Contralateral Breast Cancer and Thromboembolic Events in African American Women Treated With Tamoxifen

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Background: **Information about breast cancer treatment and prevention in African American women is scant, and recommendations for therapy from clinical trials for breast cancer are based primarily on data obtained from white women.** ***Methods:*** **We compared the effects of tamoxifen on risk of contralateral breast cancer and thromboembolic events in African American women and white women with a history of primary breast cancer. Data from 13 National Surgical Adjuvant Breast and Bowel Project clinical trials were pooled for analyses of time to contralateral breast cancer as a first event (eight trials and 10 619 patients) and of time to any thromboembolic phenomenon as a first event (all 13 trials and 20 878 patients). Risk factors for contralateral breast cancer and thromboembolic events among all women were determined using univariate proportional hazards models. (For each racial group, the rate of events associated with tamoxifen use was calculated as the ratio of the incidence rate with tamoxifen to that without tamoxifen.) Proportional hazards regression models were used to calculate 95% confidence intervals (CIs) and risk ratios. All statistical tests were two-sided.** ***Results:*** **Risk factors for contralateral breast cancer were body mass index (BMI) and lymph node positivity; those for thromboembolic events were BMI and age. In women of both ethnicities with estrogen receptor–positive breast cancer, those who took tamoxifen experienced a similar reduction in contralateral breast cancer (risk ratio for African American women = 0.74, 95% CI = 0.46 to 1.17, n = 690; risk ratio for white women = 0.76, 95% CI = 0.59 to 0.98, n = 9929; P = .92). Tamoxifen was also associated with an increase in thromboembolic events. The relative risk for thromboembolic events was higher in both African American and white women treated with tamoxifen and chemotherapy than in those who were treated with tamoxifen alone (risk ratio for African American women = 10.70, 95% CI = 5.94 to 19.28 versus 2.16, 95% CI = 1.26 to 3.71; n = 1842; risk ratio for white women = 15.49, 95% CI = 9.53 to 25.17 versus 3.13, 95% CI = 2.04 to 4.79, n = 19 036), and this effect was similar between the races (P = .10).** ***Conclusions:*** **African American and white women appear to have the same risks of contralateral breast cancer and thromboembolic events in response to tamoxifen treatment. [J Natl Cancer Inst 2004;96:1762–69]**

Women who have been diagnosed with breast cancer have an increased risk of developing cancer in the opposite or contralateral breast *(1–8);* between 2% and 15% of these women will develop contralateral breast cancer in their lifetime, depending on age at diagnosis and other factors, including histologic type of the primary tumor and obesity *(2,4,9).* Incidence rates of contralateral breast cancer by age are higher in all age categories than are incidence rates of first primary breast cancer in the general population.

Large randomized trials have demonstrated that women with a history of early-stage primary breast cancer who are treated for 5 years with tamoxifen have an overall 47% reduction in rate of contralateral breast cancer *(10).* The National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-14, in which tamoxifen was compared with placebo in a double-blind trial of women with estrogen receptor (ER)–positive, node-negative breast cancer, showed a 10-year cumulative incidence of contralateral breast cancer of 6.1% in placebo-treated patients versus 3.8% ($P = .007$) in tamoxifen-treated patients *(11).* A population-based, nested case–control study conducted at conventional medical practices found a 50% (matched odds ratio = 0.5, 95% CI = 0.3 to 0.9) reduction of contralateral breast cancer in women who took tamoxifen for more than 1 year compared with those who did not *(12).* The rationale for tamoxifen chemoprevention in breast cancer trials was based on the reduction in contralateral breast cancer observed in tamoxifen treatment trials. The NSABP's Breast Cancer Prevention Trial showed a 49% reduction (95% CI = 0.39 to 0.66; $P<.001$), relative to placebo, in the incidence of invasive breast cancer in otherwise healthy women with increased risk of developing the disease who took tamoxifen for 5 years *(13).* An overview analysis of four prospective breast cancer prevention trials reported a 38% reduction (95% CI = 18 to 46%) in the incidence of breast cancer in patients treated with tamoxifen compared with those who took placebo, *(14–17),* and the Italian Randomized Trial of Tamoxifen recently reported an 82% reduction among a high-risk population at 81 months *(18).*

The clear benefit of tamoxifen treatment demonstrated in these trials was based largely on results from white women. Relatively few data exist on the effect of tamoxifen in reducing primary and contralateral breast cancer in African American women. Moreover, tamoxifen use is associated with an increase in thromboembolic events *(19,20),* but few data exist on the

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effects of tamoxifen on thromboembolic events among African Americans, a population known to have risk factors for thromboembolic events, e.g., cardiovascular diseases and obesity. In this article, we present the results of analyses addressing two aspects of tamoxifen use in African American patients: 1) whether there is a difference in contralateral breast cancer occurrence in white and African American patients after treatment with tamoxifen for primary breast cancer and 2) whether the effect of tamoxifen on rates of thromboembolic events is different in white and African American patients who take this drug.

Subjects and Methods

Analyses are based on data from African American and white breast cancer patients who took part in 13 NSABP trials (Table 1). Two parallel analyses were carried out, one with time to contralateral breast cancer as a first event and one with time to any thromboembolic phenomenon as a first event. Previous versions of these analyses have been presented *(22,23).* Thromboembolic phenomenon events included superficial phlebitis, deep vein thrombosis with or without hospitalization, and pulmonary embolism. If a thromboembolic phenomenon occurred after a second primary cancer (including contralateral breast cancer) or a disease recurrence, it was excluded from the thromboembolic phenomenon analysis. All deep vein thrombosis and pulmonary emboli were items prompted on trial-based toxicity reports. Source documents were reviewed centrally by clinical staff at the NSABP.

NSABP Trials

Breast cancer patients who participated in adjuvant treatment trials were considered for inclusion in this analysis. As shown in Table 1, these trials targeted a variety of patient populations in terms of axillary lymph node involvement, ER status, and other patient characteristics. In addition, these trials evaluated a variety of treatment approaches (both local and systemic) and regimens differing in specific aspects of chemotherapy and hormonal therapy.

Patients

For the analysis of contralateral breast cancer, data were pooled from NSABP protocols B-14, B-15, B-16, B18 (postoperative chemotherapy arm only), B-20, B-21, B-22, and B-25. To account for the evolving belief that tamoxifen treatment is effective primarily in ER-positive patients and for the data suggesting a strong concordance between the hormone receptor status of primary breast cancer and contralateral breast cancer, we limited the analysis to ER-positive patients *(21).* The protocols examined in this analysis included 10 619 ER-positive women, 494 of whom experienced contralateral breast cancer as a first event following treatment for a primary breast cancer. Pooled data over all eight trials showed similar adherence to treatment among African American and white patients (data not shown).

Data from all patients in the contralateral breast cancer analysis were included in the analysis of thromboembolic phenomena. In addition, ER-negative patients from the same protocols were included in this analysis, as were patients from the NSABP B-13, B-19, and B-23 protocols. Patients from NSABP protocols B-17 and B-24 were included in this analysis, because we believe that ductal carcinoma *in situ* (DCIS) presents no potential bias with respect to thromboembolic phenomena as an endpoint. Taken together, the protocols examined in the analysis of thromboembolic phenomena included 20 878 women, 608 of whom experienced thromboembolic phenomena as a first event following primary breast cancer treatment. All patients gave written consent to participate in this study.

Table 1. Characteristics of National Surgical Adjuvant Breast and Bowel Project trials B-13 through B-25

Trial	No. of patients*	Axillary lymph node status	Estrogen receptor status	Treatment	Other characteristics
B-13	731	Negative	Negative	No drug vs. methotrexate/fluorouracil	
B-14	2817	Negative	Positive	Placebo vs. tamoxifen	
B-15	2295	Positive	Positive and negative	AC vs AC → CMF vs. CMF	
B-16	833	Positive	Positive and negative	TAM vs. ACT vs. PFT or PAFT	
B-17	813	Negative or unknown	Positive and negative	No therapy vs. XRT	DCIS
B-18	1493	Clinically positive and negative	Positive and negative	AC pre-op vs. AC post-op	
B-19	1074	Negative	Negative	Methotrexate → fluorouracil vs. CMF	
B-20	2299	Negative	Positive	TAM vs. methotrexate → fluorouracil + TAM vs. CMF + TAM	
B-21	968	Negative	Positive and negative	XRT + placebo vs. breast XRT + TAM vs TAM alone	Occult disease, all patients Rx with lumpectomy + axillary dissection
B-22	2254	Positive	Positive and negative	Standard AC vs. intensified AC (CY dose 1200 mg/m^2 × 2 vs. intensified AC (CY 1200 mg/m^2 × 4	
B-23	1955	Negative	Negative	CMF vs. AC ± TAM vs. placebo	
B-24	1798	Negative or unknown	Positive and negative	Placebo vs. TAM	DCIS
B-25	2508	Positive	Positive and negative	AC (CY-1200 mg/m^2 × 4) vs. AC (CY 2400 mg/m^2 × 2 vs. AC (CY 2400 mg/m^2 × 4) all + G-CSF	

*Total number of eligible, randomly assigned patients with follow-up on each trial.

Abbreviations: AC = adriamycin and cyclophosphamide; CMF = cyclophosphamide; methotrexate, and 5-fluorouracil; TAM = tamoxifen; ACT = adriamycin, cyclophosphamide, and tamoxifen; PFT = L-PAM, 5-flurouracil, and tamoxifen; PAFT = L-PAM, adriamycin, 5-flurouracil, and tamoxifen; XRT = X-ray therapy; CY = cyclophosphamide; DCIS = ductal carcinoma *in situ.*

Statistical Methods

For both contralateral breast cancer and thromboembolic phenomenon analyses, the primary question was whether African American and white patients differed in the association of tamoxifen treatment with contralateral breast cancer and thromboembolic phenomena. Incidence rates of contralateral breast cancer and thromboembolic phenomenon were calculated per 1000 person-years for African American and white patients who did and did not use tamoxifen. For each racial group, the unadjusted relative risk of event associated with tamoxifen use was calculated as the ratio of the incidence rate with tamoxifen to the incidence rate without tamoxifen. The 95% confidence intervals for unadjusted risk ratios were calculated using proportional hazards regression models. The proportionality assumption was checked graphically using log cumulative hazard plots. All statistical tests were two-sided. *P* values less than .05 were deemed statistically significant. To determine statistical significance of racial differences in association of tamoxifen treatment with contralateral breast cancer and thromboembolic phenomenon, proportional hazards regression was used to assess the statistical significance of a race–tamoxifen interaction term in models that included race (African American, white) and tamoxifen use (Y/N) as main effects.

Before the inclusion of race and tamoxifen use as model terms, potential confounding variables, including two-factor interactions, were added in a forward stepwise fashion. Main effects and interactions were retained for adjustment if they were statistically significant. For the contralateral breast cancer analysis, potential confounders were protocol, body mass index (BMI $\leq$ 25.7, $>$ 25.7), age ($<$50 years, 50–60 years and $>$60 years), positive lymph nodes at initial surgery (0, $\geq$1), lobular invasive disease (Y/N), and chemotherapy (Y/N). The cut point for BMI was set at the median value and for age was set at 50 years as a surrogate indicator for menopause. The additional age cut point of 60 years was added to identify older patients. The thromboembolic phenomenon analysis included the same potential confounders with the addition of ER status (positive, negative). Also, when interactions were found between chemotherapy and tamoxifen and between positive lymph nodes and tamoxifen in the thromboembolic phenomena analysis, the three-way interactions with race were assessed to determine whether the two-way interactions differed by race. In addition to assessing the statistical significance of the race–tamoxifen interaction, the models were used to calculate adjusted relative risks (hazard ratios) and 95% confidence intervals (CIs) for event risk associated with tamoxifen use for African American and white patients.

Results

Patient Characteristics

The characteristics of the patients studied in the contralateral breast cancer and thromboembolic phenomenon analyses are shown in Tables 2 and 3, respectively. For the patient subset included in the contralateral breast cancer analysis, African American patients were somewhat younger on average than white patients (median = 50.0 years and 52.0 years, respectively), had larger tumors (median diameter = 2.5 cm and 2.0 cm), and had higher BMI (median = 28.5 kg/m^2 and 25.4 kg/m^2). In addition, African American patients had a higher percentage of positive lymph nodes (56.5% versus 47.2%), a lower likelihood of tamoxifen treatment (52.8% versus 60.4%), and a lower percentage of lobular invasive disease (7.5% versus 9.3%). The difference in percentage of lobular disease in the two racial groups was not statistically significant, but the remaining differences were. In the patient subset analyzed for thromboembolic phenomena, all measured parameters were statistically significantly different between the two racial groups, including percentage of lobular invasive disease (Table 2). In addition, African American patients had a lower percentage of ER-positive tumors than white patients (714 [43.7%] versus 10 276 [62.8%], $P<.001$). Racial differences in patient demographics are difficult to interpret given that they could have been caused by patient selection in recruitment to the various protocols.

Contralateral Breast Cancer

Pooled contralateral event rates per 1000 person-years by race and tamoxifen use are shown in Table 4. The limited numbers of African American women in each protocol and of contralateral breast cancer events among these women made protocol-specific contralateral breast cancer rates difficult to estimate. Pooled across protocols, the contralateral breast cancer rates among African American women were 7.06 (95% CI = 4.04 to 11.47) contralateral breast cancers per 1000 person-years in women who did not receive tamoxifen and 4.84 (95% CI

Table 2. Patient characteristics by race in patients included in the analyses of contralateral breast cancer (n = 10 619)*

Characteristic/parameter	African American patients (n = 690)	White patients (n = 9929)	*P*
Age at surgery (y), median (IQR)	50.0 (17.0)	52.0 (16.0)	<.001
Tumor diameter (cm), median (IQR)	2.5 (1.5)	2.0 (1.5)	<.001
Body mass index (kg/m^2), median (IQR)	28.5 (7.5)	25.4 (6.9)	<.001
Positive lymph nodes, n (%)	390 (56.5)	4687 (47.2)	<.001
Tamoxifen treatment, n (%)	364 (52.8)	6000 (60.4)	<.001
Lobular invasive disease, n (%)	26 (7.1)	494 (9.3)	.162

*Comparisons between racial groups were two-sided and made using rank sum tests for continuous variables and Fisher's exact tests for discrete variables. IQR = interquartile range.

Table 3. Patient characteristics by race in patients included in the analysis of thromboembolic phenomena (n = 20 878)*

Characteristic/Parameter	African American patients (n = 1842)	White patients (n = 19 036)	P*
Age at surgery (y), mean (IQR)	47.0 (17.0)	51.0 (17.0)	<.001
Tumor diameter (cm), median (IQR)	2.5 (1.5)	2.0 (1.5)	<.001
Body mass index (kg/m^2), median (IQR)	29.0 (8.4)	25.4 (6.8)	<.001
Positive lymph nodes n (%)	823 (44.7)	7686 (40.4)	<.001
Positive estrogen receptor status, n (%)	714 (43.7)	10 276 (62.8)	<.001
Tamoxifen treatment, n (%)	710 (38.6)	9002 (47.3)	<.001
Lobular invasive disease, n (%)	36 (3.0)	692 (5.8)	<.001

*Comparisons between racial groups were two-sided and were made using rank sum tests for continuous variables and Fisher's exact tests for discrete variables. IQR = interquartile range.

=2.65 to 8.12) contralateral breast cancers per 1000 person-years in women who did. The crude estimated relative risk of contralateral breast cancer in African American women with and without tamoxifen is therefore 4.84/7.06 = 0.69 (95% CI = 0.33 to 1.40). The corresponding figures among white women are 7.67 (95% CI = 6.72 to 8.73) contralateral breast cancers per 1000 person-years without tamoxifen treatment and 4.51 (95% CI = 3.95 to 5.13) contralateral breast cancers per 1000 person-years with tamoxifen treatment. The crude relative risk estimate in white women was therefore 4.51/7.67 = 0.59 (95% CI = 0.49 to 0.71).

The relationship between time to contralateral breast cancer and the presence of individual risk factors was explored using proportional hazards regression. When potential confounding variables were assessed in a univariate fashion, both high BMI (P = .01) and the presence of positive lymph nodes (P = .01) were statistically significantly associated with time to contralateral breast cancer. Neither the race–BMI nor the race–nodes interaction term was statistically significant.

Proportional hazards modeling for time to contralateral breast cancer, with adjustment for protocol, age, BMI, and the presence of positive lymph nodes, yielded the estimates of relative risk after tamoxifen use in African American and white patients of 0.74 (CI = 0.46 to 1.17) and 0.76 (CI = 0.59 to 0.98), respectively (Table 4). The interaction between race and tamoxifen use was not statistically significant (P = .92).

Thromboembolic Phenomena

Thromboembolic phenomena event rates per 1000 person-years by race and tamoxifen use are shown in Table 5. Pooled across protocols, the thromboembolic phenomena rates among African American women were 4.80 (95% CI = 3.01 to 7.27) thromboembolic phenomena per 1000 person-years with tamoxifen treatment and 2.85 (95% CI = 1.76 to 4.35) thromboembolic phenomena per 1000 person-years without tamoxifen treatment. The crude estimated relative risk of thromboembolic phenomena with and without tamoxifen in African American women was therefore 4.80/2.85 = 1.68 (95% CI = 0.93 to 3.07). The corresponding figures among white women were 6.17 (95% CI = 5.60 to 6.79) and 1.95 (95% CI = 1.64 to 2.29) thromboembolic phenomena per 1000 person-years with and without tamoxifen treatment, respectively. The crude relative risk estimate for white women was 6.17/1.95 = 3.16 (95% CI = 2.63 to 3.83).

The relationship between time to thromboembolic phenomena and individual risk factors was explored using proportional hazards regression. When potential confounding variables were assessed in a univariate fashion, high BMI (P = .01) and age (P = .01) were statistically significantly associated with time to thromboembolic phenomena. Neither BMI nor age associations differed between African American and white patients (i.e., race–BMI and race–age interaction terms were not statistically

Table 4. Incidence rates of contralateral breast cancers per 1000 person-years by race and tamoxifen use*

Race	Tamoxifen treatment	No. of patients at risk	No. of events	Rate per 1000 person-years (95% CI)	Unadjusted relative risk (95% CI)†	Adjusted relative risk (95% CI)‡
African American	Yes	364	14	4.84 (2.65 to 8.12)	0.59 (0.39 to 0.89)	0.74 (0.46 to 1.17)
	No	326	16	7.06 (4.04 to 11.47)		
White	Yes	6000	232	4.51 (3.95 to 5.13)	0.59 (0.50 to 0.71)	0.76 (0.59 to 0.98)
	No	3929	232	7.67 (6.72 to 8.73)		

*The relative risk referred to is the risk of contralateral breast cancer with versus without tamoxifen use. CI = confidence interval.

†Ratio of rates per 1000 person-years with tamoxifen to without tamoxifen.

‡Hazard ratio from proportional hazards modeling adjusted for protocol, age, BMI, and positive lymph nodes. The interaction between race and tamoxifen use was not statistically significant (two-sided P = .92).

Table 5. Incidence rates of thromboembolic phenomena per 1000 person-years by race and tamoxifen use

Race	Tamoxifen treatment	No. at risk	No. of events	Rate per 1000 person-years	Unadjusted relative risk (95% CI)†
African American	Yes	710	22	4.80 (3.01 to 7.27)	2.17 (1.38 to 3.39)
	No	1132	21	2.85 (1.76 to 4.35)	
White	Yes	9002	420	6.17 (5.60 to 6.79)	3.19 (2.64 to 3.85)
	No	10034	145	1.95 (1.64 to 2.29)	

*The relative risk referred to is the risk of thromboembolic phenomena with versus without tamoxifen use.

†Hazard ratio from proportional hazards modeling including race, tamoxifen, and race–tamoxifen interaction. The interaction between race and tamoxifen was not statistically significant in the unadjusted model (two-sided $P = .10$).

significant). In the proportional hazards model of time to thromboembolic phenomena, stepwise model fitting resulted in the inclusion of protocol, age, BMI, number of positive lymph nodes, ER status, and chemotherapy as adjustment factors. In addition, the association of tamoxifen with time to thromboembolic phenomena depended on whether a patient received chemotherapy (chemotherapy–tamoxifen interaction, $P = .001$). However, the interaction was not affected by race (test for race–chemotherapy–tamoxifen interaction, $P = .82$). Among African American patients, the relative risk for thromboembolic phenomena association with tamoxifen use was 10.70 (95% CI = 5.94 to 19.28) among patients treated with chemotherapy and 2.16 (95% CI =1.26 to 3.71) for patients who were not treated with chemotherapy (Table 6). The corresponding relative risks among white patients were 15.49 (95% CI = 9.53 to 25.17) and 3.13 (95% CI = 2.04 to 4.79), respectively.

We also observed an interaction between tamoxifen and the number of positive lymph nodes ($P = .03$). Specifically, the elevated risk of thromboembolic phenomena associated with tamoxifen increased with the presence of positive lymph nodes (0 versus 1–3 versus >4). However, the three-way interaction of race, tamoxifen treatment, and number of positive nodes was not statistically significant. After adjusting for race, tamoxifen treatment, and number of positive lymph nodes, the association of race with thromboembolic phenomena was statistically significant ($P = .03$). Specifically, African American patients had a lower risk of thromboembolic phenomena than did white patients (RR = 0.69, 95% CI = 0.49 to 0.96). However, the interaction between race and tamoxifen treatment was not statistically significant ($P = .10$; Table 5).

Table 6. Relative risks of thromboembolic events with tamoxifen use by race and chemotherapy treatment

Race	Treatment with chemotherapy	Adjusted relative risk (95% CI)*
African American	Yes	10.70 (5.94 to 19.28)
	No	2.16 (1.26 to 3.71)
White	Yes	15.49 (9.53 to 25.17)
	No	3.13 (2.04 to 4.79)

*Hazard ratio (HR) comparing time to thromboembolic events in patients who took tamoxifen with that in patients who did not. Hazard ratios were obtained from proportional hazards modeling adjusted for protocol, age, body mass index, positive lymph nodes, estrogen receptor status, and use of chemotherapy. The interaction between race and tamoxifen use was not statistically significant (two-sided $P = .10$).

Discussion

This study examined what is, to our knowledge, the largest number of African American patients with early-stage breast cancer whose contralateral breast cancer and thromboembolic phenomenon rates have been examined. We found no evidence for racial differences in the effect of tamoxifen in reducing the incidence of contralateral breast cancer. Tamoxifen did increase the rate of thromboembolic phenomena but did so to a similar degree in both racial groups. Univariate analysis showed that BMI and age were risk factors for thromboembolic phenomena in both groups. The degree of the increased risk of thromboembolic phenomena associated with tamoxifen depended on whether the patient received chemotherapy and was observed in both African American and white patients (Table 5).

The results of breast cancer treatment trials are often used in chemoprevention clinical trials. Because relatively small numbers of African American women participate in breast cancer treatment trials, questions have been raised regarding the generalizability of findings about chemoprevention obtained from an aggregate group to African Americans. Many questions about the efficacy of tamoxifen as a chemopreventive agent come from women who are potential candidates for prevention studies who are unfamiliar with the drug or not aware of its use in treatment for all women with ER–positive breast cancer.

Our pooled protocols included trials that used chemotherapy agents (e.g., cyclophosphamide, anthracycline containing regimens) reported to reduce the incidence of contralateral breast cancer *(2,24).* Although our data did not show a reduced risk of contralateral breast cancer after chemotherapy, several studies have compared the efficacy of chemotherapy treatment between different racial and ethnic groups and have found similar outcomes for ER-positive patients, including rates of contralateral breast cancer as a site of recurrence or second primary tumor*(25).* Prognostic factors for breast cancer in African American and white women have been studied in clinical trials, but factors possibly associated with the development of contralateral breast cancer were not assessed *(26).* One study reported an increased risk of contralateral breast cancer in African American women from the Surveillance, Epidemiology, and End Results (SEER[1]) database (rate ratio = 1.20, 95% CI = 1.08 to 1.33), but specific information on the treatment used was not collected *(27).* We are unaware of studies that show differences in metabolism of tamoxifen between racial groups, but some investigators suggest further evaluation of the cytochrome P450 system and insulin-like growth factor in African Americans and whites as indicators of a potential difference *(28).* Our data do not

support the hypothesis that substantial pharmacokinetic differences resulting in different clinical effects exist between the two racial groups, regardless of protocol.

Most studies have shown no association between contralateral breast cancer rates and lymph node positivity *(3,4).* In our study, lymph node positivity was associated with increased risk of contralateral breast cancer among both white and African American women. One report *(29)* showed a relative hazard ratio of contralateral breast cancer of 0.28 (95% CI = 0.13 to 0.62) in patients with positive lymph nodes or tumor size greater than 3 cm who received tamoxifen compared with those who did not compared with a relative hazard ratio of 0.85 (95% CI = 0.49 to 1.46) for low-risk, lymph node–negative patients, but no increased risk of contralateral breast cancer in the high-risk group was observed. The African American women in our study had larger tumors and more lymph node–positive cancers than the white women, but the reduction in contralateral breast cancer due to tamoxifen was similar in both groups. These findings seem consistent with the concept that the stage of a tumor does not affect contralateral breast cancer rate. The median age at time of surgery of contralateral breast cancer events is lower among African Americans (50 years of age, range = 22 to 74 versus 52 years of age, range = 21–78 for whites; $P<.001$). Younger women with HER-2/*neu*–positive tumors have been reported to have increased rates of contralateral breast cancer (by 70%); 38% of the patients were treated with tamoxifen and 71% were treated with chemotherapy *(8).* Studies comparing younger African American and white women who express HER-2/*neu* and developed contralateral breast cancer have not been reported.

Lobular carcinoma histology has been associated with an increased risk of contralateral breast cancer. Lobular carcinoma rates among whites are reported to be twice those in African Americans *(1–4,19,30–32).* Anderson et al. *(30)* suggest similar patterns in the increase of incidence of lobular cancer over the past two decades, lower frequencies of it in African Americans, and an ethnic cross-over at younger ages. Our data showed no association of lobular carcinoma histology with the development of contralateral breast cancer in the two racial groups.

BMI is associated with increased rates of contralateral breast cancer in both white and African American women *(33–35).* A recent analysis of women treated on NSABP protocol B-14 showed no difference in treatment outcomes in obese women compared with lean women but 10-year cumulative incidences of contralateral breast cancer of 3.3% in underweight-to-normal-weight women (BMI $<$ 18.5 to 24.9 kg/m^2) and 5.6% in obese women (BMI $\geq$ 30.0 kg/m^2) (hazard ratio = 1.58, CI =1.10 to 2.25). Similar increases in contralateral breast cancer rates were observed in both premenopausal and postmenopausal women *(9).* African American women have higher BMI on average, than white women, and it has been reported that more than half of African American women 40 years of age or older are obese and more than 80% are overweight *(36).* Most women in our study did not meet the obesity criteria of BMI greater than 30 kg/m^2. Seventy-four percent of African American women in our contralateral breast cancer analysis had a BMI of at least 25 compared with 64.5% of the white women.

A North Carolina population-based case–control study comparing African American women and white women did not show an inverse association between BMI and risk of breast cancer among premenopausal African American women, something that has been observed among premenopausal white women *(34).* However, many younger black women were excluded from the analysis because they were not premenopausal—possibly due to their increased risk of fibroid tumors and surgically induced menopause. When African American women younger than 50 years of age at time of diagnosis were analyzed, those with a higher BMI (in the third tertile) had a 50% lower risk of breast cancer than those with a low BMI (in the first tertile)—results similar to those observed for white women. In this population-based study, high waist-to-hip ratios were also associated with increased breast cancer risk among all women. BMI was not associated with increased risk of breast cancer among postmenopausal women of either group. Other studies, which included no racial minorities, have shown BMI as a breast cancer risk factor in women under the age of 45 *(37).*

Results of venous thromboembolic events in the International Breast Cancer Intervention Study reported 2.1-fold higher rates (95% CI = 1.1 to 4.1) overall among women taking tamoxifen compared with those taking placebo *(38).* Prolonged immobility and major surgery within 3 months of the thromboembolic event was the major determinant of risk in 42% of women on the tamoxifen arm (OR = 4.7), women with or without tamoxifen. These data were also supported by a meta-analysis of 28 000 women using tamoxifen in randomized trials *(39).* Our analysis had similar results—among women treated only with tamoxifen and not with chemotherapy, adjusted relative risks of thromboembolic events in African American and white women were 2.16 and 3.13, respectively. The Genetic Attributes and Thrombosis Epidemiology Study, an ongoing case–control study in Atlanta, has noted that known genetic risk factors for thromboembolic events are rare among African Americans. Associated etiologic factors for thrombosis in African Americans include hypertension, diabetes, and kidney disease, whereas those in whites are immobilization, cancer, and recent surgery *(40).* Women in our studies were more likely to have better-controlled comorbidities during treatment and to be healthier than women in the general population. Cardiovascular risk factors for thromboembolic diseases among minorities are important considerations when selective ER modulator agents are employed, especially as chemopreventive agents. Breast cancer risk and benefit analysis tools that calculate risk indices report limitations for minority groups *(41).* In our studies, the risk of thromboembolic phenomenon with tamoxifen increased with increasing numbers of positive lymph nodes with and without chemotherapy. The risks of thromboembolic phenomenon associated with tamoxifen use were not higher in African American than in white patients (Table 6).

This study has several limitations. First, we lacked detailed information about whether there was a family history of breast cancer (and even if we'd had such information, the ages at which diagnoses were made among family members). Second, data from the Connecticut Tumor Registry that included approximately 160 African American women show cumulative incidence rates, independent of race, for DCIS at 5 and 10 years of 4.3 and 6.8 and of 11.9 and 13.9 for lobular carcinoma *in situ* (LCIS) *(42).* The studies we analyzed for contralateral breast cancer excluded patients with histories of DCIS or LCIS, but the effects we observed were also independent of race. Third, our database does not include sufficient numbers of patients in individual categories of venous thromboembolic phenomena, (e.g. pulmonary emboli) to permit detection of an association between race or race–tamoxifen interaction. In addition, report-

ing of thrombophlebitis for these treatment trials required only the presence or absence of superficial thrombophlebitis; information about diagnosis, treatment, and anatomical location was not available. Although superficial thrombophlebitis is thought of as a benign disease (and data about its progression in the venous system are scant), the overall risk of extension into the deep venous system is 3.1% with a recurrence rate of 15%–20% *(43,44)*. Further studies are needed on superficial thrombophlebitis in healthy, at-risk cancer populations, because occurrence may increase the importance of identifying risks for developing thromboembolic events. Further studies are needed on superficial thrombophlebitis in healthy, at-risk cancer populations to determined if the occurrence is associated with increased risk or progression of thromboembolic phenomena. Lastly, these data represent women who enrolled into clinical trials and therefore may not adequately represent the entire population of women treated for breast cancer. However, because the clinical trial patients in this study represent a heterogeneous health status and lifestyle population, even given the stringent criteria required for clinical trial eligibility, they provide information relevant to breast cancer treatment and prevention in the general population.

Our data provide evidence that tamoxifen is equally effective in reducing the incidence of contralateral breast cancer in African American and in white women who have been diagnosed with invasive breast cancer. We identified BMI and lymph node positivity as risk factors for contralateral breast cancer in both African Americans and whites. Rates of thromboembolic phenomenon were not higher in African American patients than in white patients, and the relative risk of thromboembolic phenomenon after using tamoxifen was not higher in African Americans than in whites. The detriment of tamoxifen seemed to be greater in chemotherapy-treated patients. In addition, we identified BMI and age as univariate risk factors for thromboembolic phenomenon. It is not unreasonable to extrapolate these findings to the prevention setting. Our data therefore provide further support for the need to assess an individual woman's health and personal history, not only her race and ethnicity, to determine the benefits and risks of tamoxifen as a chemopreventive agent.

REFERENCES

(1) Chen Y, Thompson W, Semenciw R, Mao, Y. Epidemiology of contralateral breast cancer. Cancer Epidemiol Biomarker Prev 1999;8:855–61.

(2) Hislop T, Elwood J, Coldman, AJ, Spinelli, JJ, Worth AJ, Ellison LG. Second primary cancers of the breast: incidence and risk factors. Br J Cancer 1984;49:79–85.

(3) Bernstein J, Thompson WD, Risch N, Holford TR. Risk factors predicting the incidence of second primary breast cancer among women diagnosed with a first primary breast cancer. Am J Epidemiol 1992;136:925–36.

(4) Broet P, Rochefordiere A, Scholl S, Fourquet A, Mosseriv, Durand J, et al. Contralateral breast cancer: annual incidence and risk parameters. J Clin Oncol 1995;13:1578–83.

(5) Adami H, Bergstrom R, Hansen J. Age at first primary as a determinant of the incidence of bilateral breast cancer. Cumulative and relative risks in a population-based control study. Cancer 1985;55:643–7.

(6) Hankey BF, Curtis RE, Naughton MD, Boice JD, Flannery JT. A retrospective cohort analysis of second breast cancer risk for primary breast cancer patients with an assessment of the effect of radiation therapy. J Natl Cancer Inst 1983;70:797–804.

(7) Harvey EB, Brinton LA. Second cancer following cancer of the breast in Connecticut, 1935-82. J Natl Cancer Inst Monogr 1985;68:99–103.

(8) Li CI, Malone KE, Porter PL, Daling JR. Epidemiologic and molecular risk factors for contralateral breast cancer among young women. Br J Cancer 2003;89:513–8.

(9) Dignam JL, Wieand K, Johnson KA., Fisher B, Xu L, Mamounas E. Obesity, tamoxifen use, and outcomes in women with estrogen receptor-positive early-stage breast cancer. J Natl Cancer Inst 2003;95:1467–74

(10) Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet 1998;351: 1451–67.

(11) Fisher B, Dignam J, Bryant J, DeCillis AD, Wickerham DL, Wolmark N, et al. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. J Natl Cancer Inst 1996;88:1529–42.

(12) Cook L, Weiss N, Schwartz S, White E, McKnight B, Moore DE, et al. Population-based study of tamoxifen therapy and subsequent ovarian, endometrial, and breast cancers. J Natl Cancer Inst 1995;87:1359–64.

(13) Fisher B, Costantino JP, Wickerham L, Redmond C, Kavanah M, Cronin W, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 1998;90:1371–88

(14) Powles T. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomized chemoprevention trial. Lancet 1998;352:90–101.

(15) Veronesi U, Maisonneuve P, Costa A, Sacchini V, Maltoni C, Robertson C, et al. Prevention of breast cancer with tamoxifen: preliminary findings from breast cancer with tamoxifen trial among hysterectomised women. Lancet 1998;352:93–7.

(16) IBIS Investigators. First results of the International Breast Cancer Intervention Study (IBIS-1): a randomised prevention trial. Lancet 2002;360: 817–24.

(17) Cuzick J, Powles T, Veronesi U, Forbes J, Edwards R, Ashley S, et al. Overview of the main outcomes in breast cancer prevention. Lancet 2003; 361:296–300.

(18) Veronesi U, Maisonneuve P, Rotmensz N, Costa A, Sascchini V, Travaglini R, et al. Italian randomized trial among women with hysterectomy: tamoxifen and hormone-dependent breast cancer in high-risk women. J Natl Cancer Inst 2003;95:160–5.

(19) Nevassari K, Heikkinein U, Taslonen PJ. Tamoxifen and thrombosis. Lancet 1978;2:946–7.

(20) Henderick A, Sebrammanian VP. Tamoxifen and thromboembolism. JAMA 1980;243:514–5.

(21) Swain M, Wilson JW, Mamounas EP, Bryant J, Wickerham DL, Fisher B, et al. Estrogen receptor status of primary breast cancer is predictive of estrogen receptor status of contralateral breast cancer. J Natl Cancer Inst 2004;96:516–23.

(22) Mamounas ER, Bryant J, Fisher B, Wickerham DL, Wolmark N. Primary breast cancer as a risk factor of subsequent contralateral breast cancer; NSABP experience from 9 randomized trials. 21st Annual San Antonio Breast Cancer Symposium; 1998. Breast Cancer Res Treat 1998;50:230.

(23) McCaskill-Stevens W, Bryant J, Costantino J, Wickerham DL, Vogel V, Wolmark N. Incidence of contralateral breast cancer (cbc), endometrial cancer (ec) thromboembolic events (te) in African American women receiving tamoxifen for treatment of primary breast cancer [abstract 269]. Proc ASCO 2000;70a.

(24) Arriagada R, Rutqvist LE. Adjuvant chemotherapy in early breast cancer and incidence or new primary malignancies. Lancet 1991;338:535–8.

(25) Dignam J, Redmond CK, Fisher B, Costantino JP, Edwards BK. Prognosis among African-American women and white women with lymph node negative breast carcinoma: findings from 2 randomized clinical trials of the NSABP. Cancer 1997;80:80–90.

(26) Roach M 3rd, Cirrincione C, Budman D, Hayes D, Berry D, Younger J, et al. Race and survival from breast cancer: based on Cancer and Leukemia Group B trial 8541. Cancer J Sci Am 1997;3:107–12.

(27) Gao X, Fisher SG, Emami B. Risk of second primary cancer in the contralateral breast in women treated for early-stage breast cancer: a population-based study. Int J Radiation Oncol Biol Phys 2003;56:1038–45.

(28) Flaws JA, Bush TL. Racial differences in drug metabolism: an explanation for higher breast cancer mortality in blacks? Med Hypotheses 1998;50: 327–9.

(29) Rutqvist LE, Cedermark B, Glas U, Mattsson A, Skoog L, Somell A, et al. Contralateral primary tumors in breast cancer patients in a randomized trial of adjuvant tamoxifen therapy. J Natl Cancer Inst 1991;83:1299–306.

(30) Anderson WF, Chu KC, Chang S, Sherman M. Comparison of age-specific incidence rate patterns for different histopathologic types of breast carcinoma. Cancer Epidemiol Biomarkers Prev 2004;13:1128–35.
(31) Klonoff-Cohen HS, Schaffroth LB, Edelstein SL, Molgaard C, Saltzstein SL. Breast cancer histology in Caucasians, African Americans, Hispanics, Asians, and Pacific Islanders. Ethnic Health 1998;3:189–98.
(32) Cook LS, White E, Schwartz SM, Weiss NS. A population-based study of contralateral breast cancer following a first primary breast cancer. Cancer Causes Control 1996;7:382–90.
(33) Forshee RA, Storey ML, Ritenbaugh C. Breast cancer risk and lifestyle differences among premenopausal and postmenopausal African-American women and white women. Cancer 2003;97(1 Suppl):280–8.
(34) Hall IJ, Newman B, Millikan RC, Moorman PG. Body size and breast cancer risk in black women and white women: the Carolina Breast Cancer Study. Am J Epidemiol 2000;151:754–64.
(35) Chen VW, Correa P, Jurman R, Wu XC, Eley W. Histological characteristics of breast carcinoma in blacks and whites. Cancer Epidemiol Biomarkers Prev 1994;3:127–35.
(36) Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. JAMA 2002;288:1723–7.
(37) Altuis MD, Brogan DD, Coates RJ, Daling JR, Gammon MD, Malone KE, et al. Breast cancer among very young premenopausal women (U.S.). Cancer Causes Control 2003;2:151–60.
(38) Duggan C, Marriott K, Edwards R, Cuzick J. Inherited and acquired risk factors for venous thromboembolic disease among women taking tamoxifen to prevent breast cancer. J Clin Oncol 2003;21:3588–93.
(39) Eisen A. A meta-analysis of randomized trials of tamoxifen for the prevention of breast cancer [abstract 391]. Proc ASCO 2003;98.
(40) Dowling NF, Austin H, Dilly A, Whitesell E, BL, Hooper, WC. The epidemiology of venous thrombosis in Caucasian and African American: the GATE study. J Thromb Haemostatis 2003;1:80–7.
(41) Gail M, Costantino JP, Bryant J, Croyle R, Freedman L, Helzlsouer K, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. J Natl Cancer Inst 1999;91:1829–46.
(42) Claus E, Stowe M, Carter D, Holford T. The risk of contralateral breast cancer among women diagnosed with ductal and lobular breast carcinoma in situ: data from the Connecticut Tumor Registry. The Breast 2003;12:451–6.
(43) Sullivan V, Denk PM, Sonnad SS, Eagleton MJ, Wakefield TW. Ligation versus anticoagulation: treatment of above-knee superficial thrombophlebitis not involving the deep venous system. Am Coll Surg 2000;193:556–62.
(44) Ascer E, Lorensen E, Pollina RM, Gennaro M. Preliminary results of a nonoperative approach to saphenofemoral junction thrombophlebitis. J Vasc Surg 1995;22:616–21.

NOTES

[1]*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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