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ORIGINAL ARTICLE – BREAST ONCOLOGY

Chemoprevention Uptake for Breast Cancer Risk Reduction Varies by Risk Factor

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ABSTRACT

Background/Objective. The efficacy of chemoprevention for breast cancer risk reduction has been demonstrated in randomized controlled trials; however, use remains low. We sought to determine whether uptake differed by risk factors, and to identify reasons for refusal and termination.

Methods. Women seen in a high-risk clinic from October 2014 to June 2017 considered eligible for chemoprevention (history of lobular carcinoma in situ, atypia, family history of breast/ovarian cancer, genetic mutation, or history of chest wall radiation) were retrospectively identified. Breast cancer risk factors were compared among those with and without chemoprevention use, and compliance was noted.

Results. Overall, 1506 women were identified, 24% with prior/current chemoprevention use. Women $\geq$ 50 years of age were more likely to use chemoprevention than women $<$ 50 years of age (28% vs. 11%, $p < 0.001$). Chemoprevention use by risk factor ranged from 7 to 40%. Having multiple risk factors did not increase use. Significant variation by risk factor was present among women $\geq$ 50 years of age ($p < 0.001$), but not among women $<$ 50 years of age ($p = 0.1$). Among women with a documented discussion regarding chemoprevention (575/1141), fear of adverse effects was the most common refusal reason (57/156; 36%). The majority of women (61%) who initiated chemoprevention completed 5 years.

Conclusion. Chemoprevention use among women at increased risk for breast cancer remains low, with more frequent use among women $\geq$ 50 years of age. These data highlight the need for ongoing educational efforts and counseling, as the majority who begin therapy complete 5 years of use. Given the fear of adverse effects as well as low uptake, particularly among women $<$ 50 years of age, alternative risk-reducing strategies are needed.

As the most commonly diagnosed cancer in American women, breast cancer is a disease of considerable public health importance. Factors that can significantly influence breast cancer risk include family history of breast cancer, personal history of atypical breast lesions or lobular carcinoma in situ (LCIS), mantle field radiation prior to the age of 30 years, and hereditary breast cancer syndromes. The aforementioned risk factors are associated with variable breast cancer risk, ranging from as low as a 9% 10-year risk for atypical ductal or lobular hyperplasia, to as high as a 72% lifetime risk with a BRCA mutation (Table 1).[1–13]

Chemoprevention with selective estrogen receptor modulators (SERMs) or aromatase inhibitors (AIs) is a proven, effective option for breast cancer risk reduction. Randomized controlled trials demonstrated a 38% reduction in overall breast cancer incidence among high-risk women, and a 51% reduction in estrogen receptor (ER) positive tumors with use of these agents for 5 years.[14] Based on these trials, the U.S. Food and Drug Administration approved the SERMs tamoxifen and raloxifene for breast cancer chemoprevention among women 35 years of age or older with a 5-year breast cancer risk of 1.67% or higher. The National Comprehensive Cancer Network (NCCN),[15] American Society of Clinical Oncology (ASCO),[16] and United States Preventive Services Task Force (USPSTF)[17] endorse tamoxifen and raloxifene as options to reduce the risk of ER positive breast cancer among high-risk women, while ASCO also supports the use of the AI exemestane in postmenopausal women.

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TABLE 1 Breast cancer risk factors

Risk factor	Risk
Family history	Variable based on extent of family history
Lobular carcinoma in situ	21–26% 10 years[4]
Atypical ductal or lobular hyperplasia	9–25% 10 years[4,5,7]
Chest wall irradiation < 30 years	30% age 50 years[11]
Hereditary/genetic risk	
High-penetrance mutations	
BRCA1	54–72% lifetime[3,8,10]
BRCA2	23–80% lifetime[3,8,10]
TP53 (17p1.31)	56–90% lifetime[2]
PTEN (10q23.3)	25–50% lifetime[2]
STK11 (19p13.3)	32–54% lifetime[2,13]
CDH1 (16q22.1)	42–60% lifetime[2,6]
Moderate-penetrance mutations	
ATM (11q22.3)	15–20% lifetime[2]
CHEK2 (truncating)	3.0-fold (90% CI 2.6–3.5) lifetime[12]
CHEK2 (I157T, missense)	1.6-fold (90% CI 1.42–1.75) lifetime[12]
NBN (c.657del5)	2.7-fold (90% CI 1.9–3.7) lifetime[12]
PALB2 (16p12.1)	20–40% lifetime[2]

CI confidence interval

Despite these recommendations, studies have demonstrated low chemoprevention uptake.[4,18–24]Three large, retrospective studies have demonstrated higher uptake among women with atypical hyperplasia or LCIS compared with those at elevated risk due to family history,[20,21,24] but to our knowledge there are no studies directly comparing chemoprevention uptake according to a more comprehensive group of major breast cancer risk factors. Therefore, our primary objective was to determine whether chemoprevention uptake varies according to breast cancer risk factor in a large cohort of high-risk women. Reasons for refusal and termination of chemoprevention were also analyzed.

METHODS

We conducted a retrospective study using a prospectively maintained database of women enrolled in the high-risk screening program at Memorial Sloan Kettering Cancer Center (MSKCC) seen between October 2014 and June 2017. Women were enrolled in the high-risk screening program if they had any of the following risk factors: personal history of atypical breast lesions or LCIS, family history of breast and/or ovarian cancer conferring a $\geq$ 20% lifetime risk based on the Tyrer–Cuzick model,[25] a genetic mutation predisposing to increased breast cancer risk, or radiation therapy to the chest at $\leq$ 30 years of age. Women were excluded from the study if they had a history of invasive breast cancer or ductal carcinoma in situ, or had a risk-reducing bilateral prophylactic mastectomy prior to the study period. Women were individually evaluated and provided with screening and prevention recommendations at the providers' discretion. The MSKCC Institutional Review Board approved this study.

Each woman was categorized according to high-risk features. Those with more than one high-risk feature were classified into each relevant category as well as into a separate category of multiple risk factors. Atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH) were grouped together given their similar long-term breast cancer risk.[4,5,7] Additional atypical lesions were classified separately into a group that included atypia not otherwise specified, atypia in phyllodes, adenomyoepitheliamatosis with atypia, atypical apocrine adenosis, atypical apocrine metaplasia, atypical papillary lesion, columnar cell changes with atypia, flat epithelial atypia, and cystic hypersecretory hyperplasia with atypia. Genetic mutations were combined into one category and included BRCA1, BRCA2, ATM, CDH1, CHECK-2, MSH2/MLN1, PALB2, and MUTYH.

Chemoprevention use was categorized as never versus current or prior use at the most recent clinic visit. Multiple data sources, including physician notes, patient surveys, and electronic prescription reporting were used to identify chemoprevention use and patient characteristics. Clinician notes were used as the primary source of information for all variables, with patient-provided information used as a secondary data source. Patient survey links were e-mailed prior to the visit and then completed online. Body mass index, tobacco use, medical history, and reasons for not

using or terminating chemoprevention were collected. Age $\geq$ 50 years was used as a surrogate for postmenopausal status.

Patient and disease characteristics were summarized using median for continuous variables and frequency for categorical variables. The primary outcome was use of chemoprevention overall, and according to high-risk features. Between-group comparisons were made using the Kruskal–Wallis test for continuous variables and Fisher's exact or the Chi-square test for categorical variables, as appropriate. A p value < 0.05 was considered statistically significant. Secondary outcomes included reasons for lack of chemoprevention uptake and termination. Given previous literature demonstrating differences in uptake according to menopausal status,[22–24] we tested for an interaction between risk factor and age, and found a significant interaction with respect to chemoprevention uptake ($p < 0.001$) using a likelihood ratio test. Therefore, we analyzed uptake stratified by age $<$ 50 and $\geq$ 50 years. All statistical analyses were conducted using R software version 3.4.1 (R Core Development Team, Vienna, Austria).

RESULTS

Overall, 1506 women, with a median age of 56 years, were included in this study; 24% (365/1506) had current or prior use of chemoprevention (Table 2). The most common risk factors were ADH/ALH (50.3%), followed by LCIS (41.8%) and family history (41.7%). Multiple high-risk features were present for 38.6% of women. The most common genetic mutations were BRCA1 and BRCA2 (70/78, 89.7%). Current or prior chemoprevention use was significantly higher among women age $\geq$ 50 years compared with those age $<$ 50 years (27.9% vs. 11.2%, $p < 0.001$). Only 8.3% of women who were current smokers had chemoprevention use.

Chemoprevention uptake was lowest among women with 'other' atypical lesions (7.5%) (Table 2). Multiple high-risk features, genetic mutation carriers, family history, and LCIS were associated with 27–33% chemoprevention use, whereas among women with ADH/ALH, only 18.6% used chemoprevention. On stratified analysis, there was a significant association between risk factor and use of chemoprevention among women age $\geq$ 50 years ($p < 0.001$), but not among women age $<$ 50 years (Fig. 1).

Among women without current or prior chemoprevention use, half (575/1141) had a documented discussion regarding chemoprevention at their most recent clinic visit. The most common reason for lack of chemoprevention use was patient refusal (27.1%), with fear of adverse effects being the most common reason for refusal (Table 3). Nineteen percent (112/575) of women had relative contraindications to chemoprevention. The most common contraindication was child-bearing age, followed by a history of thromboembolic disease and active tobacco use.

Among current or prior chemoprevention users, the majority took either tamoxifen or raloxifene, with a minority taking AIs or switching between agents (Table 4). Among current users, 28.9% (52/180) were taking tamoxifen, while 68.9% (124/180) were taking raloxifene. Among women with a prior history of chemoprevention use, 60.5% completed at least 5 years of therapy (Table 4). The most common reason for termination secondary to an adverse effect was development of vaginal bleeding (n = 11) or thromboembolic disease (n = 8) (Table 4).

DISCUSSION

In a large contemporary cohort of high-risk women, approximately one-quarter used chemoprevention. These results align with previous studies demonstrating low uptake despite evidence of substantial risk reduction associated with a SERM or an AI in 11 randomized chemoprevention trials.[14,26–34] Our study of over 1500 women is one of the largest evaluating chemoprevention use for a comprehensive list of risk factors. Chemoprevention use was greatest among women at highest risk, namely those with genetic mutations, chest wall irradiation, and LCIS.

Chemoprevention use in our cohort was higher than that seen in two meta-analyses reporting overall uptake of approximately 15%.[22,35] When women participating in chemoprevention trials were excluded from these analyses, uptake was even lower—4% in the study by Ropka et al.[35] and 8.7% in the study by Smith et al.[22] Ropka and colleagues described the 4% rate as reflecting realistic uptake in clinical practice. However, two of the studies included in the meta-analysis were conducted within 2 years of publication of the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trial, and low uptake may have reflected both patient and provider reluctance to take or prescribe a preventive medication with meaningful adverse effects, as well as the generally slow diffusion of trial results into practice.[36,37] Another study recruited women at elevated 5-year breast cancer risk from two healthcare organizations to participate in online education using a decision aid about tamoxifen use.[38] The burden of contacting the primary care physician was then placed on the woman, and, not surprisingly, only 0.9% of participants reported taking tamoxifen 3 months after using the decision aid. Patients would have had to be extremely

TABLE 2 Patient characteristics

	Overall [n = 1506]	Any current/prior use [n = 365]	No current/prior use [n = 1141]	p-value
Demographic				
Median age, years (min, max)	56 (23, 84)	59 (37, 82)	55 (23, 84)	**<0.001**
Age at visit, years				**<0.001**
< 50	331 (22.0)	37 (10.1)	294 (25.8)	
≥ 50	1175 (78.0)	328 (89.9)	847 (74.2)	
Smoking status				**0.048**
Current	24 (1.6)	2 (0.5)	22 (1.9)	
Former	152 (10.1)	48 (13.2)	104 (9.1)	
Never	306 (20.3)	84 (23.0)	222 (19.5)	
Unknown	1024 (68.0)	231 (63.3)	793 (69.5)	
BMI, median (min, max)	24.5 (15.6, 57)	24.3 (15.6, 48.21)	24.7 (16.33, 57)	**0.042**
Race				0.16
White	1189 (79.0)	309 (84.7)	880 (77.0)	
Black	52 (3.4)	10 (2.7)	42 (3.7)	
Hispanic	50 (3.3)	10 (2.7)	40 (3.5)	
Asian	86 (5.7)	14 (3.8)	72 (6.3)	
Other	4 (0.3)	0 (0)	4 (0.3)	
Unknown	125 (8.3)	22 (6.0)	103 (9.0)	
High-risk features[a]				
Multiple high-risk features				0.06
Yes	581 (38.6)	156 (42.7)	425 (37.2)	
No	925 (61.4)	209 (57.2)	716 (62.8)	
LCIS[b]				**<0.001**
Yes	629 (41.8)	190 (52.0)	439 (38.5)	
No	877 (58.2)	175 (48.0)	702 (61.5)	
Family history				**0.001**
Yes	628 (41.7)	180 (49.3)	448 (39.3)	
No	878 (58.3)	185 (50.7)	693 (60.7)	
ADH or ALH[b]				**<0.001**
Yes	758 (50.3)	141 (38.6)	617 (54.1)	
No	748 (49.7)	224 (61.4)	524 (45.9)	
Other atypia[b]				**<0.001**
Yes	67 (4.4)	5 (1.4)	62 (5.4)	
No	1439 (95.6)	360 (98.6)	1079 (94.6)	
Genetic mutation[c]				0.06
Yes	78 (5.2)	26 (7.1)	52 (4.5)	
No	1428 (94.8)	339 (92.9)	1089 (94.5)	
Chest wall irradiation				0.6
Yes	5 (0.3)	2 (0.5)	3 (0.3)	
No	1501 (99.7)	363 (99.5)	1138 (99.7)	

Data are expressed as n (%) unless otherwise specified

Bolded values indicate statistical significance, $p < 0.05$

[a]Includes risk factor of interest in combination with any other risk factor present for each patient; total percentages add to more than 100%

[b]Atypia, NOS (n = 1); atypia in phyllodes (n = 1); adenomyoepitheliamatosis with atypia (n = 1); atypical apocrine adenosis (n = 3); atypical apocrine metaplasia (n = 1); atypical papillary lesion (n = 5); columnar cell changes with atypia (n = 35); flat epithelial atypia (n = 3); cystic hypersecretory hyperplasia with atypia (n = 1)

[c]Deleterious gene mutations included ATM (n = 1), BRCA 1 (n = 29), BRCA 2 (n = 41), CDH-1

(n = 1), CHEK2 (n = 1), MSH2/MLN1 (n = 1), p53 (n = 1), MUTYH (n = 1), not specified (n = 1)

LCIS lobular carcinoma in situ, *ADH* atypical ductal hyperplasia, *ALH* atypical lobular hyperplasia, *min* minimum, *max* maximum, *BMI* body mass index, *NOS* not otherwise specified

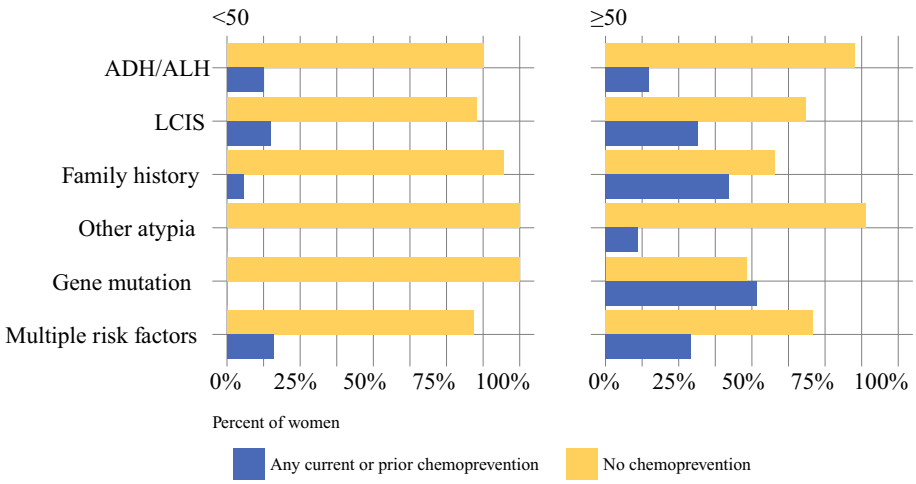

FIG. 1 Chemoprevention uptake according to risk factor, stratified by age < 50 and ≥ 50 years. *ADH* atypical ductal hyperplasia, *ALH* atypical lobular hyperplasia, *LCIS* lobular carcinoma in situ

motivated to approach a physician to obtain a prescription, and it has been shown that meeting with and receiving a physician recommendation is critical in improving chemoprevention uptake.[18,39] Thus, these studies may not reflect contemporary clinical practice in the setting of an academic medical center and/or high-risk screening program. However, even in a patient population motivated enough to be followed in a high-risk screening program, our study indicates that only a minority of women elected to take chemoprevention.

One of the unique aspects of our study was the ability to examine variation in chemoprevention use according to a comprehensive list of risk factors. We found that use largely paralleled level of risk—women with genetic mutations and LCIS had the highest proportions of uptake. Limited data are available regarding the efficacy of tamoxifen risk reduction in BRCA1 and BRCA2 mutation carriers. In a subset of BRCA mutation carriers in NSABP P-1, tamoxifen reduced breast cancer incidence among BRCA2 mutation carriers by 62%, but not among BRCA1 carriers.[40] Data on the impact of tamoxifen on contralateral risk in BRCA mutation carriers also suggest benefit. Risk reduction was demonstrated in a case–control study evaluating contralateral risk reduction among BRCA mutation carriers; among BRCA1 and BRCA2 carriers, tamoxifen led to a 62% and 37% contralateral breast cancer risk reduction, respectively.[41]

Thirty percent of women with LCIS in our cohort used chemoprevention, which is consistent with studies of high-risk women evaluated at either an academic medical center or a specialty breast clinic. These studies reported an uptake range of 27–56% among chemoprevention-eligible women with LCIS.[4,21,23,24] Use of chemoprevention among women with atypia was similar in a study of 2938 women with atypical breast lesions at three institutions where 41% of women with severe ADH and 33% with ALH took chemoprevention.[4] Even higher uptake was demonstrated in a large, retrospective, multi-institutional study of two state registries, with 66% uptake in a combined group of women with atypia and LCIS.[20] In contrast, use of chemoprevention among women with ADH/ALH in our cohort was comparatively low (18%). It is unclear why chemoprevention use is lower among ADH/ALH patients at our institution, particularly in light of the 86% risk reduction reported in NSABP P-1.[28] One explanation may be provider bias against the benefit of chemoprevention in women with small-volume atypia based on studies demonstrating a moderate level of risk with only a single focus of atypia.[4,7]

We found low uptake among young women, which was similar to an uptake rate of 10.6% among 1279 high-risk women age < 50 years undergoing active screening in the United Kingdom.[42] The association of age and chemoprevention use is reflected in several other studies, most recently in a study of 1719 women diagnosed with atypical hyperplasia, LCIS, or DCIS. On multivariate analysis, age was significantly associated with chemoprevention uptake, with women age < 45 years and those age > 75 years less likely to initiate chemoprevention.[24] Tchou et al. found the mean age of high-risk women in their cohort who accepted tamoxifen was significantly older than those who refused.[23] Reasons for this are likely multifactorial. The utility of tamoxifen as a breast cancer risk-reduction agent in women age < 35 years is unknown, and its use is contraindicated in women attempting pregnancy. Additionally, tamoxifen is the only chemoprevention agent available for premenopausal women, and, as discussed below, there are multiple concerns about tamoxifen-related adverse effects. In contrast, postmenopausal women have the option of raloxifene and AIs. In postmenopausal patients, taking raloxifene serves a dual purpose, as it can not only reduce breast cancer risk but can also increase bone density and decrease the risk of vertebral fractures.[34]

TABLE 3 Chemoprevention decision among patients with no current or prior use of chemoprevention and documented discussion of chemoprevention at the most recent clinic visit

Chemoprevention decision	No current/prior use [n = 575]
Patient refused	156 (27.1)
Fear of adverse effects	57
Not interested	12
Will consider when postmenopausal	2
Other/not documented	85
Patient deferred decision	133 (23.1)
Considering bilateral prophylactic mastectomy	11
Other/not documented	122
Contraindication	112 (19.5)
Child-bearing age or actively attempting pregnancy	36
History of thromboembolic disease	29
Currently smoking	22
Currently using hormone replacement therapy	11
Endometrial cancer or vaginal bleeding	6
Undergoing other medical treatments	5
Cataracts	3
Patient accepted, counseling provided	14 (2.4)
Reason for decline not documented	160 (27.8)

Data are expressed as n (%)

TABLE 4 Type of chemopreventive agents used among women with current or prior use, and reasons for termination of chemoprevention among women with prior use

	Current use [n = 180]	Prior use [n = 185]
Chemoprevention agent		
Tamoxifen	52 (28.9)	132 (71.4)
Raloxifene	124 (68.9)	46 (24.9)
Multiple agents	0 (0.0)	7 (3.7)
Aromatase inhibitor[a]	4 (2.2)	–
Reasons for termination of chemoprevention among women with prior use		Prior use [n = 185]
Completed therapy[b]		112 (60.5)
Adverse effects		60 (32.4)
Vaginal bleeding		11
Thromboembolic disease		8
Leg pain		7
Depression/anxiety		6
Other		28
Other/not documented		13 (7.0)

Data are expressed as n (%)

[a]Included arimidex (n = 2) and exemestane (n = 2)

[b]Completed at least 5 years of therapy

Fear of medication adverse effects is frequently cited as a reason women decline chemoprevention. In a study of over 600 high-risk women given education with an individually tailored online decision aid, 80% who indicated that they were unlikely to take tamoxifen expressed worry about adverse effects, and 59% indicated that the benefits were not worth the risk.[38] Although the adverse effects associated with chemoprevention medications are real, they are likely overestimated and misunderstood by high-risk women. In the NSABP P-1 trial, the risk of endometrial cancer associated with tamoxifen was only seen in women > 50 years of age, and the absolute increased risk over placebo was 1.4 per 1000 women.[28] Hot flashes are another adverse effect of concern, but the absolute difference of placebo versus tamoxifen in this trial was only 11%. In a qualitative study of 27 women at risk for breast cancer, in a Canadian Family Practice setting, patients were asked about perceived barriers to taking chemoprevention.

The most common concern was adverse effects, but, interestingly, many of the perceived adverse effects (hair loss, nausea) were those associated with chemotherapy, not chemoprevention.[43] Studies involving educational decision aids have unfortunately not had the desired effect of increasing uptake. In the meta-analysis by Ropka et al., five studies with educational interventions had lower uptake rates (4%) than the eight studies that did not include an intervention (31%).[35]

However, there is evidence that physician recommendation can lead to improved uptake. Among a cohort of 175 women who spoke with their primary care doctor following an informational session for NSABP P-1 enrollment, women who reported that their physician advised them to enroll in the trial were 13 times more likely to participate compared with women whose physicians advised them not to participate.[39] Bober et al. assessed the importance of physician recommendation on uptake and found that women who received a physician's recommendation, as opposed to simply being informed by the physician of their eligibility, were 47% more likely to take tamoxifen.[18] We are unaware of any studies that focus on differential uptake rates according to type of physician; however, uptake rates are consistently higher in academic settings where there may be more specialists comfortable with discussing the risks and benefits of chemopreventive medications.

Interestingly, we found that over half of the women in our study completed their 5-year therapeutic course of chemoprevention once initiated. Coopey et al. showed similar results among women with atypical hyperplasia. They found that only 13% of patients discontinued chemoprevention in < 1 year, and another 26% by 1–3 years, and that, importantly, 60% took chemoprevention for ≥ 3 years.[4] These data highlight the importance of counseling high-risk women on chemoprevention eligibility and use, as the majority of women who start chemoprevention may continue for 5 years.

Limitations of this study include those inherent to a retrospective review, including reliance on provider documentation within the electronic medical record. However, multiple sources were utilized, including prescription records, to document chemoprevention use. An additional limitation is that the level of chemoprevention endorsement likely varied among providers and may have contributed to lower levels of uptake among specific groups of women, such as those with atypia. Women who choose to participate in a high-risk screening program at an urban cancer center may represent a motivated population more likely to accept chemoprevention, and our results may not be generalizable to more rural or community practice settings.

CONCLUSIONS

Given the low chemoprevention uptake among high-risk populations, providers need to focus efforts on counseling women eligible for risk reduction with chemoprevention, improve education on adverse effects, and encourage a trial of chemoprevention when appropriate, as the majority of women who initiated chemoprevention completed a 5-year course. Efforts to develop novel therapeutic agents that reduce breast cancer risk while minimizing toxicity are ongoing and may improve chemoprevention uptake.

COMPLIANCE WITH ETHICAL STANDARDS

CONFLICT OF INTEREST Meghan R. Flanagan, Emily C. Zabor, Michelle Stempel, Debra A. Mangino, and Melissa L. Pilewskie have no conflict of interests to declare.

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