk factors (smoking status, BMI, and alcohol consumption), and other predictors found statistically significant in our previously published multivariable analyses: assigned treatment group, age, estimated breast cancer risk (15), and education. For the primary analysis, model selection began with a full model including all main effects described above, both baseline and three-month values of PROs, and interactions of PROs with treatment assignment, age, and behavioral risk factors. Terms with a *P* value of less than .1 for a main effect or interaction in the full model were retained, and goodness-of-fit among models was compared using Schwarz's Bayesian criterion (28). Results of the best fit multivariable model are reported. For terms with statistically significant interactions, estimates are provided for each level of the factors; for the continuous variable age, estimates are provided at the 5th and 95th percentiles (age 41 and 70 years) to illustrate the change in the effect across age. Analyses were performed using SAS 9.3 (Cary, NC).

Results

Of the 11 064 women enrolled in P-1 as of May 31, 1994, 114 (1.0%) did not begin treatment and 374 (3.3%) experienced events prior to 12 months that required drug discontinuation, leaving 10 576. Adherence information was missing for an additional 289 participants (2.6%). Of the remaining 10 287, the primary analysis cohort, 84.3% were adherent (85.4% of the placebo group, 83.1% of the tamoxifen group). At baseline, mean age was 53.8 years (SD = 9.1 years) (Table 1). Other demographic characteristics have been published elsewhere (14,18,19,23,25).

Table 2 provides results for analyses of each PRO separately (adjusting for assigned treatment group, age, breast cancer risk, education, smoking status, BMI, and alcohol consumption). PROs at baseline and early in the chemoprevention regimen were statistically significant predictors of adherence. Specifically, all PROs except baseline gynecologic symptoms were statistically significant, with better scores associated with adherence.

Table 3 provides results of the final multivariable model. Of the QOL measures, MCS 3 months after therapy initiation was associated with adherence (odds ratio [OR] = 1.15 per 10-point increase in MCS, 95% confidence interval [CI] = 1.06 to 1.25, $P < .001$). In contrast, the PCS and sexual function scale (data not shown) were not associated with adherence in multivariable modeling.

Gynecologic, vasomotor, sexual, and other symptoms were predictive of later adherence; some associations were modified by treatment and participant characteristics. More severe gynecologic symptoms reported at three months showed a statistically significant association with reduced adherence, and these associations were moderated by alcohol consumption ($P_{interaction} = .019$). For a 1-point increase in gynecologic symptoms, the odds ratios for adherence were 0.97 (95% CI = 0.79

Table 1. Participant characteristics: NSABP P-1 (10 287 participants eligible for the primary analysis)

Participant characteristic	Placebo (n = 5172)	Tamoxifen (n = 5115)	All (n = 10 287)
Age, mean (SD), y	53.8 (9.1)	53.9 (9.2)	53.8 (9.1)
BMI, mean (SD), kg/m2	27.4 (5.7)	27.4 (5.8)	27.4 (5.8)
Breast cancer risk, mean (SD), %	3.5 (2.3)	3.5 (2.3)	3.5 (2.3)
Education, No. (%)			
Grade school/some high school/high school	1240 (24.0)	1191 (23.3)	2431 (23.6)
Associate degree/some college/vocational training	1984 (38.4)	1993 (39.0)	3977 (38.7)
College degree/some postcollege	1128 (21.8)	1177 (23.0)	2305 (22.4)
Graduate degree	813 (15.7)	745 (14.6)	1558 (15.1)
Unknown	7 (0.1)	9 (0.2)	16 (0.2)
Race/ethnicity*, No. (%)			
White, non-Hispanic	4952 (95.7)	4907 (95.9)	9859 (95.8)
Black, non-Hispanic	78 (1.5)	87 (1.7)	165 (1.6)
Hispanic	58 (1.1)	43 (0.8)	101 (1.0)
Other	77 (1.5)	69 (1.3)	146 (1.4)
Unknown	7 (0.1)	9 (0.2)	16 (0.2)
Smoking status, No. (%)			
Not current smoker	4514 (87.3)	4459 (87.2)	8973 (87.2)
Current smoker	651 (12.6)	647 (12.6)	1298 (12.6)
Unknown	7 (0.1)	9 (0.2)	16 (0.2)
Alcohol consumption, No. (%)			
None	1056 (20.4)	1046 (20.4)	2102 (20.4)
Up to 1 drink/d	3436 (66.4)	3415 (66.8)	6851 (66.6)
More than 1 drink/d	671 (13.0)	645 (12.6)	1316 (12.8)

* Race was not a statistically significant predictor of adequate adherence at three years in our previous analyses (13) and therefore was not included in the present modeling, but the study was not designed to provide adequate statistical power to evaluate differences by race or ethnicity. BMI = body mass index; NSABP = National Surgical Adjuvant Breast and Bowel Project.

Table 2. Single participant-reported outcome analyses of 12-month adherence (accounting for treatment, age, estimated breast cancer risk, education, smoking status, body mass index, and alcohol consumption): NSABP P-1

PRO variable	Placebo	Tamoxifen	All	OR*	P†
PCS baseline, mean (SD)	52.4 (7.4)	52.3 (7.5)	52.4 (7.4)	1.19	<.001
PCS 3-mo, mean (SD)	52.0 (7.8)	52.2 (8.0)	52.1 (7.9)	1.14	.001
MCS baseline, mean (SD)	54.4 (7.2)	54.4 (7.3)	54.4 (7.2)	1.15	<.001
MCS 3-mo, mean (SD)	53.5 (8.2)	53.2 (8.5)	53.3 (8.4)	1.24	<.001
Sexual function baseline (vs active with problems), mean (IQR)	0.73 (1.00)	0.75 (1.00)	0.74 (1.00)	1.21 (inactive); 1.28 (active without problems)	.029
Sexual function 3-mo (vs active with problems), mean (IQR)	0.72 (1.00)	0.74 (1.00)	0.73 (1.00)	1.42 (inactive); 1.53 (active without problems)	<.001
Gynecologic symptoms baseline, mean (IQR)	0.26 (0.33)	0.25 (0.42)	0.26 (0.33)	0.94	.23
Gynecologic symptoms 3-mo, mean (IQR)	0.32 (0.67)	0.49 (0.67)	0.40 (0.67)	0.79	<.001
Vasomotor symptoms baseline, mean (IQR)	0.57 (1.00)	0.56 (1.00)	0.56 (1.00)	0.9	<.001
Vasomotor symptoms 3-mo, mean (IQR)	0.72 (1.33)	1.19 (2.00)	0.95 (1.67)	0.84	<.001
Sexual symptoms baseline, mean (IQR)	0.46 (0.50)	0.50 (1.00)	0.48 (0.50)	0.93	.014
Sexual symptoms 3-mo, mean (IQR)	0.52 (1.0)	0.53 (1.00)	0.53 (1.00)	0.92	.005
Other symptoms‡ baseline, mean (IQR)	0.55 (0.49)	0.55 (0.49)	0.55 (0.49)	0.69	<.001
Other symptoms 3-mo, mean (IQR)	0.60 (0.57)	0.57 (0.54)	0.59 (0.56)	0.59	<.001

* Odds ratios are per 10-point increase in physical component summary (PCS) and mental component summary (MCS), and a 1-point increase in other participant-reported outcome (PRO) variables. PCS and MCS are on a scale from 0–100 and are standardized to a population mean of 50 and a standard deviation of 10. Higher scores indicate improved quality of life. Other PROs are on a scale of 0–5. Higher scores indicate more severe symptoms. IQR = interquartile range; MCS = mental component summary of the SF-36 Quality of Life instrument; NSABP = National Surgical Adjuvant Breast and Bowel Project; OR = odds ratio; PCS = physical component summary of the SF-36 Quality of Life instrument; PRO = participant-reported outcome.
† Mixed effects logistic regression *P* values, two-sided.
‡ The other symptoms scale includes neurocognitive, musculoskeletal, gastrointestinal, and bladder symptoms; weight concerns; difficulty breathing or feelings of suffocation; chest pain; dry mouth; and breast sensitivity.

Table 3. Multivariable analysis of 12-month adherence: NSABP P-1

Predictive variables	*P** (main effect, interaction)	Odds ratios† for change in MCS or symptoms (95% CI)
3-mo PCS	.29	
3-mo MCS	<.001	1.15 (1.06 to 1.25)
3-mo gynecologic symptoms	.45, .019	
No alcohol consumption		0.97 (0.79 to 1.19)
Moderate alcohol consumption (up to 1 drink/d)		0.79 (0.72 to 0.88)
Heavy alcohol consumption (more than 1 drink/d)		1.13 (0.86 to 1.47)
Baseline vasomotor symptoms	.19, .030	
Placebo		1.03 (0.93 to 1.14)
Tamoxifen		0.88 (0.80 to 0.97)
3-mo sexual symptoms	.030, .035	
Age 41 y‡		0.89 (0.80 to 0.99)
Age 70 y‡		1.10 (0.98 to 1.25)
3-mo other symptoms§	.007	0.77 (0.63 to 0.93)

* Mixed effects logistic regression *P* values, two-sided. CI = confidence interval; MCS = mental component summary of the SF-36 Quality of Life instrument; NSABP = National Surgical Adjuvant Breast and Bowel Project; PCS = physical component summary of the SF-36 Quality of Life instrument.
† Odds ratios are provided for statistically significant main effects and interactions. These correspond to a 10-point increase in PCS and MCS, and a 1-point increase in other PROs.
‡ The model included age as a continuous variable, so estimates can be calculated for any age in the range of P-1 participants. The 5th and 95th percentiles (age 41 and 70 years) were selected to illustrate that the association between sexual symptoms and adherence was statistically significant for younger women but statistically nonsignificant for older women.
§ The other symptoms scale includes neurocognitive, musculoskeletal, gastrointestinal, and bladder symptoms; weight concerns; difficulty breathing or feelings of suffocation; chest pain; dry mouth; and breast sensitivity.

to 1.19), 0.79 (95% CI = 0.72 to 0.88), and 1.13 (95% CI = 0.86 to 1.47) for nondrinkers, moderate drinkers, and heavy drinkers, respectively, indicating that more severe gynecologic symptoms were associated with decreased adherence only among moderate alcohol drinkers. Vasomotor symptoms at baseline were associated with reduced adherence, but only among participants assigned to tamoxifen (OR = 0.88, 95% CI = 0.80 to 0.97, and OR = 1.03, 95% CI = 0.93 to 1.14, for tamoxifen and placebo groups, respectively, $P_{interaction}$ = .03). Sexual symptoms at three months were also associated with reduced adherence, but that association diminished with increasing age ($P_{interaction}$ = .035). For example: at age 41 years, the odds ratio for adherence for a 1-unit increase in sexual symptoms was 0.89 (95% CI = 0.80 to 0.99). At age 70 years, the association between sexual symptoms and adherence was statistically nonsignificant (OR = 1.10, 95% CI = 0.98 to 1.25). Other symptoms at three months predicted reduced adherence (OR = 0.77, 95% CI = 0.63 to 0.93, *P* = .007 per unit increase). In the final multivariable model, participants who smoked at baseline were less likely to adhere (*P* = .003); BMI was not associated with adherence (*P* = .093); and interactions

of QOL and symptoms with BMI and smoking status were not statistically significant.

A sensitivity analysis, with the 289 participants with missing adherence data assumed to be nonadherent, yielded largely comparable results, with the following exceptions: In the single-PRO analyses, baseline sexual function was statistically nonsignificant ($P = .09$), and in the multivariable model three-month PCS was a statistically significant predictor of adherence ($P = .034$).

Discussion

Participants who reported better QOL and less severe symptoms at baseline or at three months were more likely to adhere to their assigned agent at 12 months (accounting for treatment assignment, breast cancer risk, age, BMI, alcohol consumption, and smoking status). Mental well-being at three months was among the statistically significant predictors of adherence, pointing to the importance of monitoring and supporting mental well-being in the prevention setting. Our results also highlight the importance of querying participants soon after initiating tamoxifen about vasomotor symptoms, gynecological symptoms, sexual symptoms, and any other symptoms. Our analyses did not evaluate whether symptoms preceded a decline in mental well-being. However, mental well-being was statistically significant in the multivariable model accounting for symptoms and treatment assignment, suggesting that mental well-being and symptoms had independent associations with adherence. To illustrate the potential magnitude of the adherence effects, we consider two example participants. Both were assigned tamoxifen, drank alcohol in moderation, were overweight/obese, and had favorable baseline PCS. They differed in other respects. The first example participant was age 47 years, was a current smoker, had an estimated five-year breast cancer risk of 3%, and had baseline vasomotor symptoms reported as "quite a bit." At three months, this participant reported moderate gynecologic and other symptoms, very poor MCS, and "definite" sexual problems. Regression models estimated in our analyses predict that such a person has a 35% probability of adhering to assigned therapy at 12 months. In contrast, the second participant was age 64 years, was a nonsmoker, had estimated breast cancer risk of 15%, and had no baseline vasomotor symptoms. At three months, she had no gynecologic and minimal other symptoms, a very favorable MCS, and was sexually active without sexual problems. Such a person's estimated probability of adhering at 12 months is 94%. This model is not intended to predict the adherence probability of an individual patient, but these examples serve to illustrate the importance of the patient's symptoms and other characteristics.

The placebo-controlled design of P-1 enabled us to identify which factors of adherence were particular to tamoxifen treatment and which factors predicted adherence even in patients treated with placebo. Specifically, baseline vasomotor symptoms predicted lower adherence for participants assigned to tamoxifen, but for those assigned to placebo baseline vasomotor symptoms did not predict reduced adherence. All other identified associations were not statistically significantly different between tamoxifen and placebo groups, suggesting that these associations may be generalizable to other settings. For example, younger participants reporting sexual symptoms at three months were less likely to adhere, without regard to which treatment they were assigned. Sexual symptoms may be associated with reduced drug adherence among younger women in other treatment settings.

The measure of other symptoms (including gastrointestinal, musculoskeletal, neurological, cognitive, bladder, body image, and other problems) was also statistically significantly associated with nonadherence; indeed, this was the strongest association (OR = .77). It may be that participants found those symptoms more concerning because they were unexpected. This possibility is supported by a systematic review by Van Liew et al., who found that unexpected side effects of adjuvant hormone therapy for breast cancer were negatively associated with adherence and persistence (10). Kahn et al. found that patients who felt poorly informed about side effects associated with adjuvant hormonal breast cancer therapy were more likely to discontinue prematurely (29). Clinicians may need to monitor the patient experience and provide attention even for symptoms that are not considered causally associated with a treatment.

Lin et al. discuss the need for more studies evaluating the impact of treatment side effects on adherence, particularly among patients who smoke or drink alcohol (9). In P-1, participants who smoked were less likely to adhere, although smoking status did not modify the associations of PROs with adherence. More severe gynecological symptoms at three months were associated with reduced adherence among participants who drank alcohol in moderation (but not among those who did not drink or who drank more heavily). That result is inconsistent with our initial hypothesis that women who engaged in unhealthy behaviors, such as excessive alcohol consumption, would have less robust adherence; that is, they would be more vulnerable to decreased adherence as a response to symptoms. One can speculate that participants who consumed more alcohol or who smoked cigarettes may have used these substances in mood management, and therefore symptoms did not result in a greater loss of adherence in women with these behaviors. Women whose alcohol consumption represented addictive disorders that would preclude obtaining informed consent or interfere with protocol compliance were ineligible for the protocol.

The challenge of adherence exists not only in cancer prevention but also along the entire cancer continuum. In the treatment setting, poor adherence to tamoxifen may now be particularly important for patients with early-stage estrogen receptor–positive breast cancer, many of whom are prescribed tamoxifen without chemotherapy. One recent literature review reported that in the clinical practice setting approximately 50% of women complete a five-year course of adjuvant endocrine therapy (30). Nonadherence to endocrine breast cancer therapy has been associated with depressive symptoms, negative emotions regarding endocrine therapy, a poorer relationship with the oncologist, and other psychosocial factors (10,31). A systematic review found that many studies of adherence to adjuvant hormone therapy have not used empirically validated assessment tools and "at times, inclusion of psychosocial predictors appeared to be an afterthought" (10). In P-1, psychosocial variables were included by design.

It should be noted as a limitation that clinical trial participants are, in general, more adherent to study medications than the general population (32). Unfortunately, general population estimates of adherence to chemoprevention in the clinical practice setting in the United States are not available (30). In one recent study, investigators at Moffitt Cancer Center estimated roughly 80% adherence at one year among women in their institution who initiated chemoprevention (33). We also acknowledge that our endpoint is at one year rather than longer-term adherence. One year was selected because our interest was in the association with PROs while on therapy. Symptoms and QOL difficulties tend to begin early in therapy and remain fairly stable

or diminish over time. Among patients who maintain adherence at one year despite symptoms and QOL difficulties, factors other than PROs might be more important for long-term adherence. We also note as a limitation that 7% of 10 287 participants did not provide three-month PROs. These women were less likely to be adherent at one year (60% vs 86%). Had it been possible to measure their PROs, the estimates of association with adherence would have been either stronger or weaker, depending on whether the missing PROs were worse or better, respectively.

Finally, more work is needed to understand and address barriers to adoption of as well as adherence to chemoprevention of breast cancer. The effectiveness of breast cancer chemoprevention for women at high risk has been demonstrated (2,14), but that benefit will only be translated to the general population if women adopt and adhere to a chemopreventive agent.

This study may enable providers to identify patients who will benefit from targeted adherence support.

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