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Research Article

Cancer Prevention Research

Tamoxifen Acceptance and Adherence among Patients with Ductal Carcinoma In Situ (DCIS) Treated in a Multidisciplinary Setting

Lindsey C. Karavites[1], Anna K. Kane[2], Shruti Zaveri[2], Yanfei Xu[2], Irene Helenowski[2], Nora Hansen[2], Kevin P. Bethke[2], Laura J. Rasmussen-Torvik[3], and Seema A. Khan[2]

Abstract

Tamoxifen and other endocrine agents have proven benefits for women with ductal carcinoma *in situ* (DCIS), but low patient acceptance is widely reported. We examined factors associated with tamoxifen acceptance and adherence among DCIS patients who received a recommendation for therapy in a multidisciplinary setting. Using our institutional database, we identified women diagnosed with DCIS, 1998 to 2009, who were offered tamoxifen. We recorded data on demographics, tumor and therapy variables, tamoxifen acceptance, and adherence to therapy for ≥4 years. Univariable and multivariable analyses were conducted using logistic regression to identify factors specific to each group that were related to acceptance and adherence. A total of 555 eligible women identified, of whom 369 were offered tamoxifen; 298 (81%) accepted, among whom 214 (72%) were adherent, 59 of 298 (20%) were nonadherent, and for 25 (8%), adherence was undetermined. After stepwise elimination in adjusted logistic regression models, acceptance of breast radiotherapy was associated with acceptance of tamoxifen [OR, 2.22; 95% confidence interval (CI), 1.26–3.90; $P < 0.01$], as was a medical oncology consultation (OR, 1.76; 95% CI, 0.99–3.15; $P = 0.05$). Insured patients were more likely to adhere to tamoxifen (OR, 6.03; 95% CI, 2.60–13.98; $P < 0.01$). The majority of nonadherent women ($n = 38/56$, 68%) discontinued the drug during the first year of treatment with 48 (86%) citing adverse effect(s) as the reason. In a multidisciplinary, tertiary care setting, we observed relatively high rates of acceptance and adherence of tamoxifen. Acceptance of tamoxifen and radiotherapy were associated, and adherence was influenced by insurance status.

Key Message: Tamoxifen acceptance and adherence following resection of DCIS of the breast is related to acceptance of radiotherapy and may be improved by confirmation of the recommendation by a medical oncologist. Despite the low cost of tamoxifen, adherence to therapy is significantly impacted by lack of insurance; those who discontinue therapy report adverse effects as a major reason. *Cancer Prev Res; 10(7); 389–97. ©2017 AACR.*

Introduction

The selective estrogen receptor (ER) modulator, tamoxifen, was approved for use in women with ductal carcinoma *in situ* (DCIS) in 2000 following trials that showed a decrease in risk of in-breast recurrence and new primary breast cancer (1, 2). Although debate continues regarding the optimal management of women with DCIS (3), current guidelines recommend the use of tamoxifen in ER^+ DCIS in women undergoing breast-conserving surgery (4, 5). Despite this evidence-based recommendation, previous data from our institution showed that the acceptance of tamoxifen was lower among women with DCIS (58%) than in those with invasive cancer (98%), and was related to concerns regarding the risk–benefit balance of tamoxifen therapy (6). Paradoxically, since tamoxifen was approved for use in DCIS, ER testing has increased from 4% of DCIS cases in 2001 to 71% in 2011; however, endocrine therapy initiation decreased from 58% of ER^+ DCIS in 2001 to 2005 to 37% in 2009 to 2011 (7).

The risks associated with tamoxifen range include rare but serious adverse effects (endometrial carcinoma and venous thromboembolic events) and more common symptoms of hot flashes, vaginal dryness or discharge, and mood changes (8–11). Concern about these adverse effects has reduced the acceptance of tamoxifen by women with

[1]Department of Surgery, University of Illinois College of Medicine at Mt. Sinai Hospital, Chicago, Illinois. [2]Department of Surgery, Northwestern University Feinberg School of Medicine, Chicago, Illinois. [3]Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois.

Corresponding Author: Seema A. Khan, Feinberg School of Medicine, Northwestern University, 303 East Superior Street, Lurie 4-220, Chicago, IL 60611. Phone: 312-503-4236; Fax: 312-503-2555; E-mail: s-khan2@northwestern.edu

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DCIS and those at high risk (12). A large literature exists regarding the use of tamoxifen for primary prevention, and the acceptance of chemoprevention by women at high risk of breast cancer (5, 8, 13, 14), with clear documentation of the risks and benefits of preventive therapy with this agent, and recommendations for decision making regarding use of tamoxifen or raloxifene among postmenopausal women by age, race, and comorbidities (14). However women with DCIS are confused about the nature of their disease, consistently overestimate the risk of breast cancer death, and have anxiety levels similar to those in women with invasive cancers (15, 16). Qualitative studies have suggested that some women might perceive the risk of endometrial cancer or venous thromboembolism as more probable and possibly more dangerous than the risk of developing breast cancer (17, 18). Recent work suggests that clearly establishing a patient's individual risk/benefit profile may help to increase acceptance (9, 19, 20).

Adherence to medical therapy is known to influence outcomes. Nonadherence to adjuvant endocrine therapy is associated with lower survival of patients with invasive breast cancer (21). Attempts to identify those who have a higher risk of nonadherence have not produced clear predictors of nonadherence (7, 21–26). A recent systematic review of 29 studies of patients with breast cancer documented nonadherence rates of 12% to 59% for tamoxifen (25). Reports for adherence to tamoxifen by women with DCIS also varied widely (6, 7) and may relate to women's perceptions of less social support from health care providers (27); this may be compounded by a lack of consensus about therapy recommendations among different prescribers (28, 29).

Thus, despite the proven benefits of tamoxifen, the mixed perceptions of this benefit by patients and practitioners (6, 29, 30) mean that an important opportunity for prevention of invasive breast cancer is being lost. Our study of tamoxifen-eligible DCIS patients was designed to identify modifiable factors that are associated with a patient's decision to accept tamoxifen and adhere to it.

Materials and Methods

Patient selection

Following review and approval of our study by the Northwestern University Institutional Review Board (including waiver of informed consent), we queried the Lynn Sage Comprehensive Breast Center Database and the Enterprise Data Warehouse of Northwestern University Bioinformatics Center (Chicago, IL). We identified women aged 18 and older diagnosed with ER^+ DCIS between January 01, 1998, and December 31, 2009; we excluded patients if their surgical procedure was performed at an outside hospital, information regarding tamoxifen use was not available, and if their physician advised against taking the medication because of concern over competing illnesses, advanced age, bilateral mastectomy, or concurrent use of other hormone-modulating medications (Fig. 1).

Grouping strategy and definitions

Among all women offered tamoxifen by at least one physician, the women were categorized according to their initial decision to accept the recommended therapy (accepted vs. declined) and then subcategorized by their decision to remain on therapy after accepting (adherent vs. nonadherent). Acceptance was defined as filling at least one prescription for tamoxifen as reflected in the electronic medical record (EMR). Decliners were women who never initiated taking tamoxifen despite a recommendation to do so by one or more physician(s). Adherence was defined

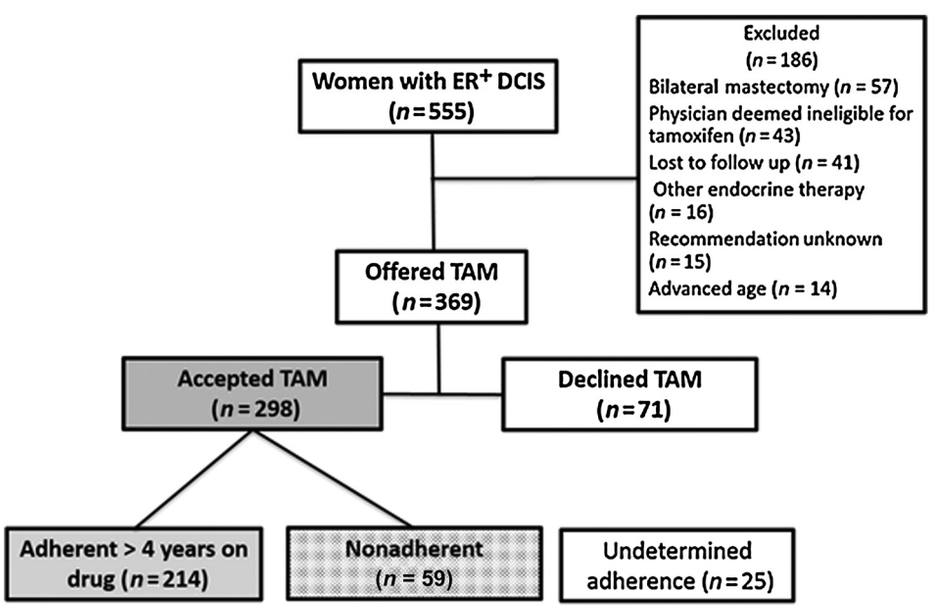

Figure 1.
Consort diagram of study population, showing the starting population, reasons for attrition, and final groups used for analysis.

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as evidence of daily use for ≥4 consecutive years. Nonadherent patients took tamoxifen for less than 4 years, as reflected by medication refill records or documentation by their prescribing physician. We chose a 4-year threshold as 5 years of tamoxifen therapy has been proven to be superior to 2 years in a clinical trial (31), and 4 years of therapy constitutes 80% of the recommended duration.

The ability to accurately assign menopausal status was limited in this retrospective review, related to variable documentation in the medical record and the relatively large fraction of women who reported irregular periods. As the original publication of the NSABP P-1 trial analyzed the quality of life and adverse event data based on age >50 compared with younger women, we used a similar approach to try to estimate acceptance of, and adherence to, tamoxifen therapy in this DCIS population.

Chart review

For women offered tamoxifen ($n = 369$), demographic information, DCIS characteristics, and details of therapy were recorded. For socioeconomic status (SES), we used patients' zip codes to acquire the median household income in U.S. dollars based on census data for the state of residence during the period in which they were diagnosed and treated (32). The study population was divided into SES tertiles, that is, the lower, middle, or upper third of median household incomes (Table 1). DCIS features were confirmed by pathology reports. Physician notes and operative reports were used to confirm medical and surgical therapies.

Referral to a medical oncologist was noted in the electronic database and confirmed by call tracking logs to patients and physicians as well as in physician notes. Reasons for declining to initiate therapy and subsequent nonadherence for those who initiated were obtained from physician notes and transcribed patient calls. Documented primary reasons for nonadherence were classified as: experiences of an adverse effect, concerns about experiencing an adverse effect, experiencing an undesired symptom attributed to tamoxifen but not known to be caused by tamoxifen, and desire to discontinue therapy without a documented explanation.

Statistical analysis

Analysis was conducted on all women who were offered tamoxifen, first comparing women who accepted with those who declined; women who accepted were then categorized as adherent or nonadherent. Categorical variables were reported as frequencies, and differences between groups were assessed via Fisher exact test; continuous variables were compared using the Mann–Whitney *U* test. Factors with $P < 0.10$ in univariable analysis were placed into multivariable logistic regression models to identify those that retained an independent association with acceptance and adherence, respectively. To accommodate the fact that women who underwent unilateral mastectomy did not need radiotherapy, we conducted the final multivariable analysis at two levels: first, classifying women as those who received "complete local therapy" (breast conservation with radiation or mastectomy) versus those who had breast conservation without radiation, and then focusing only on the breast conservation group to assess the association of the radiotherapy decision on the tamoxifen acceptance/adherence parameters. The threshold for statistical significance was set at $P < 0.05$. All *P* values are two-tailed. A Kaplan–Meier curve was generated using only patients who initiated tamoxifen therapy to show the proportion of patients who remained adherent over time. The start time was defined as the date the drug was initiated according to EMR, and the final follow-up time was defined by the time of last patient encounter. All analyses were conducted in SAS v9.4 (SAS Institute, http://www.sas.com/en_us/home.html).

Results

Patient population

Among 555 eligible women with ER^+ DCIS, 186 were excluded due to physician advice against taking tamoxifen because of comorbidities, age, having had bilateral mastectomies for their unilateral DCIS, or loss to follow-up. The final analytic sample included 369 women who were offered tamoxifen among whom 298 (81%) accepted and 71 (19%) declined. A total of 214 women (72%) of the 298 who accepted tamoxifen remained adherent for ≥4 consecutive years, whereas 59 women (20%) were not adherent. Adherence could not be determined for 25 women who were documented as having started tamoxifen therapy and were lost to follow-up or treated at an outside facility for the remainder of their care (Fig. 1).

Factors associated with acceptance and adherence

Demographic factors. As seen in Table 1, women who accepted tamoxifen were significantly older than those who declined (60 vs. 55 years, $P = 0.05$); those who were adherent were also older, but not significantly so (60 vs. 57 years, $P = 0.09$). We then examined age at diagnosis, comparing women who were ≤50 with those who were over 50 years at diagnosis. Tamoxifen acceptance was significantly more frequent in older women (82.8% of 351 women) than in younger women (70% of 53 women, $P = 0.01$). Similarly, women ≥50 years were more likely to be adherent, but not significantly so (79% of those over 50 years, compared with 70% of those ≤50 years, $P = 0.23$). Ancestry, family history of breast cancer, and SES was similar, for both acceptance of tamoxifen and adherence to therapy. Insurance status was not associated with acceptance of therapy ($P = 0.66$), but was significantly associated with adherence ($P < 0.01$).

DCIS features. When DCIS pathologic size was measureable, it was similar in women who accepted tamoxifen and

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Table 1. Characteristics of 368 women offered tamoxifen and 298 women who accepted

	All women offered tamoxifen			Women accepting tamoxifen initiation		
	Declined ($n = 71$)	Accepted ($n = 298$)	*P*	Adherent ($n = 214$)	Nonadherent ($n = 59$)	*P*
Median age (IQR)	55 (50–68)	60 (53–67)	0.05	60 (54–67)	57 (52–68)	0.09
Ancestry[a]						
Non-European	27 (38.0%)	87 (29.5%)	0.32	68 (32.2%)	12 (20.3%)	0.22
European	44 (62.0%)	210 (70.5%)		145 (67.8%)	47 (79.7%)	
Family history breast cancer						
No	31 (43.7%)	127 (42.6%)	0.75	87 (40.7%)	26 (44.1%)	0.70
Yes	35 (49.3%)	140 (47.0%)		104 (48.6%)	28 (49.1%)	
Unknown	5 (7.0%)	31 (10.4%)		23 (10.7%)	4 (6.8%)	
SES						
1st tertile	21 (29.6%)	78 (26.2%)	0.56	56 (26.2%)	15 (25.5%)	0.99
2nd tertile	30 (42.2%)	115 (38.7%)		84 (39.3%)	19 (32.2%)	
3rd tertile	20 (28.2%)	104 (34.9%)		73 (34.1%)	25 (42.4%)	
Unknown	0 (0.0%)	1 (0.2%)	0.33	1 (0.4%)	0 (0.0%)	0.28
Insurance status						
None	13 (18.3%)	44 (14.8%)	0.66	12 (5.6%)	15 (25.4%)	<0.01
Private	37 (52.1%)	170 (57.0%)		137 (64.0%)	28 (47.5%)	
Government	21 (29.6%)	84 (28.2%)		65 (30.4%)	16 (27.1%)	
DCIS size[b]						
Quantifiable						
Median mm (IQR)	10.5 (3, 33)	13 (5, 28)	0.59	15 (6, 30)	7 (3, 14)	<0.01
Nonquantifiable						
No residual DCIS *n* (%)	7 (9.9%)	24 (8.0%)	0.23	18 (8.4%)	4 (6.8%)	0.88
Extensive *n* (%)	1 (1.4%)	16 (5.4%)	0.11	8 (3.7%)	7 (11.9%)	0.04
DCIS grade						
1	15 (21.1%)	55 (18.5%)	0.85	37 (17.3%)	15 (25.4%)	0.46
2	38 (53.5%)	155 (52.0%)		113 (52.8%)	31 (52.6%)	
3	18 (25.4%)	84 (28.2%)		61 (28.5%)	12 (20.3%)	
Unknown	0 (0.0%)	4 (1.3%)		3 (1.4%)	1 (1.7%)	
Surgical therapy						
Breast conservation	56 (78.9%)	257 (86.2%)	0.14	185 (86.5%)	48 (81.4%)	0.40
Unilateral mastectomy	15 (21.1%)	41 (13.8%)		29 (13.5%)	11 (18.6%)	
Complete local therapy[c]						
No (BCS no RT)	27 (38.0%)	63 (21.4%)	<0.01	39 (18.2%)	19 (32.2%)	<0.01
Yes (mastectomy or BCS with RT)	44 (64.0%)	232 (78.6%)		174 (81.3%)	38 (64.4%)	
Radiotherapy (BCS only)[c]						
No	27 (48.2%)	63 (24.8%)	<0.01	39 (21.2%)	19 (41.3%)	<0.01
Yes	29 (51.8%)	191 (75.2%)		145 (78.8%)	25 (58.7%)	
Medical oncology referral for endocrine therapy						
No	24 (33.8%)	59 (19.8%)	<0.01	41 (19.2%)	16 (27.1%)	0.33
Yes	47 (66.2%)	206 (69.1%)		158 (73.8%)	38 (64.4%)	
Unknown	0 (0%)	33 (11.1%)		15 (7.0%)	5 (8.5%)	
New breast cancer event						
Ipsilateral	11 (15.5%)	17 (5.7%)	0.01	12 (5.6%)	5 (8.5%)	0.38
Contralateral	1 (1.4%)	17 (5.7%)	0.22	12 (5.6%)	4 (6.8%)	0.76
Length of follow-up (months)						
Median (range)	74.6 (55.9–93.6)	81.7 (64.9–95.4)	0.12	85.0 (70.2–96.3)	72.3 (59.5–94.9)	0.01

Abbreviations: BCS, breast conservation surgery; IQR, interquartile range; RT, breast radiotherapy.

[a]One woman with unknown ancestry was excluded.

[b]Patients with radiographic/pathologic evidence of extensive DCIS were not included in median size calculations.

[c]Use of radiotherapy unknown for 3 women.

those who did not (10.5 mm vs. 13.0 mm, $P = 0.59$); however, women who were adherent to therapy had significantly larger DCIS lesions than nonadherent women (15 mm vs. 7 mm, $P < 0.01$). The fraction of women with no residual DCIS in the surgical specimen was similar among women who accepted therapy or declined it (8% and 9.9%); it was also similar between women who were adherent to therapy and those who were not (8.4% and 6.8%). However, extensive DCIS was nonsignificantly more frequent among those who accepted than among those who declined tamoxifen (5.4% vs. 1.4%, $P = 0.11$). In terms of adherence, the opposite trend existed, and the fraction of women with extensive DCIS was larger in the nonadherent group than in the adherent group (11.9% vs. 3.7%, $P = 0.04$). However, 44% of women with extensive DCIS who accepted tamoxifen also opted for mastectomy,

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Table 2. Univariable models for acceptance and adherence among 368 women offered tamoxifen

Variable	OR for accepted ($n = 298$) vs. declined ($n = 71$)		OR for adherent ($n = 214$) vs. nonadherent ($n = 59$)	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.02 (0.99–1.05)	0.10	1.02 (0.99–1.05)	0.16
European ancestry	1.48 (0.86–2.54)	0.15	0.54 (0.27–1.09)	0.09
Family history	0.98 (0.57–1.68)	0.93	1.07 (0.59–1.96)	0.82
SES				
1st vs. 2nd tertile	0.97 (0.52–1.82)	0.92	0.84 (0.40–1.80)	0.66
3rd vs 2nd tertile	1.36 (0.73–2.53)	0.34	0.66 (0.34–1.30)	0.23
Having insurance	1.29 (0.66–2.56)	0.46	5.74 (2.51–13.11)	<0.01
DCIS size	1.00 (0.98–1.01)	0.70	1.02 (1.00–1.04)	0.05
DCIS grade				
2 vs. 1	1.11 (0.57–2.18)	0.76	1.48 (0.72–3.04)	0.29
3 vs. 1	1.27 (0.59–2.74)	0.54	2.06 (0.87–4.88)	0.10
Surgical therapy (mastectomy vs. BCS)	0.60 (0.31–1.15)	0.12	0.68 (0.32–1.47)	0.33
Radiotherapy[a]	2.82 (1.56–5.13)	<0.01	2.23 (1.16–4.28)	0.02
Complete local therapy	2.26 (1.30–3.93)	<0.01	2.62 (1.32–5.19)	<0.01
Medical oncology consultation	1.78 (1.01–3.15)	0.05	1.62 (0.82–3.20)	0.16

Abbreviation: BCS, breast conservation surgery.

[a]Excludes mastectomy patients since XRT is not indicated following mastectomy.

possibly decreasing their motivation to continue the medication. DCIS grade was not associated with acceptance or adherence.

Treatment patterns. The use of breast-conserving surgery was slightly more frequent among women who accepted tamoxifen therapy than among those who declined, but this was not statistically significant (86.2% vs. 78.9%, $P = 0.14$). Similarly, patterns of adherence to tamoxifen therapy among those who accepted did not differ significantly between those undergoing breast-conserving surgery and mastectomy. The pattern of radiotherapy use, however, did associate with tamoxifen acceptance in that breast-conserving surgery patients who received radiotherapy comprised 75.2% of tamoxifen acceptors, whereas radiotherapy was used by only 51.8% of decliners, $P < 0.01$. A similar difference was seen for adherence versus nonadherence (78.8% and 58.7%, $P < 0.01$). The receipt of "complete local therapy" (breast-conserving surgery with radiotherapy or mastectomy) was also strongly related to both acceptance of, and adherence to, tamoxifen. Finally, the proportion of patients evaluated by a medical oncologist also differed across acceptance groups; among women who declined tamoxifen, 33.8% were not evaluated by a medical oncologist compared with 19.8% of women who accepted ($P < 0.01$; Table 1).

Univariate logistic regression models showed that acceptance of breast radiotherapy, complete local therapy, and medical oncology consultation were each significantly associated with tamoxifen acceptance. For adherence to tamoxifen, we found significant associations with DCIS size, acceptance of radiotherapy, and complete local therapy, but not with medical oncology consultation (Table 2).

In multivariable logistic regression models shown in Table 3, we observed that the predictors of tamoxifen acceptance were complete local therapy and medical oncology consultation, regardless of whether mastectomy patients were included or excluded. For tamoxifen

Table 3. Multivariable models for tamoxifen acceptance and adherence

Characteristics	OR (95% CI)	*P*
Multivariable models for tamoxifen acceptance ($n = 368$)		
All women: 263 accepted and 71 declined		
Complete local therapy	2.03 (1.14–3.60)	0.02
Medical oncology consultation	1.79 (1.00–3.18)	0.05
BCS group only: 223 accepted and 56 declined		
Received radiotherapy	2.22 (1.26–3.90)	<0.01
Medical oncology consultation	1.76 (0.99–3.15)	0.05
Multivariable models for tamoxifen adherence ($n = 270$)		
All women: 213 were adherent and 57 discontinued		
Received radiotherapy	2.25 (1.14–4.45)	0.02
Uninsured	6.03 (2.60–13.98)	<0.01
BCS only: 184 were adherent and 46 discontinued		
Received radiotherapy	2.66 (1.30–5.43)	<0.01
Uninsured	5.64 (2.25–14.14)	<0.01

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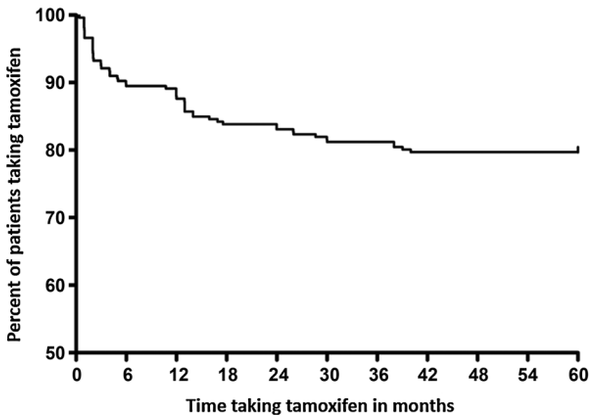

Figure 2.
Kaplan-Meier curve illustrating fall-off in adherence to tamoxifen among women who initiated therapy.

adherence, complete local therapy remained a significant predictor, but a far stronger predictor was the presence of insurance: [OR, 6.03; 95% confidence interval (CI), 2.60–13.98; $P < 0.01$] and (OR, 5.64; 95% CI, 2.25–14.14; $P < 0.01$) in the subset of patients who had breast-conserving surgery).

For women who were nonadherent (i.e., less than 4 years of use), the majority (68%) stopped during the first year of treatment, as shown in Fig. 2. Forty-eight of 56 (86%) of these nonadherent women stopped the drug for a documented adverse effect(s), with the most frequent category (30%) being quality-of-life symptoms. Documented adverse effects and other reasons for discontinuing therapy are listed in Table 4. The frequency of side effects that led to cessation of tamoxifen use was similar in older and younger women: 6 of 29 women (20.69%) aged $\leq$50 experienced side effects and 42 of 243 older women (17.28%) reported side effects and discontinued therapy.

Discussion

The use of tamoxifen by women with ER^+ DCIS has proven value, both for prevention of new primaries, and for prevention of local recurrence, but its impact is mitigated by variable acceptance of tamoxifen therapy by women with DCIS and uncertainties about adherence following initial acceptance. Recent data from health systems and large databases show that the acceptance of tamoxifen therapy following local therapy for DCIS ranges from 22% to 45% (7, 33, 34). At our institution, a previous analysis that included 99 premenopausal women with DCIS found that tamoxifen initiation occurred in 58% (6). We now report data on 368 DCIS patients of all ages who were offered tamoxifen and find a high rate of tamoxifen acceptance of 81%, with the majority of women (72%) who initiate therapy remaining adherent for at least 4 years. These high acceptance and adherence rates are in contrast to those reported from mixed-practice settings and indicate that in a multidisciplinary environment where tamoxifen therapy is offered on the basis of ER positivity of DCIS lesions, and with a structured explanation of risks and benefits, acceptance rates can be far higher than those reported to date. Nevertheless, we also find that tamoxifen acceptance following DCIS resection was significantly less frequent among women aged 50 or younger, although the rate of nonadherence was not significantly lower, and the frequency of side effects in association with discontinuation of therapy was roughly equivalent. Thus, younger women were somewhat more reluctant to accept therapy, but among those who accepted, the side-effect experience and nonadherence were similar to older women.

Table 4. Reasons for nonadherence to tamoxifen ($n = 56$)

Hot flashes, fatigue, joint pain, breast pain, nausea, malaise	17 (30.3%)
Thromboembolic event	5 (8.9%)
Gynecologic: Abnormal bleeding, endometrial hyperplasia, ovarian cyst	8 (14.3)
GI symptoms	5 (8.9%)
Miscellaneous (photopsia, rash)	2 (3.6%)
Adverse effect documented but not described	12 (21.4%)
No documented adverse effect	7 (12.5%)

Abbreviation: GI, gastrointestinal.

Notably, women who accepted tamoxifen therapy were generally compliant with other aspects of their care, including accepting radiotherapy if it was offered to them and returning for follow-up visits for a longer period of time. This was also true of adherence to tamoxifen, but the strongest independent predictor of adherence was the presence of medical insurance. The association between accepting tamoxifen and accepting radiotherapy has been reported previously (6, 7, 34, 35) and is likely to be driven by the fact that women who do not receive radiotherapy tend to have lower risk DCIS lesions. However, when the DCIS lesion has favorable features, patients may be reluctant to undergo any treatment, including tamoxifen. At our institution, surgeons offer tamoxifen therapy to DCIS patients, but even women who may not derive benefit from radiotherapy are encouraged to have a radiation oncology consultation. We did not specifically collect data on the frequency with which radiation oncologists reinforced the recommendation for tamoxifen, but this meeting likely served as an additional opportunity for counseling from another physician and may contribute to the higher tamoxifen acceptance rates among women who receive radiotherapy. We did find that a medical oncology consultation occurred more frequently in women who accepted tamoxifen, and in this respect, our findings point to the added value in having the drug recommended by more than one physician.

We also found that insurance status was a strong determinant of lack of adherence to therapy. Lack of insurance

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may drive patient adherence in a number of ways; the cost of tamoxifen ranges from $10 to $30 per month for uninsured patients (www.goodrx.com), which at first glance appears affordable. However, these women and their families may need to prioritize other needs, so that even a small monthly expense may be unaffordable. It is also possible that lack of insurance may combine with other factors, such as lower access to medical care generally, and lower adherence to other medications. These factors should be examined in further studies, as tamoxifen nonadherence may simply be a manifestation of incomplete access to the health care system. It is also possible that women who have to pay out of pocket are more likely to abandon therapy if they experience side effects. Thus, our data suggest that strategies to increase acceptance should be directed toward facilitating a better understanding of risks and benefits of tamoxifen therapy by patients, and strategies to improve adherence need to address ongoing reports of side effects that may or may not be attributable to tamoxifen, as well as insurance and resource issues. A previous report from our institution examined acceptance and adherence among stage 0–III breast cancer patients aged 45 or less and found fertility concerns to be a major factor determining both initiation and adherence to tamoxifen therapy (6). Existing interventions designed to increase uptake through education typically involve reading materials that aid in the decision to initiate therapy only and have been met with limited success (10, 11, 36, 37); clearly, more work is needed in this area. In particular, the need to convey the smaller risks of therapy in younger women, particularly those in their 40s who have completed childbearing, is not being met with current counseling strategies and deserves special emphasis.

Although the adherence to tamoxifen therapy was higher than in others, we did see, as reported by others (6, 24, 25), that nonadherent patients tend to discontinue tamoxifen within the first year of initiating therapy. Women who were nonadherent in our study most often discontinued the medication within the first 6 months, suggesting the potential value of additional counseling and reassurance during this critical period to help women adapt to symptoms induced by a new daily medication. Our practice includes and emphasizes on documenting continued use of tamoxifen once it has been initiated, and continued counseling regarding ways to limit symptoms, including the use of selective serotonin reuptake inhibitors, and the use of short tamoxifen holidays to resolve whether symptoms are truly related to tamoxifen use. Our data indicate that women who continue taking tamoxifen for at least 1 year will be likely to complete the 5-year course. This concept is generalizable to other medications, including aromatase inhibitors, and has been found in other studies (6, 21, 23, 24).

Our patients had a higher than average SES, a factor which has been variably associated with tamoxifen acceptance in previous studies (38–40); in our population, this parameter was not an independent predictor of either tamoxifen acceptance or adherence in multivariable models. The higher rates of acceptance and adherence that we observed could also be a function of including only women with known ER^+ disease. In earlier studies, ER status has not been considered in evaluating acceptance and adherence in women with DCIS (39–41). Furthermore, the median age of our population reflects a mainly postmenopausal cohort, where disruptions in fertility by tamoxifen are not pertinent.

Previous studies have relied on self-report of women to assess medication adherence, without independent verification (21, 42). A strength of our study is that detailed medical history information was used to track physician recommendations for or against medication use, and in most cases, confirmed by documented prescriptions sent to pharmacies for the duration of the treatment period. Another strength is that we have analyzed factors associated with acceptance of tamoxifen and adherence to tamoxifen separately, and find that factors influencing acceptance differed from those involved in the decision to remain adherent to therapy. Furthermore, the detailed review of EMR revealed that adverse effects were commonly cited as reasons for stopping but were undocumented in 21% nonadherent women, suggesting that better documentation of adverse effects could help guide future counseling strategies. We found an unexpectedly high fraction of women with thromboembolic events, which is likely a chance finding given the size of the population. Several previous studies assessing tamoxifen acceptance are qualitative in design, using a theoretical scenario to establish reasons for accepting or declining (19, 22, 23). Our study provides experiential data from women who were offered tamoxifen in a multidisciplinary setting that included surgeons, medical oncologists, and radiation oncologists and were followed over time by the same team. These physicians are accessible to most patients treated for DCIS, and the potential additive effect of their advice on a patient's decision to accept and adhere to tamoxifen should be confirmed in future studies.

Although the single institution experience we report here can be viewed as a limitation of our study, our results do highlight what can be achieved in terms of tamoxifen adherence and acceptance in a specialized, multidisciplinary setting where endocrine therapy for DCIS is offered in a structured way by multiple physicians. Other limitations include the retrospective design, a relatively homogenous patient population, and abstraction of adherence data from the medical record rather than pill counts or personal patient interview. As data on adverse effects were not often recorded for adherent patients, we cannot conclude that the adverse effect experience was different in adherent and nonadherent women (43, 44). Finally, given recent data on the benefits of aromatase inhibitors [refs], the

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acceptance of and adherence to these agents need to be addressed in future studies.

In summary, our generally high rates of tamoxifen acceptance and adherence may be related to consistent multidisciplinary care of DCIS patients. We hope these can be improved upon by the development of better educational interventions, which could be extended to other medications, as aromatase inhibitors are also now an option for DCIS patients and for women at increased risk for breast cancer. The association between insurance coverage and tamoxifen adherence may reflect factors beyond the actual cost of the drug, and this deserves further study. The recognition of patterns in patient decision-making behavior has the potential to increase the uptake of this and other medications, allowing our patients to derive the full benefit of advances in the treatment and prevention of breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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Authors' Contributions

Conception and design: S. Zaveri, S.A. Khan

Development of methodology: L.C. Karavites, S. Zaveri, S.A. Khan

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L.C. Karavites, A.K. Kane, S. Zaveri, Y. Xu, N. Hansen, K.P. Bethke, S.A. Khan

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L.C. Karavites, S. Zaveri, I. Helenowski, L.J. Rasmussen-Torvik, S.A. Khan

Writing, review, and/or revision of the manuscript: L.C. Karavites, S. Zaveri, L.J. Rasmussen-Torvik, S.A. Khan

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L.C. Karavites, Y. Xu, S.A. Khan

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Lindsey C. Karavites, Anna K. Kane, Shruti Zaveri, et al.

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