Carcinoma In Situ Outcomes in National Surgical Adjuvant Breast and Bowel Project Breast Cancer Chemoprevention Trials

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- Background** In the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT), the reduction in risk of noninvasive breast cancer was 50%. There were 93 cases in women receiving placebo and 60 in those receiving tamoxifen ($P = .008$). Through 7 years of follow-up, the cumulative incidence of noninvasive breast cancer among the placebo group was 15.8 per 1000 women vs 10.2 per 1000 women in the tamoxifen group. In the initial report of the Study of Tamoxifen and Raloxifene (STAR trial), the rate for noninvasive breast cancer was 1.51 per 1000 women assigned to tamoxifen and 2.11 per 1000 women assigned to raloxifene (risk ratio, 1.40; 95% confidence interval = 0.98 to 2.00).
- Methods** Additional follow-up of the NSABP STAR trial through March 31, 2009 is reported with a focus on noninvasive breast cancer events.
- Results** Through 81 months of median follow-up in the NSABP STAR trial, there are 137 cases of noninvasive breast cancer in the raloxifene group compared with 111 cases in the tamoxifen group (risk ratio = 1.02, 95% confidence interval = 0.61 to 1.70). The occurrence of ductal carcinoma in situ with raloxifene was seen more frequently among women with lower baseline Gail scores and no atypical hyperplasia than in women taking tamoxifen therapy. Raloxifene retained 76% of the effectiveness of tamoxifen in preventing invasive breast cancer.
- Conclusions** Although these data indicate that raloxifene offers less protection than tamoxifen for postmenopausal women who are at increased risk for both invasive and noninvasive breast cancer, the favorable risk-benefit profile for raloxifene affords acceptable clinical reduction in the risk of in situ cancers among postmenopausal women.

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Selective estrogen receptor modulators (SERMs) are established in the treatment of estrogen receptor (ER)-positive breast cancer, and four decades of basic and preclinical research have shown them to be ideal agents for the reduction of the risk of breast cancer in high-risk pre- and postmenopausal women. The National Surgical Adjuvant Breast and Bowel Project (NSABP) has conducted many clinical trials that used SERMs for the treatment and prevention of breast cancer. The trials were designed to assess a number of clinical and pathological outcomes including both invasive and in situ breast carcinomas. Here, we summarize the previously published data from two of those trials and also highlight the most recent data related to in situ events in the Study of Tamoxifen and Raloxifene (STAR) NSABP breast cancer risk reduction trial using tamoxifen.

In 1992, The National Cancer Institute and the NSABP launched the Breast Cancer Prevention Trial (BCPT, P-I) (1,2). The primary aim of this trial was to determine whether tamoxifen prevented invasive breast cancer in women at increased risk. Women eligible for the trial were 60 years or older, were 35-59

years of age with a 5-year predicted risk of breast cancer of at least 1.66%, or had a history of lobular carcinoma in situ (LCIS). Risk was estimated using the model developed by Gail et al. (3,4). During 5 years of recruitment, 13 388 women entered the trial and were randomly assigned to receive tamoxifen (20 mg daily) or placebo therapy.

The trial was stopped when statistical significance was achieved in a number of study endpoints after a median follow-up time of 54.6 months. Among the 13 175 women with evaluable endpoints, 368 invasive and noninvasive breast cancers occurred. There was a 49% reduction in overall risk of invasive breast cancer with tamoxifen: there were 175 cases of invasive breast cancer in the placebo group compared with 89 in the tamoxifen group (risk ratio [RR] = 0.51, 95% confidence interval [CI] = 0.39 to 0.66; $P < .0001$). The annual event rate for invasive breast cancer among women taking tamoxifen was 3.4 per 1000 women compared with 6.8 per 1000 women taking placebo.

For the purposes of this evaluation (and in the original publication), both ductal carcinoma in situ (DCIS) and LCIS—both

important precursor lesions for the development of invasive breast cancer—were considered as in situ events. For noninvasive breast cancer, the reduction in risk was 50%; there were 69 cases in women receiving placebo and 35 in those receiving tamoxifen ($P < .002$). Through 69 months of follow-up, the cumulative incidence of noninvasive breast cancer among the placebo group was 15.9 per 1000 women vs 7.7 per 1000 women in the tamoxifen group. The average annual rate of noninvasive breast cancer per 1000 women was 2.68 in the placebo group compared with 1.35 in the tamoxifen group, yielding a relative risk of 0.50 (95% CI = 0.33 to 0.77). The reduction in noninvasive cancers related to a decrease in the incidence of both DCIS and LCIS.

After 7 years of follow-up in BCPT (2), the cumulative rate of invasive breast cancer was reduced from 42.5 per 1000 women in the placebo group to 24.8 per 1000 women in the tamoxifen group, and the cumulative rate of noninvasive breast cancer was reduced from 15.8 per 1000 women in the placebo group to 10.2 per 1000 women in the tamoxifen group (63% risk reduction). The risk of pulmonary embolism was approximately 11% lower than in the original report, and the risk of endometrial cancer was about 29% higher, but these differences were not statistically significant. The net benefit achieved with tamoxifen varied according to age, race, and level of breast cancer risk. BCPT revealed that substantial net benefit accrues for women with a diagnosis of either LCIS or atypical hyperplasia who take tamoxifen (4). Among women with a history of LCIS, the reduction in risk was 56%, and among women with a history of atypical hyperplasia, the reduction in risk was 86%. In the 7-year follow-up period, tamoxifen reduced the occurrence of ER-positive tumors by 69%, but no difference in the occurrence of ER-negative tumors was seen.

NSABP STAR Trial

Based on the findings from the NSABP BCPT, tamoxifen was approved for reducing the risk of breast cancer by the US Food and Drug Administration in 1999. The NSABP STAR trial was launched to compare tamoxifen with raloxifene in a population of postmenopausal women at increased risk for breast cancer. For the purposes of this trial, menopause was defined as 1) a history of at least 12 months without spontaneous menstrual bleeding, or 2) a documented hysterectomy and bilateral salpingo-oophorectomy, or 3) age 55 years or older with a hysterectomy with or without oophorectomy, or 4) age younger than 55 years, either with a hysterectomy without oophorectomy or with unknown ovary status, and with a documented level of follicle-stimulating hormone confirming elevation in the postmenopausal range. Published studies of raloxifene used to prevent and treat postmenopausal osteoporosis indicated its ability to reduce the incidence of invasive breast cancer in women at average risk for breast cancer (5–9).

The objective of STAR was to compare raloxifene with tamoxifen in terms of their relative effects on the risk of invasive breast cancer and numerous other diseases influenced by tamoxifen in the BCPT.

Patient Characteristics

To be eligible for participation in the STAR trial, a woman had to have at least a 5-year predicted breast cancer risk of 1.66% based on

Table 1. Summary of screening, accrual, and follow-up information by treatment group, NSABP STAR (P-1) trial

Screening, accrual and follow-up item	Tamoxifen	Raloxifene	Total
Screening			
Women screened for breast cancer risk			184460
Women who were breast cancer risk eligible			96368
Women screened for medical eligibility			20616
Women meeting all eligibility criteria			20168
Accrual			
Women randomly assigned	9872	9875	19747
Not at risk*	0	3	3
Without follow-up	136	118	254
Included in this analysis	9736	9754	19490
Follow-up time (yr)			
≥2	9306	9343	18649
≥3	9047	9105	18152
≥4	8724	8825	17549
≥5	7442	7636	15078
≥6	5978	6160	12138
≥7	4437	4585	9022
≥8	2702	2752	5454
Average months of follow-up (SD)	76.3 (24.3)	77.2 (24.0)	76.8 (24.2)
Median	80.1	81.7	81.0
Total person-years of follow-up included in this analysis	61929	62743	124673

* History of bilateral mastectomy or invasive breast cancer before randomization.

the Gail model (3); be at least 35 years of age and postmenopausal; not be taking tamoxifen, raloxifene, hormone therapy, oral contraceptives, or androgens for at least the previous 3 months; not currently be taking either warfarin or cholestyramine; have no history of stroke, pulmonary embolism, or deep vein thrombosis; and no history of any malignancy diagnosed less than 5 years before random assignment except basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix; have no uncontrolled atrial fibrillation, uncontrolled diabetes, or uncontrolled hypertension; and have no psychiatric condition that would interfere with adherence or a performance status that would restrict normal activity for a significant portion of each day. Postmenopausal women aged 35 years and older could enter the trial if they had a history of LCIS treated by local excision alone.

A summary of the recruitment and follow-up of the women included in the STAR trial is shown in Table 1. Participants were screened and enrolled through nearly 200 clinical centers throughout North America. A total of 184460 women were screened to determine their breast cancer risk. Of these, 96368 had a 5-year risk of at least 1.66%. From this group, 20616 agreed to be screened to determine full eligibility for the trial based on the medical criteria defined above; 20168 were found to meet all eligibility criteria. Of this latter group, 19747 women expressed a desire to go forward with participation in the trial, signed a consent form, and were randomly assigned to receive either tamoxifen or raloxifene; 274 women were not included because no follow-up information was available for them (146 tamoxifen, 128 raloxifene).

In addition, two other women in the raloxifene group were excluded because they had received prophylactic bilateral mastectomy before random assignment and were not at risk for the development of invasive breast cancer.

The participants in this study were given a detailed description of the trial and provided written informed consent. The protocol and consent form were approved by the National Cancer Institute and the institutional review boards of all participating institutions. Participants were randomly assigned to receive either tamoxifen at a dose of 20 mg per day or raloxifene 60 mg per day over 5 years. The trial was designed to assess statistical equivalence of the two therapies and was powered to report data when 327 cases of invasive breast cancer occurred. The data reported here are based on a cutoff date of March 31, 2009 for the updated noninvasive breast cancer events through 81 months median follow-up and through December 31, 2005 for the data that appeared in the original publication of the trial results (10).

Characteristics of the participants enrolled in the STAR trial are summarized in Table 2. The mean age of participants at the time of random assignment was 58.5 years. Nine percent were younger than 50 years, 49.8% were between 50 and 59 years, and 41.2% were 60 years or older. More than 93% of participants were white, 2.5% were African American, 2.0% were Hispanic, and the remainder were of other racial or ethnic populations.

The mean time of follow-up in the original report was 3.9 years. Participant adherence to protocol therapy was within the

levels expected and planned for when designing the trial: the percentage of women persistent with the protocol regimen was 68.3% for those in the tamoxifen group and 71.5% for those in the raloxifene group. A nonadherence rate of 9.2% per year, as measured by both study dropouts and women who permanently discontinued therapy, was planned in the trial design. The mean duration of treatment was 3.1 and 3.2 years for the tamoxifen and raloxifene groups, respectively, at the time of the initial report; this differs from the mean duration of follow-up due to participants' discontinuing their study drug before the end of the 5-year period. Information on all individuals was included up to the time they underwent follow-up, regardless of whether or not they were adherent. During the course of the study, 605 women in the tamoxifen group and 532 in the raloxifene group were lost to follow-up, and this is well below the planned rate of 2% per year. Those lost to follow-up contributed an average of 24 months of information.

STAR Trial Endpoints

The primary endpoint in the STAR trial was invasive breast cancer. Secondary endpoints included endometrial cancer, in situ breast cancer, cardiovascular disease, stroke, pulmonary embolism, deep vein thrombosis, transient ischemic attack, osteoporotic fracture, cataracts, death, and quality of life. The STAR trial was monitored by an independent data monitoring committee. A consumer representative was also included as a member of the committee. The monitoring plan was based on detecting a statistically significant difference between treatment groups in the incidence of invasive breast cancer and included six interim analyses and a final analysis initiated when at least 327 cases of invasive breast cancer were diagnosed in the entire study cohort. With this number of events, the study design provided a 95% probability that we would correctly conclude that the two treatments were equivalent, if they really were so.

After a median of 3.2 years of therapy in the trial, there were 163 cases of invasive breast cancer in women assigned to tamoxifen and 168 in those assigned to raloxifene (incidence, 4.30 per 1000 vs 4.41 per 1000; RR = 1.02; 95% CI = 0.82 to 1.28). The cumulative incidence through 72 months for the two treatment groups was 25.1 and 24.8 per 1000 for the tamoxifen and raloxifene groups, respectively ($P = .83$). When the treatment groups were compared by baseline categories of age, history of LCIS, history of atypical hyperplasia, Gail model 5-year predicted risk of breast cancer, and the number of relatives with a history of breast cancer, the pattern of no differential effect by treatment assignment remained consistent. There were no differences between the treatment groups with regard to distributions by tumor size, nodal status, or ER level.

Noninvasive Breast Cancer or Atypia Present at Random Assignment in the NSABP STAR Trial

Pathology slides were neither collected nor reviewed for any of the subjects, but all reports of in situ cancers were reviewed by the authors (VGV and/or DLW) for both consistency of classification

Table 2. Participant characteristics at time of randomization for women included in the updated analyses (data through March 31, 2009, NSABP STAR (P-2) trial)

Participant characteristic	Tamoxifen, No. (%)	Raloxifene, No. (%)
Age (yr)		
≤49	884 (9.1)	878 (9.0)
50–59	4856 (49.9)	4855 (49.8)
60–69	3137 (32.2)	3174 (32.5)
≥70	859 (8.8)	847 (8.7)
Race/ethnicity		
Caucasian	9105 (93.5)	9115 (93.4)
African American	233 (2.4)	243 (2.5)
Hispanic	192 (2.0)	193 (2.0)
Other	206 (2.1)	203 (2.1)
No. first-degree relatives with breast cancer		
0	2838 (29.1)	2791 (28.6)
1	5046 (51.8)	5135 (52.6)
2	1532 (15.7)	1561 (16.0)
≥3	320 (3.3)	267 (2.7)
History of hysterectomy		
No	4739 (48.7)	4717 (48.4)
Yes	4997 (51.3)	5037 (51.6)
History of lobular carcinoma in situ		
No	8844 (90.8)	8865 (90.9)
Yes	892 (9.2)	889 (9.1)
History of breast atypical hyperplasia		
No	7545 (77.5)	7513 (77.0)
Yes	2191 (22.5)	2241 (23.0)
5-yr predicted breast cancer risk (%)		
≤2.00	1055 (10.8)	1102 (11.3)
2.01–3.00	2993 (30.7)	2893 (29.7)
3.01–5.00	3042 (31.2)	3086 (31.6)
≥5.01	2646 (27.2)	2673 (27.4)
Total	9736	9754

Table 3. Summary of in situ breast cancers in the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (P-2) at 47 months median follow-up*

Variable	Tamoxifen, No. (%)	Raloxifene, No. (%)	Total, No. (%)
Prior LCIS			
No	28 (49.1)	49 (61.3)	77 (56.2)
Yes	29 (50.9)	31 (38.7)	60 (43.8)
Prior AH			
No	35 (61.4)	51 (63.8)	86 (62.8)
Yes	22 (38.6)	29 (36.2)	51 (37.2)
Diagnosis			
DCIS	27 (47.4)	35 (43.8)	62 (45.3)
LCIS	22 (38.6)	29 (36.2)	51 (37.2)
DCIS with comedo necrosis	3 (5.3)	6 (7.5)	9 (6.6)
High-grade DCIS	2 (3.5)	3 (3.8)	5 (3.6)
Mixed	3 (5.3)	7 (8.8)	10 (7.3)
Treatment			
Unknown	11 (19.3)	9 (11.2)	20 (14.6)
Lumpectomy	32 (56.14)	42 (52.5)	74 (54.0)
Mastectomy	8 (14.0)	15 (18.8)	23 (16.8)
Excisional biopsy	2 (3.5)	2 (2.5)	4 (2.9)
Bilateral mastectomy	4 (7.0)	12 (15.0)	16 (11.7)
Total number of cases	57	80	
		Risk ratio	95% confidence interval
Annual rate per 1000 woman-years	1.51	2.11 (1.40)	0.98 to 2.00

* AH = atypical hyperplasia; DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ.

and nomenclature. Prior history of atypical hyperplasia or LCIS, along with the surgical management of women with incident in situ events, are shown in Table 3 as reported in the original publication of the trial in 2006 (10). Table 3 subdivides the two treatment groups by prior diagnosis of LCIS or atypical hyperplasia (either lobular or ductal) at the time of randomization in the trial. It also reports diagnoses of in situ events (LCIS, DCIS, DCIS with comedo necrosis, high-grade DCIS, or mixed LCIS/DCIS) that occurred while participants were in active follow-up in the trial. Finally, the table also shows the treatment that each patient received for their in situ diagnosis during the trial.

There were fewer noninvasive breast cancers in the tamoxifen group than in the raloxifene group, although this difference did not reach statistical significance. In the initial report, there were 57 incident cases of noninvasive breast cancer among the women who took tamoxifen and 80 among the women who took raloxifene. We recognized that a diagnosis of either DCIS or LCIS after enrollment in the trial could represent re-diagnosis of prevalent, rather than incident, in situ disease. When we eliminated those women

with either LCIS at baseline or with either LCIS or DCIS diagnosed within the first year of the trial, however, the excess number of cases persisted in the raloxifene group when compared with the tamoxifen group.

The rate for noninvasive breast cancer was 1.51 per 1000 women assigned to tamoxifen and 2.11 per 1000 women assigned to raloxifene (RR = 1.40; 95% CI = 0.98 to 2.00). The cumulative incidence through 6 years was 8.1 per 1000 in the tamoxifen group and 11.6 in the raloxifene group ($P = .052$). About 36% of the cases were diagnosed with LCIS and 54% with DCIS, with the balance being mixed types. The pattern of fewer cases among the tamoxifen group was evident for both LCIS and DCIS.

A nearly equal number of women in both groups had both LCIS and DCIS reported on surgical biopsy specimens. For incident DCIS lesions, women taking raloxifene had nearly a 50% greater rate of these in situ events compared with women taking tamoxifen (RR = 1.46, 95% CI = 0.90 to 2.41) at the time of the original report. Similarly, the rate of incident LCIS events after enrollment was greater in the women taking raloxifene than in those taking tamoxifen (RR = 1.37, 95% CI = 0.76 to 2.54). Neither of these differences was statistically significantly different, however.

The updated data for the noninvasive breast cancer events reported through March 31, 2009 are shown in Table 4. Again, both DCIS and LCIS were counted as in situ events. While the rates for both DCIS and mixed DCIS or LCIS incident events remained elevated for women in the raloxifene group, all of the 95% confidence intervals broadly overlapped 1.0 and were not statistically significant. Therefore, with additional follow-up, there was no indication of a greater risk for in situ carcinoma events when comparing women taking raloxifene with those taking tamoxifen. The cumulative incidence of noninvasive breast cancer in the STAR trial with prolonged follow-up is shown in Figure 1. The difference between the groups is not statistically significant.

In the 81-month analysis, the risk ratio when comparing the relative efficacy of raloxifene compared with tamoxifen for invasive breast cancer was 1.24 (95% CI = 1.05 to 1.47) and for noninvasive disease, 1.22 (95% CI = 0.95 to 1.59) (11). Compared with initial results, the risk ratios widened for invasive and narrowed for noninvasive disease (which included both DCIS and LCIS). Long-term raloxifene retained 76% of the effectiveness of tamoxifen in preventing invasive disease and grew closer over time to tamoxifen in preventing noninvasive disease, with far less toxicity (eg, highly significantly less endometrial cancer). These results clarify that both raloxifene and tamoxifen are good preventive choices for postmenopausal women with elevated risk for breast cancer.

Table 4. Annual rates of noninvasive breast cancer—National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene trial (P-2) through 81 months median follow-up*

Disease	Number of events		Rate per 1000			Risk ratio	95% confidence interval
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	Difference		
DCIS	70	86	1.15	1.40	−0.25	1.22	0.88 to 1.69
LCIS	33	34	0.54	0.55	−0.01	1.02	0.61 to 1.70
Mixed	8	17	0.13	0.28	−0.15	2.11	0.86 to 5.64
Total	111	137	1.83	2.23	−0.40	1.22	0.95 to 1.59

* DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ.

Figure 1. Cumulative incidence of non-invasive breast cancer in the NSABP Study of Tamoxifen and Raloxifene trial through 81 months of median follow-up, NSABP STAR (P-1).

Patients with a history of LCIS or atypical hyperplasia of the breast have a fourfold to 10-fold increased risk of subsequent invasive disease, and tamoxifen and raloxifene were equally effective in reducing this risk in the initially reported STAR results. The analyses at 81 months indicated that this equality was no longer the case for STAR women with a history of atypical hyperplasia (RR = 1.48; 95% CI = 1.06 to 2.09), although results for the LCIS group remain similar to those reported originally (RR = 1.13; 95% CI = 0.76 to 1.69) (11).

Discussion

In the initial report of the STAR trial, tamoxifen and raloxifene had equivalent effects in reducing risk of invasive breast cancer in all examined subgroups, including women with a history of atypical hyperplasia or LCIS, who had the highest annual rates of invasive breast cancer. Updated data for invasive breast cancer show that raloxifene retains 76% of its effectiveness relative to tamoxifen in preventing new events (11). The reason for this decline over time is unexplained.

We found no statistically significant difference between raloxifene and tamoxifen in the risk of noninvasive disease (LCIS and DCIS) (incidence, 1.83 vs 2.23 per 1000 per year; RR = 1.22; 95% CI = 0.95 to 1.59) in the updated analysis. However, the STAR trial may have been underpowered to detect such a difference. Therefore, the clinical impact of this finding remains to be seen. Similar results were found in the Multiple Outcome of Raloxifene Evaluation and Continuing Outcomes Related to Evista studies (8,9,12), in which raloxifene did not reduce the risk of noninvasive breast cancer when compared with placebo, although the number of events in those studies was very small.

The initial STAR report suggested that raloxifene may not be as effective as tamoxifen in preventing the development of non-invasive breast cancers (LCIS and DCIS combined). The updated

results show that the difference between the treatment groups has narrowed, and, much like its effect in invasive breast cancer, raloxifene is about 78% as effective as tamoxifen in reducing the risk of noninvasive breast cancer. Patients with a history of LCIS or atypical hyperplasia of the breast have a fourfold to 10-fold increased risk of subsequent invasive disease, and in the initial STAR report, tamoxifen and raloxifene were equally effective in reducing that risk. That is no longer the case for those with a history of atypical hyperplasia (RR = 1.48; 95% CI = 1.06 to 2.09, comparing raloxifene with tamoxifen), although results for the LCIS group remain similar to those originally reported (RR = 1.13; 95% CI = 0.76 to 1.69).

Most of the STAR cases of DCIS were diagnosed as a result of mammograms that demonstrated increasing calcifications. One possibility is that raloxifene reduced mammographic density to a greater degree than did tamoxifen resulting in differential “unmasking” of in situ cancers among the women taking raloxifene as compared with those taking tamoxifen. Published literature speaks against this possibility, however, showing little effect on mammographic density by raloxifene (13,14) and variable effects with tamoxifen (15,16).

The LCIS subgroup rates reported in the STAR trial for development of invasive breast cancer of 9.83 (tamoxifen) and 9.61 (raloxifene) per 1000 women were about 2.5 times higher than those for women who participated in the study and had no history of LCIS (3.76 [tamoxifen] and 3.86 [raloxifene] per 1000). The annual rates of invasive breast cancer among women aged 50 years or older at baseline with no history of LCIS were similar in the two prevention studies (3.30 per 1000 in the BCPT and 4.3 per 1000 in STAR) (1,2,10). However, the rates in women with an LCIS history were about 1.7 times higher in the STAR trial than in the tamoxifen group of the BCPT. Similar patterns emerged when we compared the STAR trial and the BCPT in terms of breast cancer

results in women with or without a baseline history of atypical hyperplasia. The greater mean age at entry and the higher 5-year risk of breast cancer in STAR participants may be the explanation for these differences. Pathological size of incident invasive breast cancers was similar between study groups, and the status of the axillary lymph nodes or presence of ER protein was not significantly different between the groups.

The superiority of tamoxifen over raloxifene in reducing breast cancer risk is associated with significantly more endometrial cancers, hysterectomies for benign disease, thromboembolic events, and cataracts (11). These toxicities may be acceptable for the treatment of breast cancer but are barriers to its use to prevent primary breast cancers. Tamoxifen is approved for use in premenopausal women. In the NSABP BCPT, there was no excess risk of endometrial cancers or thromboembolic events in the tamoxifen-treated premenopausal group compared with the placebo group. For premenopausal women at increased risk, particularly those with LCIS or atypical hyperplasia, tamoxifen has a positive risk-benefit ratio and should be presented as a treatment option to these women to reduce the risk of both invasive and noninvasive breast cancer. A similar risk-benefit ratio may exist in younger postmenopausal women with elevated Gail scores and a prior hysterectomy. The data also demonstrate that raloxifene retains substantial benefit in reducing the risk of invasive breast cancer with fewer life-threatening side effects than tamoxifen, including significantly fewer endometrial cancers, which is in keeping with the placebo-controlled raloxifene trials.

Conclusions

Tamoxifen and raloxifene have different effects on the development of both invasive and noninvasive breast cancer in high-risk postmenopausal women. The rate of development of in situ breast cancer in the STAR trial was greater with raloxifene than with tamoxifen although not statistically significant, but the difference in the rate of development of DCIS was only 0.40 cases per 1000 woman-years. The occurrence of DCIS with raloxifene was seen more frequently among women with lower baseline Gail scores and no atypical hyperplasia than in women taking tamoxifen therapy. All of these results taken together suggest that different SERMs have unique and specific mixes of benefits and risks and that neither a benefit nor a risk seen with one SERM can be generalized across the entire class. Although these data indicate that raloxifene offers less protection than tamoxifen for postmenopausal women who are at increased risk for both invasive and noninvasive breast cancer, the favorable risk-benefit profile for raloxifene still affords acceptable clinical reduction in the risk of in situ cancers among postmenopausal women.

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Notes

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