

Predicting Adherence to Tamoxifen for Breast Cancer Adjuvant Therapy and Prevention

Jennifer H. Lin, Shumin M. Zhang, and JoAnn E. Manson

Abstract

Treatment with the selective estrogen receptor modulator (SERM) tamoxifen for 5 years has produced dramatic breast cancer–related benefits in (a) the adjuvant setting, with 30% to 50% reductions in recurrence, contralateral disease, and mortality and (b) the prevention setting of healthy high-risk women, where tamoxifen reduces the risk of invasive and noninvasive breast cancer by 50%. Despite these striking data, adherence to tamoxifen is low, and low adherence is associated with poor survival. Although toxicity is a major predictor of poor adherence after starting therapy, pretreatment (baseline) predictors of poor tamoxifen adherence have been minimally studied. The adherence–survival link underscores the critical need to identify early predictors of poor adherence, and recent work is beginning to address this need. A major baseline predictor of poor adherence to prevention is current smoking, which is interestingly absent from studies of adherence to adjuvant therapy. Other important prevention adherence factors include breast cancer risk, extremes of age, non-white ethnicity, low socioeconomic status, and alcohol use. The strongest adjuvant therapy predictors are age (especially very young), ethnicity, and socioeconomic status. Future studies involving prospective systematic evaluation of these and other potential predictors in endocrine chemoprevention (e.g., other SERMs and aromatase inhibitors) are critical, as is the development of effective/targeted interventions to improve adherence and thus treatment outcomes in at-risk women. *Cancer Prev Res*; 4(9); 1360–5. ©2011 AACR.

Introduction

The selective estrogen receptor modulator (SERM) tamoxifen has been studied extensively in the settings of adjuvant therapy for breast cancer patients and prevention for healthy women at a high risk of breast cancer (1). A meta-analysis of 55 clinical trials involving 37,000 early-stage breast cancer patients has revealed risk reductions in recurrence of 47% and in mortality of 26% with adjuvant tamoxifen therapy for 5 years (2). This therapy also achieved a notable 47% reduction in the incidence of contralateral breast cancer. Furthermore, the risk reductions in the adjuvant setting are greater with 5 than with 1 or 2 years of therapy but use beyond 5 years provides no further advantage, and the benefit of 5 years persists for at least 10 years after treatment stops. With the substantial benefits in reducing risk for recurrence, mortality, and contralateral disease, tamoxifen (taken for

5 years) has been approved since 1990 by the U.S. Food and Drug Administration (FDA) for adjuvant use. These benefits also led to subsequent studies of tamoxifen for chemoprevention.

Tamoxifen use for 5 years reduced the risk of both invasive and noninvasive breast cancer by approximately 50% and overall mortality by 19% in the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (NSABP-P1) in 13,388 women aged 35 years or older who were at an increased risk for breast cancer (defined as a 5-year risk of 1.66% or greater according to the Gail model, age ≥ 60 years, or a history of lobular carcinoma *in situ*; ref. 3). In addition, the benefits were relevant only to women with hormone receptor–positive disease, which accounted for more than 70% of all breast cancer cases (3). Tamoxifen also had a similar risk-reducing effect in the International Breast Intervention Study (IBIS-1; ref. 4), which persisted at least 5 years past stopping treatment (5). An updated analysis of NSABP-P1 through 7 years of follow-up indicated that the treatment group was at a 32% lower risk for fracture compared with the placebo group (6). Since 1998, tamoxifen (taken for 5 years) has been FDA approved for use in preventing breast cancer in premenopausal and postmenopausal women who are at an increased risk for the disease.

Tamoxifen use, however, is also associated with an increased risk for several adverse events (e.g., endometrial cancer) and side effects, which were first known from

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doi: 10.1158/1940-6207.CAPR-11-0380

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the adjuvant therapy setting before designing NSABP-P1 but were later clarified and extended by data from NSABP-P1 and other studies. To date, well-known adverse effects of tamoxifen use include venous thromboembolism, endometrial cancer, cataracts, and exacerbation of hot flashes and other menopausal symptoms (7). Evidence from clinical and observational studies has suggested that fears of developing these side effects of the medication may undermine women's adherence to it (8–10).

Poor adherence tends to attenuate or eliminate the drug's therapeutic effects, which results in an increase in physician visits, higher hospitalization rates, and longer hospital stays (11, 12). Lack of adherence also prevents care providers from conducting accurate assessments of the therapeutic and toxic effects of the drug and evaluating the dosing requirement for optimal efficacy (13). Subsequently, patients may develop negative views about their care, and the relationship between patients and care providers may be compromised.

The concept of "adherence" and related terms can mean different things to different experts. Commonly used and variable assessments include assessed by self-reports, staff assessments, and customized monitoring system. Common definitions include noninitiation (failure to fill the initial prescription), adherence [taking doses as prescribed for a defined duration; defined variably as full (100%) or adequate (75%–80%)], and persistence (not discontinuing entirely). These definitions apply to the related terms used in this minireview.

Early Disease/Adjuvant Therapy

Despite the dramatic benefits associated with adjuvant tamoxifen therapy for 5 years, tamoxifen adherence in this setting is suboptimal. Previous reports have shown that approximately 1 in 5 adjuvant tamoxifen users fail to achieve an optimal adherence threshold of 80% or greater during the first year of treatment, and there is a 7% to 10% discontinuation rate per year (12, 14, 15). By year 4 or 5 of treatment, the full adherence rate drops to 50% (14, 16). Similarly, nonpersistence with adjuvant tamoxifen is about 20% to 30% at year 1 or 2 (15, 17, 18) and climbs to as high as 49% before the completion of 5 years (15, 16, 19). Available data on the association between adherence to adjuvant tamoxifen therapy and breast cancer outcomes have suggested that poor tamoxifen adherence contributes to therapeutic failure with an increased risk for poor outcomes. Two studies have shown that lack of complete adherence was associated with risks for mortality that were elevated by 10% and 49% during the treatment periods of 2.4 and 4.5 years, respectively (15, 20). In a study with 12 years of follow-up, patients with 80% or higher adherence had a $\geq 26\%$ lower risk for breast cancer recurrence, compared with patients with less than 80% adherence (21).

Nonadherence to prescribed medications and medical treatment is a complex and multifaceted issue. To date, the factors that may affect nonadherence to tamoxifen have not

been well documented. Severe adverse events and side effects, or concerns about their development, are certainly likely to cause women to discontinue the treatment (9, 10). There is some evidence that ethnicity, demographic factors, including socioeconomic status, education level, and age, especially extremes of age under 40–45 and over 75–85, have also been linked to lower adherence (14, 16, 19, 22–24) (Table 1). Of the 2 pivotal adherence analyses in the adjuvant setting, Partridge and colleagues (14) found that age younger than 45 years or 85 years or older and nonwhite ancestry were the major predictors for poor (<80%) adherence to tamoxifen at 4 years in 2,378 adjuvant patients. In addition, Hershman and colleagues (16) found that age younger than 40 or older than 75 years and African American ethnicity were associated with poor (<80%) adherence to tamoxifen or aromatase inhibitors (the discontinuation and nonadherence rates were similar for the 2 drugs) in 8,769 patients. The strongest overall predictor in the latter study was women younger than 40 years, who had the highest rate of nonadherence and of discontinuing therapy during 4.5 years. These investigators noted that the adherence behavior of younger women in the adjuvant setting is not well recognized and that younger women face dire medical and ancillary consequences of poor outcomes due to lack of adherence, highlighting the need for interventions to improve the adherence of younger women to tamoxifen treatment.

It has also been suggested that patients' perceptions of the importance of health, breast cancer risk, and medications are also likely to influence adherence (9, 25, 26). For example, women with negative or neutral beliefs about the utility of tamoxifen, possibly due to incomplete or inaccurate understanding of risk/benefits of the therapy, were more likely to discontinue the treatment than would those who have positive views at baseline or improved perceptions during follow-up (18, 27). Other potential barriers to adherence include poor patient–provider communication, medication cost, and psychological problems such as depression (13). Finally, it has been suggested that longer pill-refill intervals are associated with better adherence, although more data are needed to ensure whether the inconvenience involved in frequent refilling reduces adherence rates (16).

In an observational study of adjuvant therapy with tamoxifen or aromatase inhibitors (AI) in 1,491 insured and low-income breast cancer patients (24), the adherence rate was 60% after 1 year of follow-up, which is 20% lower than the rates observed in the NSABP-P1 trial and several other studies. Surprisingly, only marital status was associated with adherence during the first year of therapy; single women were more likely than married women to adhere to therapy (OR = 1.90; 95% CI: 1.20–3.00). Age, race, type of surgery, stage at diagnosis, and receipt of adjuvant chemotherapy or radiation had no effects on adherence rates. These observations underscore the importance of evaluating adherence-associated factors within the context of the socioeconomic and cultural characteristics of the participating women.

Table 1. Baseline predictors of adherence^a in studies of tamoxifen for prevention and/or adjuvant therapy of breast cancer

Predictor	Prevention ^b	Adjuvant therapy ^b	Key ref(s).
Current smoking	++	NWS	Land et al. (29), Maurice et al. (30)
Younger age	+ (<60 y)	++ (<40 or <45 y)	Partridge et al. (14), Hershman et al. (16), Land et al. (29)
Older age	+ (>75 y)	++ (≥85, ≥80, or >75 y)	Partridge et al. (14), Owusu et al. (19), Hershman et al. (16), Land et al. (29)
BC risk	++	NWS	Land et al. (29)
Non-white ethnicity	+ (Hispanic)	++ (African American)	Hershman et al. (16), Land et al. (29)
Alcohol (<1 drink/d)	+	NWS	Land et al. (29)
SES/income	++	++	Kimmick et al. (24), Land et al. (29)
Marital status	+	++	Kimmick et al. (24), Land et al. (29)
Education	+	+	Land et al. (29)
Obesity	0	NWS	Land et al. (29)
Low physical activity	0	NWS	Land et al. (29)
Adverse effects of tamoxifen = greatest overall association with adherence			Day et al. (8), Demissie et al. (10), Grunfeld et al. (9)

Abbreviations: BC, breast cancer; NWS, not well studied; SES, socioeconomic status.

^aThe term adherence here refers to several definitions related to adherence (e.g., persistence/discontinuation of drug; see text).

^bThe symbols in columns 2 and 3 referring to predictor associations have the following meanings: ++, significant and consistent; +, less strong; 0, no association.

Healthy, High Risk/Prevention

Tamoxifen has been associated with reduced adherence overall in long-term analyses of the large, randomized controlled trials of tamoxifen for breast cancer prevention. Among the 13,338 women of the NSABP-P1 trial, 23.7% of the tamoxifen arm versus 19.7% of the placebo arm discontinued treatment by year 4.5 (3). Among the 7,152 women of IBIS-1, full compliance at 5 years was 64% in the tamoxifen arm versus 74% in the placebo arm ($P < 0.001$; ref. 5). Among the 19,471 women of the NSABP Study of Tamoxifen and Raloxifene (STAR), 70.8% in the tamoxifen arm and 73.9% in the raloxifene arm were adherent at 5 years ($P < 0.001$; ref. 28).

Land and colleagues recently reported the first comprehensive analysis of adherence in a tamoxifen prevention trial (reported elsewhere in this issue of the journal; ref. 29), which was the NSABP-P1 trial. At early closure and unblinding, 11,064 women were on treatment for more than 3 years and thus were included in the present adherence analysis. Land and colleagues used the following adherence-related definitions: non-adherence as noninitiation or nonpersistence (early discontinuation of drug), excluding patients who discontinued therapy because of severe adverse effects including endometrial cancer; full adherence as taking 100% of study pills; and adequate adherence as taking 76% to 99% of study pills. Trial staff assessed the percentage of pills taken in determining adherence status. Pretreat-

ment (baseline) predictors of adherence were assessed at 1 and 36 months.

Land and colleagues found that 91% of the participants were adequately adherent at 1 month, of whom 75% were fully adherent (29). However, only 79% of women remained adequately adherent (41% fully adherent) at 36 months. The adverse effects of tamoxifen cited earlier were the most frequently reported problems linked to inadequate adherence at both 1 and 36 months. Lifestyle factors linked to adherence were current smoking (13% of the study population) and heavy drinking (>1 drink per day; 13% of the study population). Current smokers were less adherent than former and nonsmokers at 36 months ($P = 0.003$), and heavy drinkers were less likely to fully adhere to treatment at 1 (significantly) and 36 months (trend). The smoking association is the major finding of this analysis. Adherence data in smokers were obtained at 8 time points during the 36 months, showing a gradual decline in adequate adherence that became highly significant at 3 years. These smoking and adherence data are consistent with a small adherence substudy ($n = 100$) of IBIS-1 (30) and with data from the NSABP STAR showing an association of smoking history with decreased adherence to either tamoxifen or raloxifene (31). Of interest, tamoxifen adverse events (e.g., depression and migraines) correlated with current smoking (vs. nonsmoking) in a separate study (32), and a previous study by Land and colleagues showed a strong association of smoking with an increased risk of breast cancer ($P = 0.007$; ref. 33).

Land and colleagues also found in the recent adherence study from NSAPB-P1 that participants older than 60 years were less adherent than were those 60 years or older. Tamoxifen has been associated with a reduction in second primary breast cancer in *BRCA1* or *BRCA2* mutation carriers, and nonadherence in this setting is associated with a young age (<40 years; refs. 34, 35). Of interest, smoking (36) and young age (37) have been associated with nonadherence to breast cancer screening. Higher income, being at a higher risk for breast cancer, and non-Hispanic ethnicity also were somewhat associated with better adherence at either 1 or 36 months. Similarly, a small substudy of the MAP.3 prevention trial (exemestane vs. placebo) found worse adherence for ethnic minorities versus whites ($P = 0.009$; ref. 38). Physical activity and body weight, which have been associated with breast cancer risk and prognosis (39), did not appear to be related to adherence rates.

Lifestyle factors may differentially affect adherence behavior over the time course of the treatment. For instance, smokers may be more likely than nonsmokers to develop adverse side effects (e.g., cardiovascular events) after a certain period of time (e.g., 36 months), which subsequently influences their adherence to the therapy. Also, drinking behavior may change during the follow-up and, thus, may have an inconsistent association. Some side effects of the treatment, including vasomotor symptoms (which tend to be more prevalent in women who smoke cigarettes or drink alcohol), may vary depending on a woman's age and reproductive stage. As such, the study of a 1-time assessment of predictors at baseline would not be able to address the changes within patients over time. The different patterns of the relationship seen in this study at both short (1 month)- and long (36 months)-term follow-up also point to the need to conduct time-varying evaluations of the predictors associated with adherence over the course of administering a medication.

To date, only a handful of lifestyle factors, such as body weight, physical activity, alcohol use, and smoking status, have been studied in relation to adherence. Other potentially related factors are also in need of testing. For example, menopausal status, use of hormonal therapy at diagnosis, or status of vasomotor symptoms may be linked to adherence. Use of dietary supplements or low-fat diets, which tend to reflect a healthy lifestyle pattern among patients, are also likely correlated with patients' view of tamoxifen use for the prevention of breast cancer.

Conclusions

Despite the substantial benefits associated with tamoxifen therapy against breast cancer development, adherence to such use of tamoxifen is unsatisfactory, and low adherence is associated with poor survival. Medication toxicity has been suggested to be the major obstacle that reduces women's adherence to tamoxifen treatment. Nevertheless, other proven, less-toxic chemopreventive medications,

including raloxifene and AIs, are also associated with adherence problems, including close to 30% dropout rates, in 2 recent randomized trials (40, 41), suggesting that factors other than adverse events and side effects also contribute to nonadherence. The recent adherence analysis by Land and colleagues suggests that young age and current smoking, among other factors, predict poor adherence to tamoxifen chemoprevention. The potential role of these factors in adherence to other treatments, including raloxifene and AIs, remains unstudied, and research on these factors is needed from large chemoprevention trials. In addition, smoking does not appear to have been well studied and needs more research, in the adjuvant setting.

According to the National Health Interview Survey (NHIS) in 2000, at least 15% of U.S. women 35 to 79 years old are eligible, according to the FDA criteria, for tamoxifen chemoprevention (42). Furthermore, close to 5% of U.S. white women would have benefits that outweigh the risks (42). The prevalence of tamoxifen use for chemoprevention in U.S. women 40 to 79 years old, however, is less than one quarter of 1% ($\leq 0.2\%$; ref. 43). The overwhelmingly low number of women accepting the option of tamoxifen therapy in the real world further complicates the adherence problems surrounding breast cancer chemoprevention. These results and our review of treatment adherence underscore the urgent need to develop tailored interventions among women who are more likely to opt out of treatment and have adherence problems. It is possible that younger women and smokers may be more likely to have an optimistic bias in the perception of their disease risk, and health care professionals may help raise their awareness of the importance of medications and possible clinical consequences as a result of nonadherence (44). In addition, interventions with educational and psychosocial support may show promise for improving adherence to endocrine therapy among African Americans, who are more likely to be at a disadvantage in receiving health-related information and thus may have medical mistrust and lowered estimates of personal risk (45, 46). In conclusion, recognizing the adherence predictors in endocrine chemoprevention will assist in the development of effective interventions which optimize women's decision making and promote their adherence to tamoxifen therapy and other treatment modalities, thus holding promise for improving disease outcomes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

The work was supported by grant CA126846 from the National Cancer Institute.

Received July 18, 2011; revised July 25, 2011; accepted July 27, 2011; published online September 5, 2011.

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Cancer Prev Res 2011;4:1360-1365.

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