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Research Article

Cancer Prevention Research

A System-Level Approach to Improve the Uptake of Antiestrogen Preventive Therapy among Women with Atypical Hyperplasia and Lobular Cancer *In Situ*

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Abstract

Background: The low uptake of antiestrogen preventive therapy among women at high risk of developing breast cancer remains a challenge. We implemented a performance improvement program to increase the uptake of preventive therapy among women with atypical hyperplasia (AH) and lobular cancer *in situ* (LCIS).

Methods: A performance improvement program was implemented at the MD Anderson Cancer Center (Houston, TX), November 2015 to February 2017, for patients with a new (<6 months) or existing (≥6 months) diagnosis of AH/LCIS. The program consisted of an audit of eligible women who were recommended and prescribed preventive therapy and the provision of clinical performance feedback to providers. The baseline uptake of preventive therapy was estimated from patients enrolled in a high-risk breast cohort.

Results: Baseline uptake of preventive therapy was 44%. The program registered 408 patients with a new ($n = 87$) or existing diagnosis ($n = 321$) of AH/LCIS; mean age was 57 and 71% were non-Hispanic white. Ninety-eight percent of patients received a recommendation for preventive therapy. The overall prescribing of preventive therapy to patients with a new or existing diagnosis was 82% (monthly range, 40%–100%; $P_{trend} = 0.76$) and 48% (monthly range, 27%–57%; $P_{trend} < 0.01$), respectively. Adherence among patients with a new or existing diagnosis was 76% and 48% ($P < 0.01$) at 6 months, respectively.

Conclusion: A system-level approach improved the uptake of preventive therapy. Identifying women at the time of diagnosis of AH/LCIS and offering a strong recommendation are key components for improving acceptance and adherence with preventive therapy. *Cancer Prev Res; 11(5); 295–302. ©2018 AACR.*

Introduction

A meta-analysis of randomized trials showed that selective estrogen receptor modulators (SERM) reduce the risk of estrogen receptor–positive invasive breast cancers by approximately 49% in high-risk women (1). In the Breast Cancer Prevention Trial, a risk reduction of 86% and 56% was observed among women with atypical hyperplasia (AH) and lobular cancer *in situ* (LCIS), respectively, who were randomized to receive tamoxifen (2) and the effect endured with longer follow-up (3). Subset analyses from the IBIS-II study suggested that participants with AH/LCIS who were randomized to receive anastrozole had a statistically significant 69% reduction in the risk of invasive breast cancer (4).

On the basis of the strength of this evidence, several organizations recommend that clinicians discuss preventive therapy [i.e., SERMs (tamoxifen, raloxifene) or aromatase inhibitors (anastrozole or exemestane)] with women at high risk of developing breast cancer (5, 6). The National Comprehensive Care Network guidelines state that clinicians should strongly recommend preventive therapy to women with AH and LCIS (7) given their moderately high risk of developing breast cancer (7%–25% at 10 years; refs. 8–10) and greater benefit from preventive therapy (1, 2). The strong recommendation is

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Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

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also supported by decision model analyses that have shown a survival and quality-adjusted survival benefit of tamoxifen, after accounting for the potential risks associated with therapy, among women with AH/LCIS (11). Despite calls for providers to adopt these guidelines, uptake has remained low with <1% of eligible women in the general population (12) and 20% to 30% of women with AH/LCIS in high-risk clinics estimated to have received preventive therapy (13, 14).

To date, interventions to increase uptake of preventive therapy have largely focused on using decision support or educational tools with patients and have had limited success (15, 16). There is an opportunity to use audit and feedback as a strategy to improve providers' recommending and prescribing preventive therapy. This type of intervention has been shown to improve providers' clinical performance, although there is a limited understanding of the theoretical mechanisms underlying the behavioral change (17, 18). We implemented a performance improvement program that consisted of the assessment of eligible women with AH/LCIS who were recommended and prescribed preventive therapy (audit) and the provision of the clinical performance summary (feedback) to individual providers. The goals of the program were to increase the uptake of preventive therapy among women with AH/LCIS and to assess their short-term adherence.

Materials and Methods

Practice settings

The performance improvement program was implemented at the MD Anderson Cancer Prevention Center (Houston, TX) and its satellite clinics (i.e., Houston Area Locations). The providers in these practice settings consisted of physicians ($n = 14$) and advanced nurse practitioners ($n = 12$).

Dissemination of evidence-based clinical practice guidelines

An evidence-based Breast Cancer Preventive Therapy algorithm for the management of patients at high risk of developing breast cancer was developed and approved by the Executive Committee of the Medical Staff at MD Anderson Cancer Center (https://www.mdanderson.org/content/dam/mdanderson/documents/for-physicians/algorithms/screening/risk-reduction-breast-web-algorithm.pdf) and was disseminated to providers. Meeting presentations were conducted to review the scientific evidence and national guidelines for preventive therapy and to discuss strategies for overcoming barriers to prescribing preventive therapy. Given the potential negative connotation of the term "chemoprevention" (19), providers were encouraged to use the terms "preventive therapy" or "risk reduction therapy" when discussing preventive therapy with their patients. Providers were also encouraged to consistently communicate a strong recommendation for preventive therapy (7).

Implementation of the performance improvement program

The program was implemented from November 2015 to February 2017. Patients with AH/LCIS were screened prior to their clinic appointment to determine eligibility for registration. Providers were alerted to their patients registered on the program. The registration criteria included (i) age $\geq$35; (ii) diagnosis of AH/LCIS; and (iii) had not previously completed 5 years of preventive therapy. We excluded premenopausal women with a medical contraindication to tamoxifen, for example, history of thromboembolic disease as they were also not eligible for aromatase inhibitors. Women diagnosed with AH/LCIS $\leq$6 months and >6 months prior to their clinic appointment were categorized as having a "new diagnosis" and "existing diagnosis," respectively. Immediately after the clinic visit, providers and patients were asked to complete a self-administered survey. The provider survey included questions about the strength of their recommendation for preventive therapy on a scale of 1 (not recommended) to 5 (highly recommended). The patient survey included questions about the strength of the provider's recommendation for preventive therapy on the scale of 1 to 5 and the reasons why the patient accepted or declined preventive therapy. If a patient declined or was undecided about preventive therapy, she was scheduled for a follow-up appointment in 6 months and continued on the program.

Performance targets were set for recommending preventive therapy to 100% of eligible patients and prescribing preventive therapy to 80% of eligible patients. The choice of preventive therapy (i.e., SERM or aromatase inhibitor) was left to each provider's discretion. Providers received a monthly clinic-level summary of the percentage of patients who received a recommendation and prescription for preventive therapy. Quarterly, each provider received a confidential summary of the percentage of patients seen by that provider who received a recommendation and prescription for preventive therapy. The study protocol was approved by the MD Anderson Cancer Center Quality Improvement Assessment Board.

Assessment of adherence

Patient self-reported adherence with taking preventive therapy was assessed at their 3- and/or 6-month follow-up visit. Appointment reminders were communicated via mail and the electronic medical record. Patients who failed to return for either the 3- or 6-month follow-up visit were assumed to be nonadherent at that time point.

Assessment of baseline uptake of preventive therapy

The baseline uptake of preventive therapy among patients with AH/LCIS seen in the Cancer Prevention

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Table 1. Baseline uptake of preventive therapy among women with atypical hyperplasia/lobular cancer *in situ* enrolled in the high-risk breast cohort ($n = 626$), September, 2011–October, 2015

		Preventive therapy		
	Total $n = 626$	Yes ($n = 279$) *n* (%)	No ($n = 347$) *n* (%)	*P*
Type of lesion				
Lobular carcinoma *in situ*	110	57 (51.8)	53 (48.2)	
Atypical hyperplasia	516	222 (43.0)	294 (57.0)	0.11
Age				
≤40	30	4 (13.3)	26 (86.7)	
41–50	136	63 (46.3)	73 (53.7)	
51–60	243	106 (43.6)	137 (56.4)	
>60	217	106 (48.8)	111 (51.2)	<0.01
Race/ethnicity				
Non-Hispanic White	473	222 (46.9)	251 (53.1)	
Non-Hispanic Black	45	15 (33.3)	30 (66.6)	
Asian	28	8 (28.6)	20 (71.4)	
Hispanic	61	28 (45.9)	33 (54.1)	
Other	19	6 (31.6)	13 (68.4)	0.21
Education status				
High school and below	90	41 (45.6)	49 (54.4)	
Above high school	536	238 (44.4)	298 (55.6)	0.90
Marital status				
Married	479	218 (45.5)	261 (54.5)	
Widowed	38	19 (50.0)	19 (50.0)	
Divorced/separated	80	31 (38.7)	49 (61.3)	
Never married	28	10 (35.7)	18 (64.3)	
Missing	1	1 (100.0)	0 (0.0)	0.46
Employment status				
Employed	352	163 (46.3)	189 (53.7)	
Homemaker	91	37 (40.7)	54 (59.3)	
Retired	139	66 (47.5)	73 (52.5)	
Disabled/unemployed	21	8 (38.1)	13 (61.9)	
Student/other	22	4 (18.2)	18 (81.8)	
Missing	1	1 (100.0)	0 (0.0)	0.08

Center was estimated using data collected from the Longitudinal High Risk Breast Cohort ($n = 2{,}161$), which began enrolling high-risk women seen in the Cancer Prevention Center, September 1, 2011. The inclusion criteria are age ≥18 years, cancer-free, and at high risk of developing breast cancer as defined by either: Gail model 5-year risk of developing invasive cancer of ≥1.66% or lifetime risk ≥20%, history of ductal cancer *in situ*, LCIS, or AH, history of germline mutation in a breast cancer susceptibility gene, or mantle radiation prior to age 30. Participants of the High Risk Breast Cohort are asked to complete a self-administered questionnaire at the time of enrollment (baseline) and annually. The baseline and annual questionnaires include questions about demographic information, breast cancer risk factors, and current or past use of preventive therapy (i.e., tamoxifen, raloxifene, anastrozole, exemestane).

We reviewed the data from a subset of the cohort participants with a diagnosis of AH/LCIS ($n = 630$) who enrolled from September 1, 2011, to October 2015. The percentage of women who reported current or past use of preventive therapy was assessed from the baseline and annual follow-up questionnaires. Women with missing information on use of antiestrogen preventive therapy on all of the questionnaires administered were excluded ($n = 4$). The final study analysis consisted of 626 women with AH/LCIS. The study protocol was approved by the MD Anderson Cancer Center Institutional Review Board.

Statistical analysis

χ^2 and Fisher exact tests were used to test the association between the categorical variables and preventive therapy acceptance status. Descriptive statistics of survey responses were generated. We performed the χ^2 test for trend in proportions to test the significance of the trend of prescribing of preventive therapy for patients with a new or existing diagnosis in R (version 3.2.0). All statistical tests were performed at two-sided significance level of 0.05. Data were processed and analyzed with SAS version 9.3 software (SAS Institute Inc., Cary, NC) and R (version 3.2.0).

Results

Baseline uptake of preventive therapy

Table 1 lists the demographic characteristics of participants with AH/LCIS ($n = 626$) enrolled in the High Risk Cohort who were included in the study analysis. Approximately 44% of participants with AH/LCIS reported current or past use of preventive therapy. Among participants who reported using preventive therapy, 71% received

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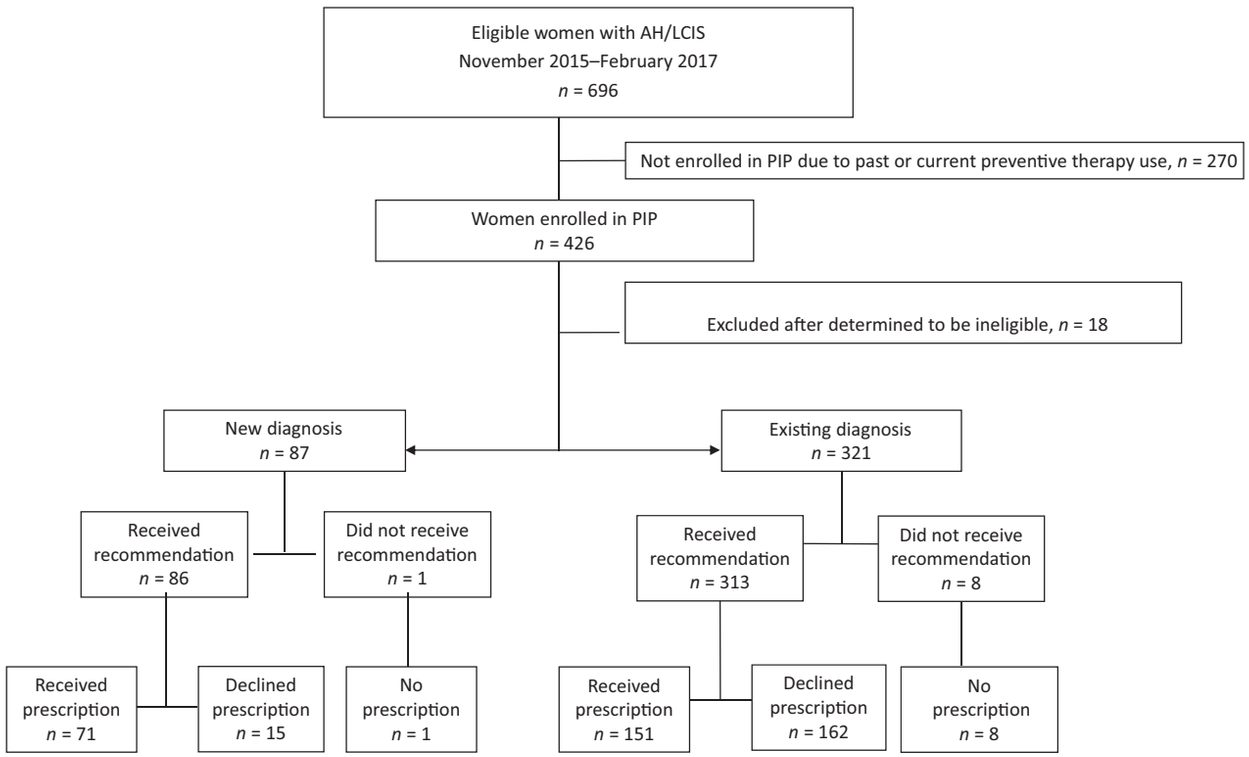

Figure 1.
Flow chart of patients enrolled in performance improvement program.

tamoxifen, 28% received raloxifene, and 1% received an aromatase inhibitor. Age was associated with use of preventive therapy ($P < 0.01$).

Characteristics of patients enrolled on the performance improvement program

Between November 2015 and February 2017, 696 eligible patients with a new or existing diagnosis of AH/LCIS were evaluated for registration in the program and 270 (39%) had past or current preventive therapy use (Fig. 1). A total of 426 patients were enrolled in the program. Eighteen patients were subsequently deemed to be ineligible for preventive therapy due to the presence of multiple comorbidities. Therefore, 408 patients with a new ($n = 87$) or existing diagnosis ($n = 321$) of AH/LCIS were included in the study analysis. The mean age was 57 (range, 35–79) and 71% were non-Hispanic white (Table 2).

Provider recommending and prescribing of preventive therapy

The majority of patients (98%) received a recommendation for preventive therapy, and a monthly 93% to 100% recommendation rate was sustained over the program period (Supplementary Fig. S1).

Among patients who received a recommendation, 82% with a new and 48% with an existing diagnosis of AH/LCIS accepted therapy. The monthly trend of prescribing preventive therapy in patients with a new or existing diagnosis of AH/LCIS ranged from 40% to 100% ($P_{trend} = 0.76$) and 27% to 57% ($P_{trend} \leq 0.01$), respectively (Fig. 2). The clinical factors associated with accepting preventive therapy were having a new versus existing diagnosis of AH/LCIS ($P < 0.01$). Among patients with an existing diagnosis, shorter time from diagnosis of AH/LCIS to enrollment was associated with accepting preventive therapy ($P_{trend} = 0.04$; Table 2). There was no statistically significant association between the type of proliferative lesion, age, or race/ethnicity and accepting preventive therapy. There was also no correlation between the timing of receipt of the quarterly individual provider-level performance measure and the percentage of patients who were prescribed preventive therapy (Fig. 2). The agents prescribed were tamoxifen (56%), raloxifene (40%), and an aromatase inhibitor (4%).

Patient-reported reasons for declining preventive therapy

Surveys were administered to 320 patients (78%) enrolled in the program. The patient and provider survey completion rates were 70% and 87%, respectively. Providers gave a strong (score 4–5) recommendation for preventive therapy at 97% of the appointments, whereas 85%

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Table 2. Demographic and clinical characteristics of patients enrolled in the performance improvement program ($n = 408$), November 2015–February 2017

		Preventive therapy		
		Yes ($n = 222$)	No ($n = 186$)	
	Total $n = 408$	n (%)	n (%)	P
Type of lesion				
Lobular carcinoma *in situ*	68	40 (58.8)	28 (41.2)	
Atypical hyperplasia	340	182 (53.5)	158 (46.5)	0.50
Age				
≤40	9	8 (88.8)	1 (11.2)	
41–50	81	44 (54.3)	37 (45.7)	
51–60	175	96 (54.8)	79 (45.2)	
≥61	143	74 (51.7)	69 (48.3)	0.19
Race/ethnicity				
White	291	161 (55.3)	130 (44.7)	
Black	35	17 (48.6)	18 (51.4)	
Hispanic	45	27 (60.0)	18 (40.0)	
Asian	30	15 (50.0)	15 (50.0)	
Other	7	2 (28.6)	5 (71.4)	0.53
Diagnosis status				
New	87	71 (81.6)	16 (18.4)	
Existing	321	151 (47.0)	170 (53.0)	<0.01
Time from diagnosis to enrollment (years)[a]				
Median 6.2 (range, 0.6–33.2)				
≤3	87	49 (56.3)	38 (43.7)	
>3–9	142	61 (42.9)	81 (57.1)	
>9–15	66	32 (48.5)	34 (51.5)	
>15	24	7 (12.2)	17 (70.8)	0.07
				$P_{trend} = 0.04$

[a]Among patients with an existing diagnosis of atypical hyperplasia/lobular cancer *in situ*.

of patients reported receiving a strong (score 4–5) recommendation for preventive therapy. Sixty-two percent of patients with an existing diagnosis of AH/LCIS reported being very concerned about side effects as the reason for declining preventive therapy compared with 25% with a new diagnosis ($P = 0.06$; Fig. 3). Twenty-five percent of patients with a new diagnosis compared with 2% with an existing diagnosis of AH/LCIS reported that their provider did not strongly recommend preventive therapy as their reason for declining therapy ($P = 0.03$; Fig. 3).

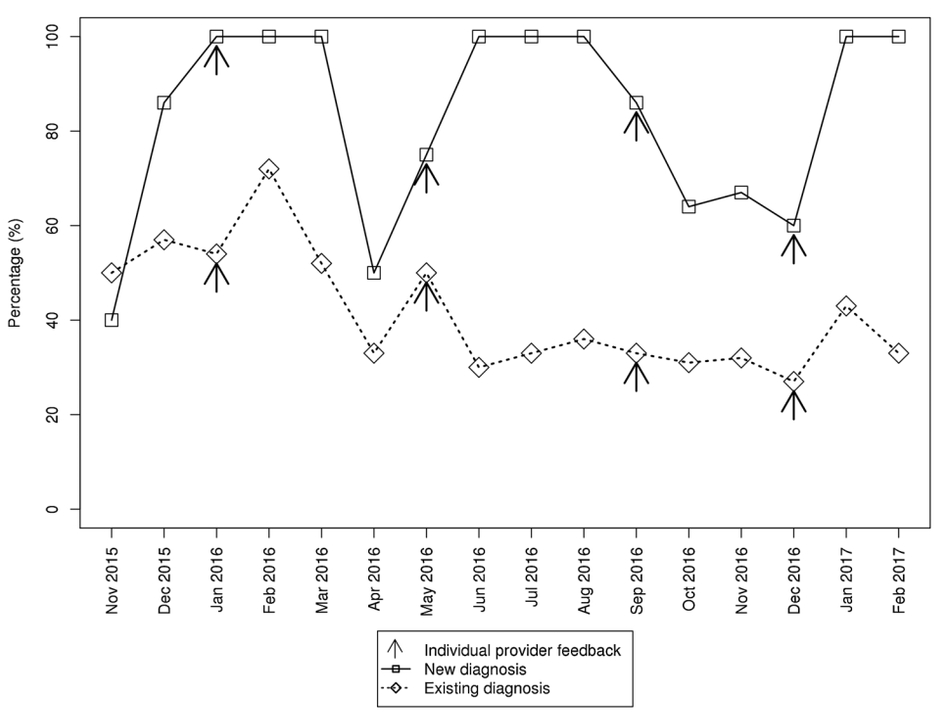

Figure 2.
Trend of percentage of patients prescribed preventive therapy by diagnosis status, November 2015–February 2017.

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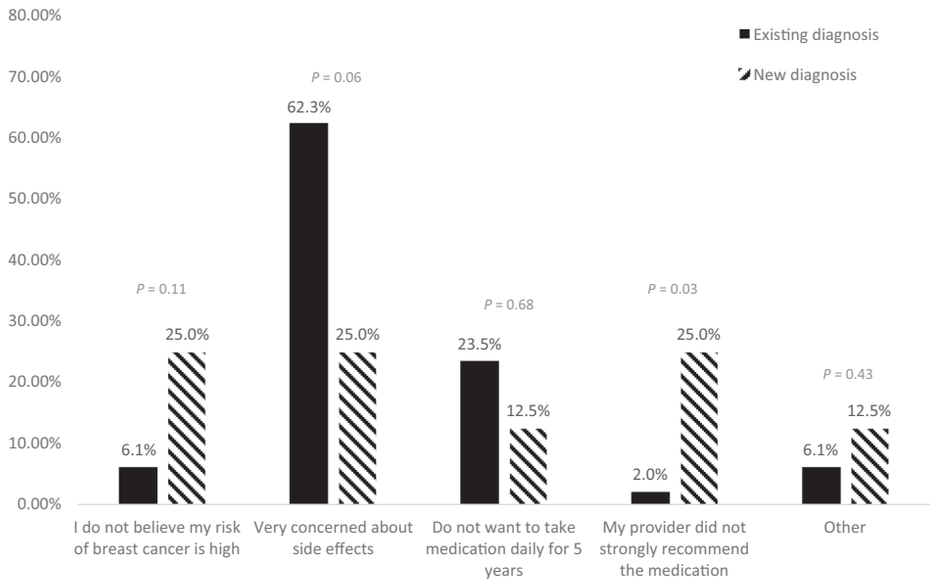

Figure 3.
Patient-reported reasons for declining preventive therapy by diagnosis status.

Adherence with preventive therapy

A total of 201 (90%) and 160 patients (72%) who accepted preventive therapy were due for a 3- and 6-month follow-up visit, respectively. The frequency of no-shows was 35% and 13% at the 3- and 6-month follow-up visit. Overall adherence with preventive therapy was 38% and 51% at the 3- and 6-month follow-up. Adherence with preventive therapy was higher among patients with a new compared with an existing diagnosis at both 3 months (48% vs. 33%, $P = 0.04$) and 6 months (76% vs. 48%, $P < 0.01$), respectively (Supplementary Fig. S2).

Discussion

The measuring and reporting of performance measures is increasingly being used in health care systems to improve the quality and delivery of preventive care (20). We conducted a proof-of-principle study to determine whether a performance improvement program using an audit and feedback strategy could achieve an increase in the uptake of preventive therapy. The program resulted in providers recommending preventive therapy to 98% of eligible patients and prescribing preventive therapy to 82% of eligible women with a new diagnosis of AH/LCIS.

Barriers to prescribing preventive therapy that have been reported by primary care providers include lack of knowledge about preventive options, lack of time with patients, and lack of training in risk/benefit counseling (21–23). Paradoxically, risk/benefit counseling has been shown to reduce the uptake of preventive therapy (15) presumably by causing women to overestimate the risks of treatment (24). The high acceptance of preventive therapy and lower concern about potential side effects that was observed among women with a new diagnosis of AH/LCIS could be attributed to providers giving an initial "strong recommendation" for preventive therapy. It is well recognized that patients are more likely to accept preventive services if recommended by their providers (25, 26); however, there are other factors including the patient's own perspectives, values, and experiences that are known to play an important role in the decision-making process about preventive therapy (27).

The most commonly cited reasons by patients for declining preventive therapy are fear of side effects, including endometrial cancer, thromboembolic disease, and menopausal symptoms (22, 23, 28). Indeed, we found that concern about side effects was the primary reason for declining preventive therapy in addition to other previously reported barriers such as having an aversion to additional medications (29) and risk of breast cancer not perceived to be sufficiently high (30). The longer the time from diagnosis of AH/LCIS to enrollment in the program, the less likely women were to accept or be adherent with preventive therapy supporting prior findings that perceptions of personal risk and breast cancer–related anxiety evolve over time and can affect decision making and treatment satisfaction (31–33). Other studies have reported suboptimal adherence to preventive therapy with 40% to 70% complete adherence among women enrolled in clinical trials (34–37) and 60% adherence in the clinical setting (38). Interventions to improve adherence with preventive therapy are needed, preferably that focus on provider–patient communication on managing side effects (39).

There were several limitations of the study. We were unable to evaluate the specific components of the program that contributed to the improvement in prescribing preventive therapy or the role of other factors not evaluated in the study. For example, uptake trends did not correlate with receipt of the clinic-level or individual provider-level

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feedback. Patient characteristics, for example, socioeconomic status, education level, and presence of comorbidities, were not assessed and may have influenced acceptance and adherence with preventive therapy. It is possible that the baseline uptake of preventive therapy estimated from the self-reported use of preventive therapy among participants in the High Risk Breast Cohort may not have accurately represented uptake among patients with AH/LCIS enrolled in the performance improvement program. However, the uptake of preventive therapy among participants in the High Risk Breast Cohort is likely to be higher than would be expected in the clinic setting as women who volunteer for research studies are also more predisposed to accept preventive therapy (31), reflective of a healthy volunteer bias.

In conclusion, we have demonstrated the feasibility of changing clinical practice and influencing patient decision making about preventive therapy over a short period of time with the implementation of a performance improvement program. Identifying women at the time of their diagnosis of AH/LCIS and offering a timely strong recommendation for preventive therapy appear to be key components for improving patient acceptance and adherence with preventive therapy. Future research is needed to evaluate the feasibility of disseminating a preventive therapy performance measure to the primary care setting for women with AH/LCIS and other high-risk women whose suitability may need to be further assessed using risk/benefit assessment tools (40).

Disclosure of Potential Conflicts of Interest

T. Bevers has received speakers bureau honoraria from NCCN. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: A.M. Brewster, P. Brown, L. Middleton, T. Bevers

Development of methodology: A.M. Brewster, P. Thomas, R. Coyne, L. Middleton, K. Do, T. Bevers

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.M. Brewster, P. Thomas, P. Brown, R. Coyne, C. Checka, L. Middleton, T. Bevers

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.M. Brewster, P. Thomas, P. Brown, Y. Yan, K. Do, T. Bevers

Writing, review, and/or revision of the manuscript: A.M. Brewster, P. Thomas, P. Brown, Y. Yan, C. Checka, L. Middleton, K. Do, T. Bevers

Study supervision: A.M. Brewster

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