Research Article

Cancer Prevention Research

Chemoprevention Uptake among Women with Atypical Hyperplasia and Lobular and Ductal Carcinoma *In Situ*

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Abstract

Women with atypical hyperplasia and lobular or ductal carcinoma *in situ* (LCIS/DCIS) are at increased risk of developing invasive breast cancer. Chemoprevention with selective estrogen receptor modulators or aromatase inhibitors can reduce breast cancer risk; however, uptake is estimated to be less than 15% in these populations. We sought to determine which factors are associated with chemoprevention uptake in a population of women with atypical hyperplasia, LCIS, and DCIS. Women diagnosed with atypical hyperplasia/LCIS/DCIS between 2007 and 2015 without a history of invasive breast cancer were identified ($N = 1{,}719$). A subset of women ($n = 73$) completed questionnaires on breast cancer and chemoprevention knowledge, risk perception, and behavioral intentions. Descriptive statistics were generated and univariate and multivariable log-binomial regression were used to estimate the association between sociodemographic and clinical factors and chemoprevention uptake. In our sample, 29.3% had atypical hyperplasia, 23.3% had LCIS, and 47.4% had DCIS; 29.4% used chemoprevention. Compared with women with atypical hyperplasia, LCIS [RR, 1.43; 95% confidence interval (CI), 1.16–1.76] and DCIS (RR, 1.54; 95% CI, 1.28–1.86) were significantly associated with chemoprevention uptake, as was medical oncology referral (RR, 5.79; 95% CI, 4.80–6.98). Younger women were less likely to take chemoprevention (RR, 0.61; 95% CI, 0.42–0.87), and there was a trend toward increased uptake in Hispanic compared with non-Hispanic white women. The survey data revealed a strong interest in learning about chemoprevention, but there were misperceptions in personal breast cancer risk and side effects of chemoprevention. Improving communication about breast cancer risk and chemoprevention may allow clinicians to facilitate informed decision-making about preventative therapy. *Cancer Prev Res; 10(8); 434–41. ©2017 AACR.*

Introduction

Breast cancer is the most commonly diagnosed cancer among women in the United States, leading to over 40,000 deaths annually (1). The national costs of surveillance and treatment of breast cancer are expected to surpass $20 billion by 2020 (2). It is estimated that at least 15% of women, ages 35 to 75 years, in the United States are considered at high risk for breast cancer, defined as having a greater than 1.67% 5-year risk or greater than 20% lifetime risk of developing invasive breast cancer according to the Gail model (3). Factors that greatly increase the risk of invasive breast cancer development include atypical hyperplasia, lobular carcinoma *in situ* (LCIS), or ductal carcinoma *in situ* (DCIS). It is estimated that atypical hyperplasia increases the risk for invasive breast cancer by 3.7 to 5.3 times relative to women with nonproliferative breast disease (4). Coopey and colleagues reported that the 10-year risk of invasive and noninvasive breast cancer after a diagnosis of atypical ductal or lobular hyperplasia is 17.3% and 20.7%, respectively (5). LCIS is estimated to increase the risk of breast cancer by approximately 7 to 10 times the general population with an estimated 10-year breast cancer risk of 23.7% (5, 6). DCIS also significantly increases the risk of invasive breast cancer, with an estimated 11.2% of women developing a subsequent invasive breast cancer within 10 years (7). One preventative strategy available to these high-risk women is the use of chemoprevention with selective estrogen receptor modulators (SERM) and aromatase inhibitors (AI) to reduce the risk of estrogen receptor–positive (ER^+) breast cancer.

The FDA approved the SERM tamoxifen in 1999 and raloxifene in 2007 for the primary prevention of breast cancer among women who met high-risk criteria (8, 9). In a randomized controlled, double-blind trial of tamoxifen for 5 years versus placebo, high-risk women who took tamoxifen had an RR of breast cancer of 0.57 [95% confidence interval (CI), 0.46–0.70; ref. 10]. Although raloxifene has only 81% of the efficacy of tamoxifen in reducing the risk of breast cancer, there is a lower risk of serious side effects, such as endometrial cancer and thromboembolism, and a decrease in the risk for osteoporotic fractures (11, 12). In the randomized, double-blind, placebo-controlled trial of the AI, exemestane, for chemoprevention published in 2011, there was a 65% RR reduction in invasive breast cancer (HR, 0.35; 95% CI, 0.18–0.70) when compared with placebo (13). The

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IBIS-II trial investigated the efficacy of anastrozole, another AI, in preventing breast cancer in high-risk postmenopausal women. Compared with placebo, there was a 50% risk reduction in invasive breast cancer (HR, 0.50; 95% CI, 0.32–0.76; ref. 14). The risk of serious side effects among women who take AIs is lower compared with tamoxifen (13, 14). Among women with LCIS and atypical hyperplasia, the data suggest that SERMs and AIs could afford greater benefits to these particularly high-risk populations (10, 14). Although not all of the chemoprevention trials included women with DCIS, three large randomized controlled trials demonstrated that adjuvant tamoxifen or anastrozole for 5 years significantly prevented subsequent breast cancers in women with DCIS undergoing lumpectomy plus radiation (15–17).

The U.S. Preventive Services Task Force has recommended that physicians discuss chemoprevention options with their high-risk patients (18). Despite the potential of these therapies to reduce the incidence of invasive breast cancer in the United States, their uptake among high-risk women has been estimated to be lower than 15% (19). Multiple factors contribute to the low uptake of breast cancer chemoprevention, including concerns about side effects and lack of clinician knowledge about use of SERMs or AIs for breast cancer risk reduction (19, 20). Limited research has been published analyzing the sociodemographic and clinical factors associated with chemoprevention uptake among high-risk women, including those with atypical hyperplasia, LCIS, and DCIS (5, 21). The objective of our study is to identify which demographic and clinical factors are associated with the decision to use chemoprevention among women with a history of atypical hyperplasia, LCIS, or DCIS seen at an academic medical center. We also examined breast cancer risk perceptions, beliefs, and attitudes about chemoprevention decision-making among a subset of these high-risk women.

Materials and Methods

Study population and selection criteria

We conducted a retrospective cohort study of patients who received a diagnosis of atypical hyperplasia, LCIS, or DCIS at Columbia University Medical Center (CUMC) in New York, NY, between 2007 and 2015 to determine predictors of chemoprevention uptake. Inclusion criteria for the study included: (i) history of atypical hyperplasia, LCIS, or DCIS without concurrent or prior invasive breast cancer; (ii) for subjects with DCIS, evidence of ER^+ and/or progesterone receptor–positive (PR^+) tumor status. Subjects with a history of bilateral mastectomy were excluded. All subjects were considered eligible for chemoprevention use based on their diagnosis of atypical hyperplasia, LCIS, or ER^+ and/or PR^+ DCIS. This study was approved by the Institutional Review Board at CUMC and was conducted in accordance with recognized ethical guidelines.

Data collection from the electronic health record

Subject demographics, breast cancer risk factors, and medical information were collected through a chart review and data extraction of the electronic health record (EHR) at CUMC. The EHR captured data from diagnostic codes, breast pathology reports, and outpatient clinic notes, including referrals to breast oncology. The EHR data extraction also included the New York-Presbyterian Hospital tumor registry, which identified incident cases of LCIS and DCIS. All subjects with a diagnosis of atypical hyperplasia or LCIS/DCIS were initially identified by their corresponding ICD-9/10 codes in these databases, 610.9/N60.99 and 233.0/D05.90, respectively. As LCIS and DCIS share the same ICD-9 and 10 codes, the NYP tumor registry and outpatient medical records were used to ascertain the appropriate diagnosis for each subject. If subjects had more than one diagnosis, they were classified by their most advanced breast lesion (DCIS > LCIS > atypical hyperplasia). Any chart documentation of invasive breast cancer was identified with the ICD-9 code 174.9. Tumor registry and pathology reports were used to identify subjects who had invasive breast cancer prior to or concurrently with being diagnosed with atypical hyperplasia, LCIS, or DCIS.

Other covariates collected included age, race, and ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian, and other), menopausal status, body mass index (BMI), hormone replacement therapy (HRT) use, family history of breast cancer (yes/no), history of hysterectomy, history of thromboembolism (deep vein thrombosis, pulmonary embolus, or stroke), history of uterine cancer, and medical oncology referral. Subjects who were missing information on their menopausal status were considered postmenopausal if they were over 55. Subjects missing information for their BMI were classified as unknown.

The primary outcome of interest was SERM or AI use as documented in the medication list of the EHR at any point in time and was dichotomized as yes/no ever use. Type of chemoprevention used was also identified and categorized as tamoxifen, raloxifene, AI (e.g., anastrozole, exemestane, letrozole), or multiple agents (i.e., patients may switch medications due to toxicities).

Data collection from patient-administered questionnaires

A subset of participants from the larger retrospective cohort was recruited to complete questionnaires during their first visit with a medical oncologist at CUMC. After providing informed consent, all subjects completed a baseline self-administered questionnaire in English or Spanish. Breast cancer knowledge was assessed with a 4-item scale, with adequate knowledge defined as >50% correct responses (22). Breast cancer risk perception was assessed by asking subjects to rate their chance of developing breast cancer and how it compares with other women (23). Breast cancer worry was a composite of patient responses to two questions on a 7-point Likert scale (24, 25). Subjects were presented with 12 reasons for taking preventive action to lower risk for breast cancer and asked to rate how true each statement was on a 5-point Likert scale (26). Chemoprevention behavioral intention and decision satisfaction were assessed using items defined by Korfage and colleagues (27). Knowledge and worry about chemoprevention side effects were assessed using items defined by Fagerlin and colleagues (28). Acculturation, health literacy, and numeracy were assessed using brief validated measures of each construct (29–31).

Statistical analysis

Subjects were stratified according to whether or not they had ever taken chemoprevention, and descriptive statistics of sociodemographic and clinical characteristics were generated. χ^2 test or Fisher exact test for cell ranges below 5 were used to compare the distribution of risk factors between those who did and did not take chemoprevention. Univariate analysis was conducted to give an unadjusted estimate of the risk associated with each variable on the outcome of chemoprevention use. Because the primary outcome of chemoprevention uptake was relatively

common in our study population, log-binomial regression was used to calculate and report RR rather than ORs (32). A multivariable model was constructed using log-binomial regression to assess the relationship between breast disease (atypical hyperplasia, LCIS, DCIS) and chemoprevention uptake when adjusted for other variables. The model was adjusted *a priori* for breast disease, age, and race/ethnicity. Variables that had an association of $P < 0.05$ in univariate analysis were also included in the final model. Menopausal status was excluded from the final model because it is highly correlated with age. For the subset of subjects who received the patient-administered questionnaire, descriptive statistics of sociodemographic and clinical characteristics, as well as survey responses, were generated. All statistical analysis was conducted using SAS version 9.4 (SAS Institute), and a P value of <0.05 was considered statistically significant.

Results

Results of EHR analysis

During the study period of January 2007 to December 2015, approximately 2,933 subjects with an ICD-9/10 code for atypical hyperplasia or LCIS/DCIS were initially identified through the EHR. Of these subjects, 1,719 (58.6%) met all inclusion criteria and were included in our final analysis. Of the 1,214 subjects excluded from the original dataset, 1,066 (87.8%) had evidence of invasive breast cancer either before or concurrently with their diagnosis of atypical hyperplasia, LCIS, or DCIS. An additional 58 (4.8%) were excluded due to history of bilateral mastectomy or ER/PR–negative DCIS, and 90 (7.4%) were excluded because there was no clarification of whether they had LCIS or DCIS in their medical record. Figure 1 depicts a CONSORT diagram describing our study population.

Table 1 describes the baseline characteristics of the study population. The mean age of our sample was 60 years, with a range of 21 to 98 years, and over two thirds were postmenopausal. Our sample was racially and ethnically diverse with 44.9% non-Hispanic white, 9.2% non-Hispanic black, 23.1% Hispanic, 5.9% Asian, and 16.9% other. In our total sample, 815 (47.4%) had DCIS, 401 (23.3%) had LCIS, and 503 (29.3%) had atypical hyperplasia. About a third of these women had been seen by a medical oncologist. Relatively few subjects had chart documentation of hysterectomy (2.6%), HRT use (2.9%), history of thromboembolism (2.2%), or uterine cancer (0.6%).

Among the 1,719 subjects included in our final analysis, 505 (29.4%) had a history of ever using SERMs or AIs. Approximately 16.5% of patients with atypical hyperplasia used a SERM or AI, compared with 26.7% of patients with LCIS, and 38.7% of patients with DCIS. The breakdown of chemoprevention used was 274 (54.3%) tamoxifen, 78 (15.4%) raloxifene, 97 (19.2%) aromatase inhibitors, and 56 (11.1%) used multiple agents. Figure 2 describes the distribution of type of chemoprevention stratified by breast histology type.

In univariate analysis (Table 2), type of breast disease, age, menopausal status, race/ethnicity, BMI, family history of breast cancer, HRT use, and medical oncology referral were associated with chemoprevention uptake. Our multivariable model was adjusted for age, race/ethnicity, family history, breast disease, HRT use, and medical oncology referral. Compared with women with atypical hyperplasia, those with a history of LCIS were 1.43 (95% CI, 1.16–1.76) times as likely and subjects with DCIS were 1.54 (95% CI, 1.28–1.86) times as likely to take chemoprevention. Age was also significantly associated with chemoprevention uptake. Women less than 45 years old and those over age 75 were also less likely to initiate chemoprevention. Race and ethnicity were no longer significantly associated in the multivariable model; however, the association between Hispanic women and chemoprevention use approached significance ($P = 0.075$). The strongest predictor of chemoprevention uptake was medical oncology referral. Subjects who were seen by a medical oncologist were 5.79 times as likely to take chemoprevention when compared with those who did not receive a referral (95% CI, 4.80–6.98).

Results of patient-administered questionnaires

A subset of 73 women completed validated questionnaires after an initial visit with a medical oncologist. The subset was slightly younger than the full cohort (mean age, 53.5 years and 54.8% postmenopausal), and the distribution of race/ethnicity was similar to that of the full cohort. Thirty-five women (47.8%) had atypical hyperplasia, 17 (23.3%) had LCIS, and 21 (28.77%) had ER^+ and/or PR^+ DCIS. Thirty-one (42.8%) subjects opted for chemoprevention, with 54.8% of those patients taking tamoxifen, 25.8% taking AIs, 9.7% taking raloxifene, and 9.7% taking multiple medications.

The sample generally showed high levels of acculturation, health literacy, and numeracy. Scores on a breast cancer knowledge index were relatively high, with 61.4% of subjects demonstrating adequate breast cancer knowledge. When these high-risk women were asked to rate their chance of developing breast cancer, 49.3% of subjects rated their chance as "moderately" or "very" high. Similarly, 52.2% of subjects considered their chance of developing breast cancer to be much higher than their peers. The majority of respondents agreed or strongly agreed with statements that reflected personal reasons for seeking out treatment for lowering breast cancer risk. "I want to improve my health" (93.1%), "I want to live longer" (95.8%), and "I want to avoid getting breast cancer treatment" (85.9%) were the most commonly cited reasons for taking action to reduce risk. Less common responses were those that related to family or friends getting breast cancer or encouragement from others to take action. With respect to side effects of chemoprevention, 71.6% of subjects were very worried or extremely worried about the side effects, and 56.9% thought the side effects were very serious or extremely serious. Approximately 50.7% of subjects reported that they did not want to take a pill every day. Despite discussing chemoprevention with a medical oncologist, only 50% thought the benefits of preventative therapy were worth the risks.

After initial consultation with a medical oncologist, 52.9% of subjects felt they had enough information about chemoprevention to make a decision on whether or not to take it. The majority of participants (78.6%) indicated that they would be very or extremely likely to speak with their health care provider about chemoprevention drugs in the future. Among subjects who had taken chemoprevention, 50% indicated that they were very or extremely satisfied with their decision and an additional 37.5% were moderately satisfied.

Discussion

A prior systematic review reported chemoprevention uptake to be approximately 14.8% among high-risk women who are offered

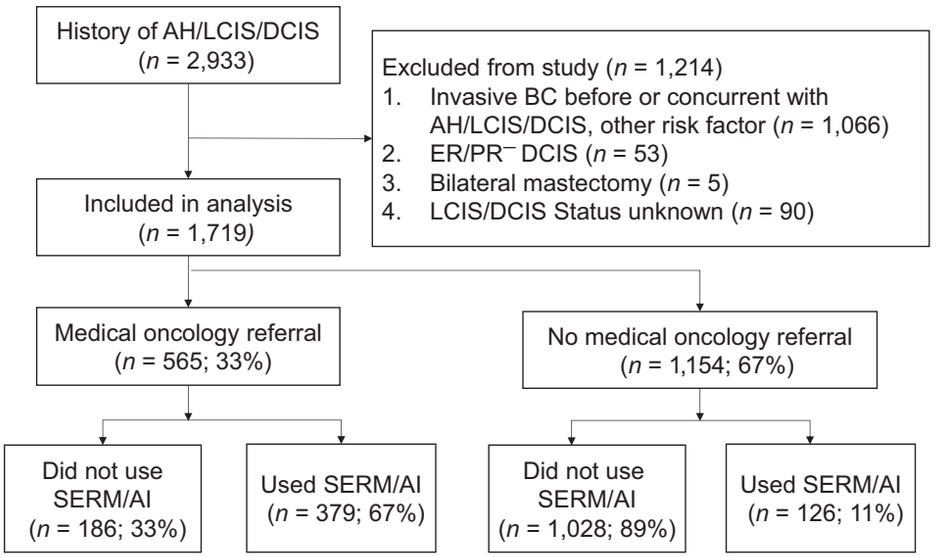

Figure 1.
CONSORT diagram of subjects by eligibility for analysis and chemoprevention use. AH, atypical hyperplasia; BC, breast cancer.

SERM or AI therapy; however, chemoprevention uptake was close to 30% in our cohort (19). Factors found to be associated with chemoprevention uptake in our study include referral to a medical oncologist and higher risk breast histology (DCIS > LCIS > atypical hyperplasia). Age less than 45 years was inversely associated with chemoprevention uptake.

The strongest predictor of chemoprevention uptake was a medical oncology referral. Physician recommendation for chemoprevention has been found to be associated with uptake in several studies (21). Lack of physician knowledge has been cited as an important factor in influencing low chemoprevention uptake (20). In addition, insufficient reimbursement to internal

Table 1. Baseline characteristics of women diagnosed with atypical hyperplasia and LCIS or DCIS at CUMC, New York, NY (2007–2015)

Characteristics		No chemoprevention (n = 1,214; 70.62%)	Chemoprevention (n = 505; 29.38%)	Total (n = 1,719, %)	P
Breast histology	Atypical hyperplasia	420 (34.60)	83 (13.44)	503 (29.26)	
	LCIS	294 (24.22)	107 (21.19)	401 (23.33)	
	DCIS	500 (41.19)	315 (62.38)	815 (47.41)	**<0.0001**
Age	Mean age - years (SD)	60.11 (12.61)	60.48 (9.95)	60.22 (11.88)	
	<45 years	114 (9.39)	23 (4.55)	137 (7.97)	
	45–54 years	328 (27.02)	118 (23.27)	446 (25.95)	
	55–64 years	351 (28.91)	185 (36.63)	536 (31.18)	
	65–74 years	255 (21.00)	128 (25.35)	383 (22.28)	
	75+	166 (13.67)	51 (10.10)	217 (12.62)	**<0.0001**
Menopause	No	420 (34.60)	120 (23.76)	540 (31.41)	
	Yes	794 (65.40)	385 (76.24)	1,179 (68.59)	**<0.0001**
Race and ethnicity	Non-Hispanic white	551 (45.39)	221 (43.76)	772 (44.91)	
	Non-Hispanic black	98 (8.07)	60 (11.88)	158 (9.19)	
	Hispanic	255 (21.00)	142 (28.12)	397 (23.09)	
	Asian	60 (4.94)	41 (8.12)	101 (5.88)	
	Other	250 (20.59)	41 (8.12)	291 (16.93)	**<0.0001**
BMI (kg/m^2)	Mean BMI - score (SD)	27.06 (6.16)	28.05 (6.20)	27.39 (6.19)	
	<18.5	34 (2.80)	8 (1.58)	42 (2.44)	
	18.5–24.99	384 (31.63)	167 (33.07)	551 (32.05)	
	25–29.99	301 (24.79)	154 (30.50)	455 (26.47)	
	30+	264 (21.75)	162 (32.08)	426 (24.78)	
	Unknown	231 (19.03)	14 (2.77)	245 (14.25)	**<0.0001**
Family history of breast cancer	No	1,120 (92.60)	368 (72.87)	1,488 (86.56)	
	Yes	94 (7.74)	137 (27.13)	231 (13.44)	**<0.0001**
Hysterectomy	No	1,183 (97.45)	491 (97.23)	1,674 (97.38)	
	Yes	31 (2.55)	14 (2.77)	45 (2.62)	0.7959
Comorbidities[a]	No	1,177 (96.95)	494 (97.82)	1,671 (97.21)	
	DVT/PE/stroke	30 (2.47)	8 (1.58)	38 (2.21)	
	Uterine Cancer	7 (0.58)	3 (0.59)	10 (0.58)	0.5223
HRT use	No	1,204 (99.18)	466 (92.28)	1,670 (97.15)	
	Yes	10 (0.82)	39 (7.72)	49 (2.85)	**<0.0001**
Medical oncology referral	No	1,028 (84.68)	126 (24.95)	1,154 (67.13)	
	Yes	186 (15.32)	379 (75.05)	565 (32.87)	**<0.0001**

NOTE: Bold values indicate meeting a threshold for statistical significance.
[a]Deep vein thrombosis (DVT) and pulmonary embolism (PE).

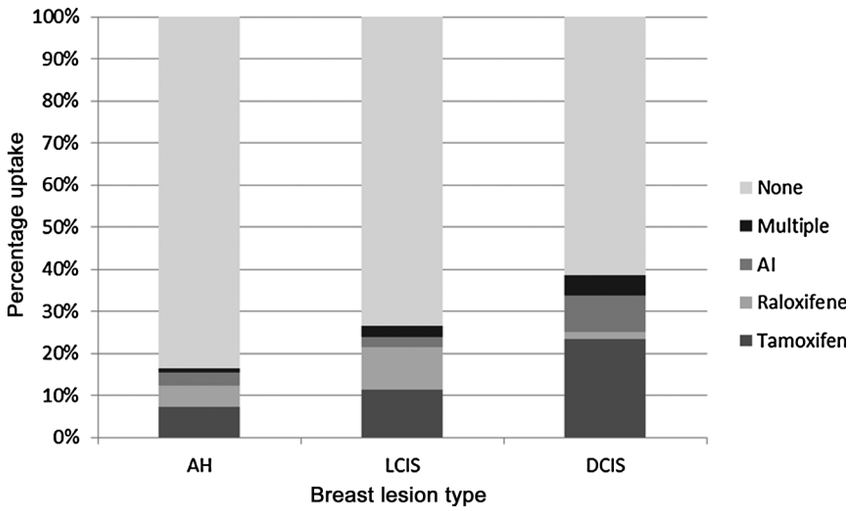

Figure 2.
Distribution of chemoprevention uptake by breast lesion type. AH, atypical hyperplasia.

medicine physicians, family medicine physicians, and obstetricians/gynecologists has been shown to be a barrier for chemoprevention counseling (33). About a third of our study population was seen by a breast oncologist, who may be more knowledgeable about the risks and benefits of chemoprevention and therefore more willing to prescribe SERM or AI therapy as compared with a primary care physician or gynecologist. Our study was conducted at a tertiary care academic medical center with access to a high-risk breast clinic. However, patients seen in community practices may not have access to specialized risk counseling. To increase uptake of chemoprevention for breast cancer risk reduction in all settings, interventions should be targeted at primary care providers who may not be aware of a woman's high-risk status or have experience with prescribing SERMs or AIs for chemoprevention. One such intervention developed by our group is the Breast cancer risk NAVigation (BNAV)

Table 2. Log-binomial univariate and multivariable model of the association between sociodemographic and clinical factors and chemoprevention use; multivariable model adjusted for age, race/ethnicity, family history, HRT use, and medical oncology referral

Characteristics		Univariate RR (95% CI)	*P*	Multivariable RR (95% CI)	*P*
Breast histology	Atypical hyperplasia	Reference			
	LCIS	1.62 (1.25–2.09)	**0.0002**	1.43 (1.16–1.76)	**0.0009**
	DCIS	2.34 (1.89–2.90)	<**0.0001**	1.54 (1.28–1.86)	<**0.0001**
Age	<45 years	0.63 (0.42–0.95)	**0.0272**	0.61 (0.42–0.87)	**0.0069**
	45–54 years	Reference			
	55–64 years	1.29 (1.07–1.58)	**0.0072**	1.27 (1.10–1.47)	**0.0012**
	65–74 years	1.26 (1.02–1.56)	**0.0289**	1.22 (1.05–1.43)	0.0116
	75+	0.89 (0.67–1.18)	0.4163	1.06 (0.85–1.31)	0.6119
Menopause	No	Reference			
	Yes	1.47 (1.23–1.76)	<0.0001		
Race and ethnicity	Non-Hispanic white	Reference			
	Non-Hispanic black	1.33 (1.06–1.67)	**0.0153**	0.99 (0.85–1.16)	0.9076
	Hispanic	1.25 (1.05–1.48)	**0.0114**	1.10 (0.99–1.22)	0.075
	Asian	1.42 (1.09–1.84)	**0.0087**	0.99 (0.82–1.18)	0.8942
	Other	0.49 (0.36–0.67)	<**0.0001**	0.92 (0.72–1.19)	0.5403
BMI (kg/m^2)	<18.5	0.63 (0.33–1.19)	0.1524		
	18.5–24.99	Reference			
	25–29.99	1.12 (0.93–1.34)	0.2303		
	30+	1.25 (1.05–1.50)	0.0112		
	Unknown	0.19 (0.11–0.32)	<0.0001		
Family history of breast cancer	No	Reference			
	Yes	2.40 (2.09–2.76)	<**0.0001**	0.98 (0.87–1.09)	0.6526
Hysterectomy	No	Reference			
	Yes	1.06 (0.68–1.65)	0.7935		
Comorbidities[a]	No	Reference			
	DVT/PE/stroke	0.71 (0.38–1.32)	0.2833		
	Uterine cancer	1.01 (0.39–2.62)	0.9758		
HRT use	No	Reference			
	Yes	2.85 (2.43–3.35)	<**0.0001**	1.04 (0.90–1.19)	0.5941
Medical oncology referral	No	Reference			
	Yes	6.14 (5.16–7.32)	<**0.0001**	5.79 (4.80–6.98)	<**0.0001**

NOTE: Bold values indicate meeting a threshold for statistical significance.
[a]Deep vein thrombosis (DVT) and pulmonary embolism (PE).

tool, which is a web-based tool for primary care providers. BNAV serves as a repository of information and resources to help providers in the primary care setting assess breast cancer risk and understand the risks and benefits of chemoprevention (34). We also developed a patient-facing decision aid, *RealRisks*, for women found to be at high risk for breast cancer. A randomized clinical trial evaluating these patient and provider decision support tools on chemoprevention uptake is currently under way (NCT03069742).

Our results also indicated that chemoprevention uptake is relatively high among women with high-risk breast lesions compared with other high-risk populations (i.e., 5-year Gail risk score $\geq$1.67% or strong family history of breast cancer; ref. 19). As DCIS and LCIS are stronger risk factors for breast cancer than atypical hyperplasia, it is possible that women with higher risk breast lesions are more likely to be recommended chemoprevention by their physician. Tamoxifen has been part of the standard of care for patients with DCIS since the results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 trial were first published in 1999 (16). Data from the NSABP B-35 trial supporting the use of anastrozole for postmenopausal women with hormone receptor–positive DCIS were only recently published in 2016 (15). The Breast Cancer Prevention Trial (BCPT) of tamoxifen for primary prevention also found that women with atypical hyperplasia and LCIS have a greater risk reduction from tamoxifen than women without high-risk breast lesions (10, 35). In the BCPT study, use of tamoxifen reduced the risk of invasive breast cancer by 86% in women with history of atypical hyperplasia and 56% in women with history of LCIS (35). Similarly, the International Breast Cancer Intervention Study (IBIS-II) published in 2014 found that although at-risk women saw a 53% breast cancer risk reduction (HR, 0.47; 95% CI, 0.32–0.68) with anastrozole compared with placebo, the subgroup of atypical hyperplasia and LCIS patients saw a risk reduction of 69% (HR, 0.31; 95% CI, 0.12–0.84; ref. 14). Given that women with atypical hyperplasia and LCIS may have a higher baseline risk of breast cancer (10-year risk ranging from 20% to 23%; refs. 5, 6), they will likely derive a greater absolute risk reduction from chemoprevention use compared with other high-risk women. Therefore, targeted interventions to increase chemoprevention uptake specifically in these high-risk populations may be an effective public health strategy to reduce breast cancer incidence.

Chemoprevention uptake varied by age as well. Younger women were less likely to take chemoprevention compared with older women. Older age has been found to be associated with chemoprevention uptake in a number of studies, although there is evidence that younger women are more likely to adhere to the 5-year course of therapy (36–38). The increased uptake of chemoprevention among older women can potentially be explained by the fact that tamoxifen is the only FDA-approved chemoprevention medication for high-risk premenopausal women, whereas those who have experienced menopause can also be prescribed raloxifene or aromatase inhibitors (39). Although the majority of patients in this study used tamoxifen as the chemopreventive agent of choice, this may be a result of the timeframe of the study (2007–2015). Aromatase inhibitors were not introduced for primary prevention of breast cancer or treatment of DCIS until after 2011 (13–15). It remains to be seen whether AIs for breast cancer chemoprevention will gain wider acceptance compared with SERMs.

We additionally found a trend toward increased chemoprevention uptake in Hispanic women ($P = 0.075$). This is in contrast to another study published by Kaplan and colleagues that found that Latinas had the lowest proportion of willingness to take chemoprevention with tamoxifen when compared with whites, Asians, and African Americans (22). Of note, the Gail model, which is frequently used to determine eligibility for chemoprevention, may underestimate breast cancer risk among Hispanic women affecting their eligibility for chemoprevention use (40–42). Although all of our subjects were eligible for chemoprevention due to their diagnosis of atypical hyperplasia, LCIS, or DCIS, our finding suggests that Hispanic women may have greater interest in initiating chemoprevention despite the fact that the Gail model may underestimate their breast cancer risk. Additional research should be done to further validate breast cancer risk models for Hispanic women and to investigate chemoprevention use in diverse populations.

Socioeconomic status (SES) including educational level, income, and medical insurance coverage were not collected in this study due to lack of availability within the EHR. Our group has previously published findings on the impact of these factors on chemoprevention uptake among a similar population of high-risk women with self-reported data on SES. Among 316 high-risk women eligible for chemoprevention seen in our breast clinic, chemoprevention uptake was 51% and educational level, insurance status, and annual household income were not significant predictors of chemoprevention uptake (21). Cost of chemoprevention agents and lack of insurance coverage have also been shown to be barriers to uptake, particularly among those of lower income (43, 44).

From the analysis of the questionnaire data in a subset of women with atypical hyperplasia, LCIS, and DCIS, we found that only about 50% of these high-risk women perceived their personal risk of developing breast cancer to be higher than an average-risk woman. In addition, over 70% of the survey participants were worried about the side effects of chemoprevention. Our findings concur with the findings in previous studies that demonstrate inaccurate risk perception is associated with an overestimation of the side effects of chemoprevention (45, 46). Concern about side effects is often cited as a major factor in decision-making about chemoprevention, and many high-risk women believe the benefits of tamoxifen are not worth the risks of thromboembolism and uterine cancer (47–49). Our findings suggest that future interventions developed to increase chemoprevention uptake among high-risk women should in part aim to improve risk perception so that patients can make more informed decisions about the risks and benefits of SERM and AI use.

Consistent with our results, a focus group study of women at risk for breast cancer found that risk awareness is only one of many factors that are involved in chemoprevention decision-making (50). Holmberg and colleagues found that women's decisions to participate in the Study of Tamoxifen and Raloxifene (STAR) was most often based on personal experiences, and few women mentioned risk estimates unless they were specifically prompted (50). Similarly, some of the major reasons cited by our subjects for wanting to take preventative action included wanting to "feel better" and "be there for their family." This suggests that decision-making about chemoprevention is a highly personal choice based on more than just risk numbers, even among women who would benefit most from use based on risk status. The most commonly

cited reason for taking action to lower breast cancer risk was a desire to "live longer." Although chemoprevention can reduce the incidence of breast cancer, no survival benefit has been shown in randomized controlled trials (10, 11, 13, 14). This finding indicates that there are also misconceptions about the benefits of chemoprevention.

There are several limitations to our study. We conducted a single-institution study in an urban academic medical center with access to a high-risk clinic; therefore, our results may not be generalizable to community practices or more rural settings. Given the retrospective nature of the cohort study, there were about 20% missing data for race/ethnicity and BMI. Race/ethnicity was significant in univariate analysis, but was no longer significant in multivariable analysis. Although we included current use of HRT in our model, it was not found to be significant in multivariable analysis. However, we did not have data on history of prior HRT use, and this limitation likely resulted in underreporting of HRT use. In addition, we did not have data on chemoprevention adherence, persistence, discontinuation rates, and reasons for discontinuation. Some of our subjects likely had significant comorbidities that may have superseded the need for chemoprevention, but we did not include a measure of these comorbidities in our analysis. Selection bias in the survey study may have been introduced as only subjects seen by a medical oncologist were recruited. Participants who followed through with a medical oncology consultation were specifically counseled on breast cancer risk and use of chemoprevention.

Our study has several strengths, including having a racially and ethnically diverse population of women with atypical hyperplasia, LCIS, and DCIS. Age and race/ethnicity were all well distributed within our cohort. Our retrospective cohort study also had a large sample size and assessed the uptake of chemoprevention among a high-risk population that would benefit most from SERM or AI use. From the survey data, we were also able to capture information on perceived breast cancer risk and chemoprevention knowledge using validated measures before subjects had made a decision about whether or not to use chemoprevention.

Chemoprevention agents have been shown in randomized controlled trials to dramatically reduce the incidence of breast cancer for high-risk women. Our study provides evidence that women with atypical hyperplasia, LCIS, or DCIS may take chemoprevention at a higher rate than other high-risk populations and that consultation with a medical oncologist also increases chemoprevention uptake. Concern about the frequency and severity of side effects may limit the number of women who are willing to take chemoprevention. Improving communication about breast cancer risk, as well as the risks and benefits of chemoprevention, may facilitate informed decision-making about SERM or AI therapy for breast cancer risk reduction.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.S. Trivedi, A.M. Coe, K.D. Crew
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