Research Article

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# Risk versus Benefit of Chemoprevention among Raloxifene and Tamoxifen Users with a Family History of Breast Cancer

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## Abstract

Tamoxifen and raloxifene have been approved for the primary prevention of breast cancer in high-risk women, but are associated with an increased risk of serious side effects. Few studies have characterized risk–benefit profiles for chemoprevention among women who initiate tamoxifen or raloxifene outside of a clinical trial setting. Use of raloxifene and tamoxifen for chemoprevention was self-reported in 2014 to 2016 by participants in The Sister Study, a prospective cohort of women with a sister who had been diagnosed with breast cancer. After exclusions, 432 current raloxifene users and 96 current tamoxifen users were matched to 4,307 and 953 nonusers, respectively, on age and year of cohort enrollment. Conditional logistic regression was used to evaluate characteristics associated with chemoprevention use. Risk–benefit profiles were examined using published indices that assess the level of evidence (none, moderate, strong) that the benefits of chemoprevention outweigh the risk of serious side effects. Among current chemoprevention users, 44% of tamoxifen users and 5% of raloxifene users had no evidence of a net benefit. In analyses of factors associated with chemoprevention use, having strong evidence of benefit was a significant predictor of raloxifene use, but not of tamoxifen use. In our sample of women with a first-degree family history of breast cancer, raloxifene was more commonly used for breast cancer prevention than tamoxifen. Most raloxifene users, but <60% of tamoxifen users, were likely to benefit. Use of risk–benefit tables can help women and their healthcare providers make an informed decision about breast cancer chemoprevention.

## Introduction

Tamoxifen, a selective estrogen receptor modulator (SERM), has been approved for the primary prevention of invasive breast cancer by the FDA since 1998, following its association with a 49% reduction in breast cancer risk among high-risk women in the Breast Cancer Prevention Trial (BCPT; ref. 1). Although its efficacy has been demonstrated in the BCPT and other chemoprevention trials (1–4), tamoxifen carries a risk of serious adverse events, including endometrial cancer and stroke, which may be of concern for high-risk women considering tamoxifen initiation. Raloxifene, another SERM, has also been shown to decrease breast cancer risk among postmenopausal women in large clinical trials (5–8). In the Study of Tamoxifen and Raloxifene, raloxifene was demonstrated as effective as tamoxifen in reducing invasive breast cancer risk in postmenopausal women, with a lower associated risk of endometrial cancer, thromboembolic events, and cataracts, and a similar risk of ischemic heart disease, fractures, and stroke (7). In 2007, the FDA approved the use of raloxifene for chemoprevention in postmenopausal women with osteoporosis or a high risk of breast cancer. Unlike tamoxifen, raloxifene is not currently approved for chemoprevention in premenopausal women. Though national guidelines encourage clinicians to discuss pharmacologic interventions for breast cancer risk reduction with high-risk women (9, 10), the prevalence of tamoxifen or raloxifene use for prevention remains low among eligible women in the general U.S. population (<1%; ref. 11), reflecting the difficulties in decision-making surrounding use of these agents.

To aid in the counseling of women regarding the initiation of chemoprevention, Gail and colleagues (12) and Freedman and colleagues (13) developed risk–benefit indices for tamoxifen and raloxifene, which incorporate information on both the risk of invasive breast cancer and

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the risk of serious adverse events associated with these agents, to identify women for whom the benefits of use exceed the risks. However, to date, little research has characterized the risk–benefit profiles of women who initiate tamoxifen or raloxifene outside of the clinical trial setting. A previous report from the Sister Study, a prospective cohort of women with a first-degree family history of breast cancer, included 788 women who reported use of tamoxifen for breast cancer prevention at study enrollment, and found that approximately one in five of these users had no evidence of a net benefit of tamoxifen (14). As raloxifene was not FDA-approved for breast cancer primary prevention until 2007, it was not queried at the time of Sister Study enrollment (2003–2009). In this report, we assessed risk–benefit profiles among Sister Study participants who reported currently using either tamoxifen or raloxifene for chemoprevention on their most recent comprehensive follow-up questionnaire (September 2014 to August 2016). We also evaluated characteristics associated with use of these chemopreventive agents.

## Materials and Methods

The Sister Study is a prospective cohort of 50,884 women that was established to investigate environmental and genetic risk factors for breast cancer (15). Women ages 35 to 74 years from the United States and Puerto Rico were recruited into the Sister Study between 2003 and 2009, using a national multimedia campaign and a network of recruitment volunteers. Eligible women had a full or half-sister who had been diagnosed with breast cancer, but were free of breast cancer themselves at enrollment. Sister Study participants completed extensive questionnaires at enrollment for assessment of sociodemographic and lifestyle information, medical and family history, reproductive history, and medication use. Women complete brief health updates annually and detailed follow-up questionnaires every 2 to 3 years. The study was approved by the Institutional Review Boards of the National Institute of Environmental Health Sciences and the Copernicus Group. All participants provided written informed consent.

### Study design

On the third detailed follow-up questionnaire, completed approximately 8 years after enrollment (in 2014–2016), women were asked about use of tamoxifen and raloxifene. They were asked to report the number of months they had used these agents since completion of the previous detailed follow-up questionnaire (~2–3 years earlier), whether they were currently using them, and their reason for use. Possible response options for reason for use included: to treat breast cancer, to prevent breast cancer, or for another reason. Only one reason could be selected. Questions about tamoxifen and raloxifene use from enrollment and earlier follow-up questionnaires were used to define an index age of first use; however, these earlier questionnaires did not query the indication for use for raloxifene. Therefore, for our analyses, we assumed that the current reason for use reported on the third detailed follow-up questionnaire was the original indication for raloxifene initiation. Although use of anastrozole, an aromatase inhibitor (AI), for breast cancer prevention was also queried on the third detailed follow-up questionnaire, women who reported anastrozole use were not included as chemoprevention users for the current analyses because we lacked sufficient information on usage history to define an index age.

Out of a total of 41,422 Sister Study participants who completed the third detailed follow-up questionnaire, we identified 191 and 535 women who reported current use of tamoxifen or raloxifene, respectively, for the purpose of breast cancer prevention. We excluded users with a missing index age ($N = 10$ tamoxifen users, 14 raloxifene users) and users with a diagnosis of *in situ* or invasive breast cancer prior to the index age ($N = 42$ tamoxifen users, 6 raloxifene users). We also excluded users who switched from tamoxifen to raloxifene, or vice versa, between the index age and the third detailed follow-up ($N = 11$ from raloxifene to tamoxifen, 32 from tamoxifen to raloxifene); users with a self-reported *BRCA* 1/2 mutation ($N = 10$ tamoxifen users, 4 raloxifene users); users with a history of a contraindicating medical condition [defined as stroke, transient ischemic attack (TIA), pulmonary embolism, and deep vein thrombosis (DVT) for both raloxifene and tamoxifen, and endometrial cancer and cataracts for tamoxifen only] as of the index age ($N = 22$ tamoxifen users, 12 raloxifene users); and raloxifene users who reported initiation prior to 1997, the year raloxifene was first approved by the FDA ($N = 35$). Among tamoxifen users, those excluded due to contraindicating conditions were 17 women with cataracts, 2 with DVT, 1 with a stroke, 1 with a TIA, and 1 with endometrial cancer. Among current raloxifene users, those excluded were 6 women with DVT, 3 with a TIA, 2 with a stroke, and 1 with both DVT and a pulmonary embolism. After these exclusions, 96 tamoxifen and 432 raloxifene users contributed to our analyses.

For each chemoprevention user, we selected up to 10 comparison participants from the cohort, matched on age and enrollment year, who had not reported use of either raloxifene or tamoxifen as of the index age of the matched user. A woman was ineligible to be selected as a comparator if she had a history of *in situ* or invasive breast cancer as of the index age, had a self-reported *BRCA* 1/2 mutation, reported use of anastrozole at the third detailed follow-up, had a prophylactic mastectomy as of the index age, or had a history of a contraindicating medical condition as of the index age. Matching was performed with replacement, so that each comparator could potentially be matched to multiple users. Chemoprevention users were also eligible to be selected as comparators for other users with an earlier index age.

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### Participant characteristics

Demographic characteristics were ascertained from enrollment questionnaires. Hysterectomy, oophorectomy, menopausal status, and history of contraindicating conditions (among chemoprevention users only) as of the index age were defined from questionnaires completed at enrollment and detailed follow-ups. Women were considered premenopausal if they reported one or more menstrual cycles in the prior 12-month period, or if they were aged 55 and younger and their only reported reason for not experiencing menses was hysterectomy (without bilateral oophorectomy). All other women were considered postmenopausal. We used the Breast Cancer Risk Assessment Tool (BCRAT), designed by the National Cancer Institute and the National Surgical Adjuvant Breast and Bowel Project (12, 16–20), to calculate a 5-year risk of developing invasive breast cancer. Index age was used in the risk calculation. Other components of the BCRAT, including race/ethnicity, age at menarche, nulliparity or age at first live birth, first-degree family history of breast cancer, and breast biopsy history (ever had a breast biopsy and total number of breast biopsies), were defined using enrollment questionnaires. Information on history of a breast biopsy with atypical hyperplasia, also a component of the BCRAT, was not available and was therefore categorized as "unknown" in the risk calculation for all women.

### Risk–benefit index

We used the risk–benefit index published by Gail and colleagues (12) and updated by Freedman and colleagues (13) to categorize women according to the level of evidence (none, moderate, strong) that the benefits of tamoxifen or raloxifene for breast cancer and fracture prevention exceed the risk of serious side effects, including stroke, endometrial cancer, pulmonary embolism, DVT, and cataract. This index incorporates information on age, hysterectomy, race, and estimated 5-year risk of invasive breast cancer (BCRAT). Categories have not been published for women younger than 35 years, Hispanic women younger than 50 years, women with a BCRAT score less than 1.5%, and women of race/ethnicities other than non-Hispanic White, non-Hispanic Black, or Hispanic; therefore, we could not examine risk–benefit profiles in these groups. Because raloxifene is only approved for chemoprevention in postmenopausal women, categories have also not been published for raloxifene for women younger than 50 years.

### Statistical analysis

Conditional logistic regression was used to estimate ORs and 95% confidence intervals (CI) for characteristics associated with chemoprevention use, including risk–benefit index categories. Because some components of the BCRAT score were defined at enrollment, rather than at the index age, we performed sensitivity analyses excluding women with more than 3 years between enrollment and the index age. Some raloxifene users may have initiated raloxifene at the index age for indications other than breast cancer primary prevention; therefore, we repeated raloxifene analyses excluding women who self-reported osteoporosis or osteopenia prior to the index age or who initiated raloxifene prior to 2007, the year the raloxifene was approved by the FDA for breast cancer prevention. All analyses were performed using Sister Study data release 6.0 and SAS version 9.4 (SAS Institute, Inc.).

## Results

Current raloxifene ($N = 432$) and tamoxifen ($N = 96$) users were matched to 4,307 and 953 nonusers, respectively. Among both users and matched nonusers of both drugs, the majority were non-Hispanic White, had a Bachelor's degree or higher, and had not undergone a hysterectomy as of the index age (Table 1).

The average age at initiation was 52 years among current tamoxifen users and 56 years among current raloxifene users. Over half of all tamoxifen users ($N = 56$; 59%) and approximately one fifth of raloxifene users ($N = 80$; 19%) were premenopausal at chemoprevention initiation. Among those who initiated chemoprevention while still premenopausal, the average age at initiation was older among raloxifene users (51 years; SD = 4) than among tamoxifen users (47 years; SD = 3). Of those who initiated raloxifene use while premenopausal, 34% had a hysterectomy before initiation. The median calendar years of initiation were 2011 and 2004 for tamoxifen and raloxifene, respectively. As of the index age, a total of 161 (37%) of the current raloxifene users had a self-reported diagnosis of osteoporosis ($N = 143$) or osteopenia ($N = 18$).

### Characteristics associated with tamoxifen or raloxifene use

In multivariable-adjusted models of characteristics associated with chemoprevention use (vs. nonuse), women of race/ethnicities other than non-Hispanic White were less likely to use raloxifene than non-Hispanic White women (OR, 0.42; 95% CI, 0.25–0.70; Table 2). Estimates for tamoxifen use were in the opposite direction (OR, 1.30; 95% CI, 0.68–2.51), though CIs were wide due to small numbers of women who were not non-Hispanic White. Women who had a high school education or less (OR, 0.73; 95% CI, 0.53–1.02) or who attended some college (OR, 0.72; 95% CI, 0.57–0.91) were less likely to be raloxifene users than those with a Bachelor's degree or higher. Those with a high school education or less also appeared less likely to be tamoxifen users (OR, 0.44; 95% CI, 0.18–1.06). Hysterectomy status was not significantly associated with either tamoxifen or raloxifene use. BCRAT score was positively associated with both tamoxifen use (OR per 1% increase, 1.30; 95% CI, 1.12–1.51) and raloxifene use (OR per 1% increase, 1.29; 95% CI, 1.23–1.36).

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**Table 1.** Characteristics of tamoxifen and raloxifene users and matched nonusers

| | Tamoxifen | | Raloxifene | |
|---|---|---|---|---|
| | Users *N* (%) | Nonusers *N* (%) | Users *N* (%) | Nonusers *N* (%) |
| Total | 96 (100%) | 953 (100%) | 432 (100%) | 4,307 (100%) |
| Index age | | | | |
| <55 | 64 (67%) | 633 (66%) | 162 (38%) | 1,617 (39%) |
| 55–59 | 12 (13%) | 120 (13%) | 150 (35%) | 1,499 (34%) |
| 60–64 | 14 (15%) | 140 (15%) | 84 (19%) | 840 (19%) |
| 65+ | 6 (6%) | 60 (6%) | 36 (8%) | 351 (8%) |
| Mean (SD) | 52 (7) | 52 (7) | 56 (6) | 56 (6) |
| Menopausal status at index age | | | | |
| Premenopausal | 56 (59%) | 497 (52%) | 80 (19%) | 1,106 (27%) |
| Postmenopausal | 39 (41%) | 451 (48%) | 351 (81%) | 3,199 (73%) |
| Missing | 1 | 5 | 1 | 2 |
| Race/ethnicity | | | | |
| Non-Hispanic White | 83 (86%) | 839 (88%) | 415 (96%) | 3,870 (90%) |
| Other | 13 (14%)[a] | 114 (12%)[b] | 17 (4%)[c] | 437 (10%)[d] |
| Education | | | | |
| High school or less | 7 (7%) | 122 (13%) | 51 (12%) | 588 (14%) |
| Some college | 29 (30%) | 291 (31%) | 117 (27%) | 1,451 (34%) |
| Bachelor's degree or higher | 60 (63%) | 540 (57%) | 264 (61%) | 2,268 (52%) |
| Hysterectomy before index age | | | | |
| No | 82 (86%) | 743 (79%) | 303 (70%) | 2,928 (69%) |
| Yes | 13 (14%) | 198 (21%) | 129 (30%) | 1,358 (31%) |
| Missing | 1 | 12 | 0 | 21 |
| Osteoporosis or osteopenia diagnosis before index age | | | | |
| No | 75 (78%) | 782 (82%) | 271 (63%) | 3,451 (80%) |
| Yes | 21 (22%) | 171 (18%) | 161 (37%) | 856 (20%) |
| Number of first-degree relatives with breast cancer | | | | |
| 0[e] | 2 (2%) | 29 (3%) | 5 (1%) | 88 (2%) |
| 1 | 57 (59%) | 704 (74%) | 208 (48%) | 3,202 (74%) |
| 2+ | 37 (39%) | 220 (23%) | 219 (51%) | 1,017 (24%) |
| BCRAT score (%)[f] | | | | |
| <1.67 | 12 (13%) | 189 (20%) | 12 (3%) | 219 (6%) |
| 1.67–2.99 | 39 (41%) | 448 (47%) | 118 (27%) | 2,168 (50%) |
| 3.00–5.99 | 38 (40%) | 272 (29%) | 227 (53%) | 1,559 (36%) |
| ≥6.00 | 7 (7%) | 44 (5%) | 75 (17%) | 361 (8%) |
| Mean (SD) | 3.2 (1.7) | 2.8 (1.5) | 4.2 (1.9) | 3.4 (1.7) |
| Years since chemoprevention initiation | | | | |
| 0.2–4.9 | 56 (58%) | | 43 (10%) | |
| 5–9.9 | 38 (40%) | | 146 (34%) | |
| 10+ | 2 (2%) | | 243 (56%) | |
| Median (IQR) | 4 (3, 6) | | 11 (8, 14) | |

[a]Includes 9% non-Hispanic Black, 2% Hispanic, 2% other.
[b]Includes 6% non-Hispanic Black, 3% Hispanic, 3% other.
[c]Includes 1% non-Hispanic Black, 2% Hispanic, 1% other.
[d]Includes 5% non-Hispanic Black, 3% Hispanic, 2% other.
[e]Half-sister only.
[f]Information on history of a breast biopsy with atypical hyperplasia, a component of the BCRAT, was categorized as "unknown" in the risk calculation for all women.

### Risk–benefit profiles for tamoxifen use

The risk–benefit index could be evaluated for 84 (88%) of the current tamoxifen users. We could not evaluate the risk–benefit index for those with a 5-year breast cancer risk of <1.5% ($N = 8$), those who were Hispanic and younger than age 50 years ($N = 1$), those of race/ethnicities other than non-Hispanic White, non-Hispanic Black, and Hispanic ($N = 2$), and those with missing hysterectomy information ($N = 1$). Overall, 44% of women using tamoxifen had no evidence that the benefits outweighed the risks (Table 3). Proportions with moderate and strong evidence among users were 17% and 39%, respectively. Among matched nonusers for whom the risk–benefit index could be evaluated ($N = 803$), proportions with none, moderate, and strong evidence were 44%, 11%, and 45%, respectively. Risk–benefit index category was not significantly associated with likelihood of current tamoxifen use (OR, 0.46; 95% CI, 0.16–1.33) for strong versus no evidence of net benefit (Table 3). Characteristics of users and nonusers categorized as having a strong evidence of benefit were generally similar except that users were more likely to be premenopausal at the index age (91% vs. 77%), to have a Bachelor's degree or higher (85% vs. 55%), and to have at least two first-degree relatives with a breast cancer diagnosis (48% vs. 31%; Supplementary Table S1). Among users, strong evidence of a net benefit was most common among non-Hispanic white women (43%), women aged <55 years (57%), and women with a hysterectomy before the index age (42%; Table 4).

### Risk–benefit profiles for raloxifene use

The risk–benefit index was evaluated for 373 (86%) of the current raloxifene users. We could not evaluate the risk–benefit index for those with a 5-year breast cancer risk of <1.5% ($N = 9$), those who younger than age 50 years ($N = 46$), and those of race/ethnicities other than non-Hispanic White, non-Hispanic Black, and Hispanic ($N = 4$). Overall, 5% of raloxifene users had no evidence that the benefits outweighed the risks, whereas 43% and 52% had moderate and strong evidence, respectively. Among matched nonusers for whom the risk–benefit index could be evaluated ($N = 3{,}649$), proportions with none, moderate, and strong evidence were 15%, 54%, and 32%, respectively. Relative to women categorized as having no evidence of a net benefit, the likelihood of current raloxifene use was elevated among those with moderate (OR, 2.56; 95% CI, 1.56–4.22) or strong (OR, 5.98; 95% CI, 3.60–9.95) evidence that the benefits of use outweighed the risks (Table 3). Users with strong evidence were less likely than nonusers with strong evidence to have had a hysterectomy before the index age (36% vs. 50%), but were more likely to have at least two first-degree relatives with a breast cancer history (80% vs. 62%) and to have a BCRAT score of ≥3.0% (95% vs. 85%; Supplementary Table S1). Among users, strong evidence of a net benefit was most common among women ages 55 to 59 years (70%), non-Hispanic white women (53%), women with a hysterectomy before the index age (65%), and women with a BCRAT score of ≥6.00% (86%; Table 4).

Results were generally similar when women with greater than 3 years between enrollment and the index age were excluded (Supplementary Table S2) and when raloxifene analyses were repeated excluding women who self-reported osteoporosis or osteopenia prior to the

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**Table 2.** ORs and 95% CIs for tamoxifen and raloxifene use according to participant characteristics

| | Tamoxifen | | Raloxifene | |
|---|---|---|---|---|
| | **Unadjusted OR (95% CI)** | **Adjusted OR (95% CI)[a]** | **Unadjusted OR (95% CI)** | **Adjusted OR (95% CI)[a]** |
| Race/ethnicity | | | | |
| Non-Hispanic White | 1 | 1 | 1 | 1 |
| Other | 1.17 (0.62–2.22) | 1.30 (0.68–2.51) | 0.36 (0.22–0.59) | 0.42 (0.25–0.70) |
| Education | | | | |
| High school or less | 0.52 (0.23–1.16) | 0.44 (0.18–1.06) | 0.75 (0.54–1.02) | 0.73 (0.53–1.02) |
| Some college | 0.89 (0.56–1.43) | 0.97 (0.60–1.57) | 0.69 (0.55–0.87) | 0.72 (0.57–0.91) |
| Bachelor's degree or higher | 1 | 1 | 1 | 1 |
| Hysterectomy before index age | | | | |
| No | 1 | 1 | 1 | 1 |
| Yes | 0.59 (0.32–1.09) | 0.63 (0.33–1.18) | 0.91 (0.73–1.14) | 0.98 (0.78–1.23) |
| Osteoporosis or osteopenia diagnosis before index age | | | | |
| No | 1 | 1 | 1 | 1 |
| Yes | 1.35 (0.77–2.35) | 1.44 (0.82–2.54) | 2.59 (2.08–3.23) | 2.50 (1.99–3.14) |
| Number of first-degree relatives with breast cancer | | | | |
| 0 or 1 | 1 | 1 | 1 | 1 |
| 2+ | 2.10 (1.36–3.26) | 2.26 (1.45–3.53) | 3.38 (2.75–4.14) | 3.30 (2.68–4.06) |
| BCRAT score (%)[b,c] | | | | |
| <1.67 | 0.57 (0.27–1.19) | 0.59 (0.28–1.25) | 0.86 (0.44–1.67) | 0.91 (0.46–1.78) |
| 1.67–2.99 | 1 | 1 | 1 | 1 |
| 3.00–5.99 | 1.92 (1.16–3.19) | 2.11 (1.26–3.55) | 3.02 (2.37–3.84) | 2.92 (2.29–3.72) |
| ≥6.00 | 2.58 (1.00–6.65) | 3.66 (1.36–9.86) | 4.85 (3.47–6.78) | 4.91 (3.48–6.91) |
| Continuous (per 1% increase) | 1.24 (1.07–1.43) | 1.30 (1.12–1.51) | 1.29 (1.22–1.35) | 1.29 (1.23–1.36) |

[a]Adjusted for education, race/ethnicity, number of first-degree relatives with breast cancer, osteoporosis/osteopenia, and hysterectomy.
[b]Adjusted for education, osteoporosis/osteopenia, and hysterectomy.
[c]Information on history of a breast biopsy with atypical hyperplasia, a component of the BCRAT, was categorized as "unknown" in the risk calculation for all women.

index age (Supplementary Table S3). Patterns were also similar when raloxifene analyses were restricted to those who initiated raloxifene in 2007 or later, though ORs for associations between risk–benefit index categories and chemoprevention use were somewhat attenuated (Supplementary Table S4).

## Discussion

In this study of women with a family history of breast cancer, current use of SERMs for breast cancer chemoprevention was rare overall, though raloxifene was more commonly used than tamoxifen. Among current raloxifene users, nearly all had moderate or strong evidence that the benefits of use outweighed the risks of adverse effects. In contrast, only 56% of current tamoxifen users had moderate or strong evidence of a net benefit, whereas 44% had no evidence. Our analyses also identified a substantial proportion of matched nonusers of chemoprevention who would potentially benefit from raloxifene or tamoxifen use. Expanding the use of risk–benefit tables in routine clinical care may facilitate the identification of women most likely to benefit from breast cancer chemoprevention.

**Table 3.** ORs and 95% CIs for tamoxifen and raloxifene use according to risk–benefit index category

| | **Users *N* (%)** | **Nonusers *N* (%)** | **Unadjusted OR (95% CI)** | **Adjusted[a] OR (95% CI)** |
|---|---|---|---|---|
| Tamoxifen | | | | |
| Risk–benefit index | | | | |
| None | 37 (44%) | 357 (44%) | 1 | 1 |
| Moderate | 14 (17%) | 87 (11%) | 1.51 (0.79–2.88) | 1.61 (0.83–3.11) |
| Strong | 33 (39%) | 359 (45%) | 0.44 (0.16–1.24) | 0.46 (0.16–1.33) |
| Raloxifene | | | | |
| Risk–benefit index | | | | |
| None | 19 (5%) | 540 (15%) | 1 | 1 |
| Moderate | 160 (43%) | 1,954 (54%) | 2.64 (1.61–4.32) | 2.56 (1.56–4.22) |
| Strong | 194 (52%) | 1,155 (32%) | 5.97 (3.62–9.87) | 5.98 (3.60–9.95) |

[a]Adjusted for education and osteoporosis/osteopenia before the index age.

At the population level, breast cancer risk-reducing medications are a potentially effective strategy for reducing morbidity from invasive breast cancer. In 2013, a U.S. Preventive Services Task Force report concluded that the benefits of FDA-approved tamoxifen and raloxifene are likely to exceed the harms for women with an estimated 5-year breast cancer risk of at least 3% (9). However, some evidence suggests that use of raloxifene and tamoxifen for chemoprevention remains low, even among women above this risk threshold. A recent analysis using data from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial and Medicare claims found that 6.6% and 0.85% of women ages 65 and older with a 5-year breast cancer risk of ≥3.0% used raloxifene and tamoxifen, respectively, during 2010–2014 (21). Likewise, a metaanalysis of studies published between 2001 and 2010 reported a pooled uptake estimate of 8.7% for chemopreventive agents among women with a high risk of breast cancer in nontrial settings (22). Potential reasons for noninitiation of these agents include not only women's concerns about the risk of serious adverse effects, but also a lack of routine use of breast cancer risk assessment tools and risk–benefit tables in the primary care setting (23). Though AIs, such as exemestane and anastrozole, have been investigated in chemoprevention clinical trials among postmenopausal women (24, 25) and may also be used off-label for breast cancer risk

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**Table 4.** Distribution of risk–benefit categories according to characteristics among current tamoxifen and raloxifene users

| | Tamoxifen ($N = 84$) | | | Raloxifene ($N = 373$) | | |
|---|---|---|---|---|---|---|
| | None *N* (Row %) | Moderate *N* (Row %) | Strong *N* (Row %) | None *N* (Row %) | Moderate *N* (Row %) | Strong *N* (Row %) |
| Age at initiation | | | | | | |
| <55 | 18 (34) | 5 (9) | 30 (57) | 7 (6) | 44 (40) | 58 (53) |
| 55–59 | 7 (58) | 4 (33) | 1 (8) | 2 (1) | 43 (29) | 104 (70) |
| 60–64 | 9 (69) | 3 (23) | 1 (8) | 4 (5) | 56 (69) | 21 (26) |
| 65+ | 3 (50) | 2 (33) | 1 (17) | 6 (18) | 17 (50) | 11 (32) |
| Race/ethnicity | | | | | | |
| Non-Hispanic white | 33 (43) | 11 (14) | 33 (43) | 14 (4) | 159 (44) | 192 (53) |
| Other | 4 (57) | 3 (43) | 0 (0) | 5 (63) | 1 (13) | 2 (25) |
| Hysterectomy before initiation | | | | | | |
| No | 37 (51) | 7 (10) | 28 (39) | 14 (5) | 128 (48) | 125 (47) |
| Yes | 0 (0) | 7 (58) | 5 (42) | 5 (5) | 32 (30) | 69 (65) |
| BCRAT score (%)[a] | | | | | | |
| <1.67 | 0 (0) | 0 (0) | 4 (100) | 0 (0) | 1 (50) | 1 (50) |
| 1.67–2.99 | 13 (37) | 4 (11) | 18 (51) | 18 (18) | 72 (73) | 8 (8) |
| 3.00–5.99 | 22 (58) | 9 (24) | 7 (18) | 1 (0) | 77 (38) | 125 (62) |
| ≥6.00 | 2 (29) | 1 (14) | 4 (57) | 0 (0) | 10 (14) | 60 (86) |

[a]Information on history of a breast biopsy with atypical hyperplasia, a component of the BCRAT, was categorized as "unknown" in the risk calculation for all women.

reduction, these drugs have not yet been FDA-approved for this purpose, and risk–benefit indices for AIs have not been developed for clinical use.

Findings from the current study highlight several characteristics associated with use of tamoxifen or raloxifene for chemoprevention in real-world settings. Associations with BCRAT score were in the expected direction for both raloxifene and tamoxifen, with a greater likelihood of chemoprevention use among women with a higher 5-year risk of invasive breast cancer. However, having strong evidence of a net benefit, as determined by risk–benefit indices that integrate information on age, race/ethnicity, hysterectomy status, and BCRAT score (12, 13), was associated with raloxifene use, but not tamoxifen use in our sample. In contrast, in a prior Sister Study analysis, women with strong evidence of benefit were more than 4 times as likely to use tamoxifen than those with no evidence (OR. 4.33; 95% CI, 3.27–5.74; ref. 14). Differences between the two reports may reflect changes in prescribing patterns or patient adoption over time, as the median calendar year of tamoxifen initiation in the earlier report was 10 years before that among tamoxifen users in the current study (2001 vs. 2011).

Limited research to date has examined risk–benefit profiles of women who choose to use tamoxifen or raloxifene for chemoprevention outside of clinical trials. In a study of 90 chemoprevention users identified in the Kaiser Permanente Northern California integrated healthcare system between 2005 and 2013, 23% of combined tamoxifen and raloxifene users had no evidence that the benefits of use for breast cancer prevention outweighed the risks (26). The proportions with strong and moderate evidence of benefit were 67% and 10%, respectively. Although results were not reported separately for tamoxifen and raloxifene, most women with an unfavorable risk–benefit profile were tamoxifen users, non-Hispanic white, age 50+, and had an intact uterus. In the prior report describing tamoxifen use for chemoprevention using data from Sister Study enrollment, 20% of tamoxifen users had no evidence of a net benefit; older age and having an intact uterus were characteristics associated with a less favorable risk–benefit profile (14). We observed similar patterns for tamoxifen in the current study, consistent with the evidence of increased risk of adverse events, such as endometrial cancer and thromboembolic events, associated with tamoxifen use.

Our results suggest a much higher prevalence of a favorable risk–benefit profile (moderate or strong evidence of benefit) among raloxifene users (95%) than among tamoxifen users (56%) in a contemporary sample of women currently using chemoprevention. These results likely reflect, in part, the lower risk of serious or life-threatening adverse events associated with raloxifene than with tamoxifen and emphasize the potential clinical value of using the risk–benefit tables for decision-making. Although excluded from analyses in the current study, we also identified 22 tamoxifen users and 12 raloxifene users with a history of medical conditions that we considered to be contraindications for use of their respective chemoprevention drug. The most common contraindication among tamoxifen users was a history of cataracts, a condition which is not life-threatening and therefore may not always deter women from initiating tamoxifen for breast cancer prevention. As expected, other more serious contraindications, such as stroke and pulmonary embolism, were rare among both tamoxifen and raloxifene users that we identified.

This study is one of few to date to examine risk–benefit profiles and characteristics of women who initiated raloxifene or tamoxifen for primary prevention outside of the clinical trial setting. However, our study has several limitations. For some components of the BCRAT score (e.g., breast biopsy history, number of first-degree relatives with breast cancer), we lacked information specific to the index

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age, and therefore relied on information collected at Sister Study enrollment. However, the average number of years between the enrollment and index age in our sample was only 1.4 years, and results were generally similar when women with greater than 3 years between enrollment and the index age were excluded. In addition, we did not have detailed information on breast biopsy results from either enrollment or the index age, and therefore history of atypical hyperplasia, a component of the BCRAT score, was coded as unknown for all women in our sample. This may have led the BCRAT score to be underestimated in some women, and could explain why a small number of women with a low BCRAT score in our analyses were identified as chemoprevention users. The risk–benefit indices used in our analyses also have their own limitations, as described previously (13). Another limitation is the potential for indication misclassification among raloxifene users. Though all raloxifene users included in our analyses reported breast cancer prevention as their current reason for use at the most recent Sister Study follow-up, we lacked information on their original indication for initiating raloxifene. Thus for some raloxifene users, it is possible that initiation at the index age was for osteoporosis prevention or treatment, rather than breast cancer prevention. This may be particularly true for the substantial proportion of raloxifene users who initiated use 10 or more years prior to completing the follow-up questionnaire. However, our conclusions were largely unchanged when we excluded women who initiated raloxifene prior to 2007, the year raloxifene was approved for breast cancer prevention by the FDA (7). Finally, the Sister Study cohort is predominately non-Hispanic White, and our sample included few chemoprevention users of other race/ethnicities. Therefore, we were limited in our ability to draw conclusions about associations between race/ethnicity and chemoprevention use.

Among a nationwide sample of women with a first-degree family history of breast cancer, nearly all raloxifene users, but only 56% of tamoxifen users, had evidence that the benefits of chemoprevention outweighed the risk of serious side effects. Use of breast cancer risk assessment tools and risk–benefit tables can help women and their health care providers to make an informed decision about breast cancer chemoprevention. Given the small number of raloxifene and tamoxifen users that we were able to identify within a large, family-history–based cohort, development of additional approaches to breast cancer prevention that have fewer potential side effects should be prioritized.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Authors' Contributions

**Conception and design:** H.B. Nichols, D.P. Sandler
**Development of methodology:** H.B. Nichols
**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** H.B. Nichols, D.P. Sandler
**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** C. Anderson, H.B. Nichols
**Writing, review, and/or revision of the manuscript:** C. Anderson, H.B. Nichols, M. House, D.P. Sandler
**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** M. House
**Study supervision:** D.P. Sandler

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