Effect of Factor V Leiden and Prothrombin G20210→A Mutations on Thromboembolic Risk in the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial

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**Background:** In the National Surgical Adjuvant Breast and Bowel Project’s Breast Cancer Prevention Project (BCPT), tamoxifen use was associated with an increased relative risk for venous thromboembolic events, including deep vein thrombosis and pulmonary emboli, compared with placebo. However, the involvement of hypercoagulability factors in this association is unclear. **Methods:** To examine possible associations among the risk of venous thromboembolic events, tamoxifen use, and Factor V Leiden (FVL) and prothrombin G20210→A (PT20210) mutations, which are involved in promoting blood coagulation, we used a nested, matched, case-control (1:4) design and compared women in the BCPT who had experienced venous thromboembolic events (n = 76) with women who did not (n = 295). FVL and PT20210 mutations were detected in genomic DNA that was isolated from blood samples collected at trial enrollment. **Results:** Venous thromboembolic events occurred in 28 women (deep vein thrombosis in 22 and pulmonary emboli in six) who were taking placebo and in 53 women (deep vein thrombosis in 35 and pulmonary emboli in 18) who were taking tamoxifen (relative risk = 1.90, 95% confidence interval = 1.18 to 3.12). Excessive risk for venous thromboembolic events was observed only in the first 36 months of therapy. There were no differences in age, smoking, and race between the groups, but women with venous thromboembolic events had a higher body mass index than women without (mean ± standard deviation, 30 kg/m² ± 7.7 versus 27.1 ± 5.6; P < 0.001). FVL and/or PT20210 mutations were found in nine women (four on tamoxifen and five on placebo) with venous thromboembolic events and in 20 control subjects (nine on tamoxifen and 11 on placebo). No associations were found between risk of venous thromboembolic events and mutation status in either treatment group. **Conclusions:** Venous thromboembolic disease in the BCPT women is associated with tamoxifen use and body mass index, but not with FVL and PT20210 mutations. Screening women at risk for breast cancer for FVL and/or PT20210 appears to offer no benefit in determining the risk of tamoxifen-associated thromboembolic events. [J Natl Cancer Inst 2006;98:904–10]

It has been posited that tamoxifen, which is widely used to treat and prevent breast cancer, increases hypercoagulability (1,2). The National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT), a randomized, double-blinded study of tamoxifen and placebo in healthy women at high risk for breast cancer (3), provided a unique opportunity to determine the true magnitude of risks of thromboembolic events that might be associated with the use of tamoxifen. When women who took tamoxifen in the BCPT were compared with those who took placebo, the relative risk for deep vein thrombosis was 1.60 (95% confidence interval [CI] = 0.91 to 2.86) and that for pulmonary emboli was 3.01 (95% CI = 1.15 to 9.27). This observation was consistent with results from a subsequent tamoxifen prevention study (4) and other findings from treatment trials on breast cancer (5).

The complications of thromboembolic events are important and potentially serious enough to raise concerns about using tamoxifen to prevent breast cancer in women. Theoretically, tamoxifen’s benefit-risk ratio in prevention therapy would be enhanced substantially if other factors associated with thromboembolic events, such as well-recognized predisposing factors for hypercoagulability, could be identified and either reduced or eliminated.

Thrombin has a key role in blood coagulation. In the cascade of signals that lead to the formation of a blood clot, prothrombin is converted to thrombin, which proteolytically cleaves fibrinogen to form fibrin fibers. However, thrombin is also involved in the anticoagulation process. It is bound by endothelial thrombomodulin and initiates the production of activated protein C (APC), an enzyme that inhibits the activity of activated clotting proteins, including activated Factor V. Factor V Leiden (FVL) arises from a point mutation that alters the recognition site for APC-induced cleavage and makes it resistant to enzymatic degradation by APC. Also, a mutation in the prothrombin gene—prothrombin G20210→A (PT20210)—has been associated with increased clotting. This mutation, a guanine-to-adenine transition at nucleotide position 20210 in an untranslated region of the gene, results in elevated prothrombin levels (6).

An association among FVL, PT20210, and hypercoagulability has been demonstrated (6–13). When patients are evaluated for hypercoagulability after having episodes of clotting, these autosomal-dominant mutations are often discovered, especially in white people of European origin (13,14). FVL is an especially
important factor predisposing to thromboembolic disease associated with exposure to high levels of estrogen. The presence of FVL and/or PT20210 in patients with recent clotting events may result in the extension of anticoagulation therapy for somewhat longer periods. However, identification of these mutations in asymptomatic carriers is not considered an indication for prophylactic anticoagulation therapy. There are no current guidelines for the consideration of anticoagulation therapy in the setting of oral contraceptives, hormone replacement therapy, or tamoxifen.

In this study, we assessed participants in the BCPT for the presence of FVL and PT20210 and examined the potential interaction of these mutations with tamoxifen for the development of thromboembolic events. Because more than 95% of participants in the BCPT were white, this group was an appropriate one in which to study the question of a possible relationship among FVL and PT20210, tamoxifen, and thromboembolic events. Also, because the BCPT population was limited to women who were at high risk for developing breast cancer and with no history of thromboembolic events, the study results are applicable to the population of women who would be eligible for preventive treatment with tamoxifen.

In a previous retrospective analysis of the BCPT, we examined most of the factors associated with hypercoagulability in subjects who had developed thromboembolic events. We found no definite association among thromboembolic events, laboratory-discovered hypercoagulability factors, and the use of tamoxifen (15). However, in that study, only relatively few affected patients were available for retrospective analysis, and there was no assessment of control (nonaffected) subjects from the BCPT. Thus, in this report we present the results of a more complete case-control study of the role of FVL and PT20210 in thromboembolic events in the BCPT.

**Patients and Methods**

**Segment of Study Population Examined**

This study is a correlative study of the BCPT; the details of the BCPT methodology and the demographic characteristics of the study cohort have been previously described (1). Women who participated in the BCPT provided written informed consent, and the overall study was approved by the institutional review boards (IRBs) of the participating institutions. For the current (FVL and PT20210) ancillary study, IRB approvals were provided by the University of Washington IRB, where DNA was extracted from the stored blood samples; the Yale University School of Medicine IRB, where Dr. Berliner performed the sequencing; the Allegheny General Hospital IRB, which is the IRB of record for NSABP Operations; and University of Pittsburgh IRB, which has oversight of the NSABP Biostatistical Center.

Using a nested, matched case-control design we examined, as case patients, women who participated in the BCPT and who had experienced a pulmonary embolism or a deep vein thrombosis. Pulmonary embolism in our study was defined as a clinical diagnosis confirmed by a ventilation-perfusion scan. Deep venous thrombosis was defined clinically and confirmed by venography, venous Doppler, venous duplex imaging, or fibrinogen scan. Control subjects were selected at random from within groups of non-diseased (i.e., no pulmonary embolism or deep vein thrombosis) BCPT participants who matched each case patient on age at entry (+3 years), race (white, African American, other), treatment (tamoxifen, placebo), smoking status at entry (current smoker, former smoker, never smoker), and duration of treatment (+3 months). Four control subjects were selected for every case patient. When four matched control subjects for each case patient could not be obtained by using these criteria, the age range used for matching a control subject was extended (+5 years), or the range of treatment duration was increased (+6 months). For some case patients, even with the extended matching criteria, it was not possible to obtain four matched control subjects. A total of 76 case patients and 295 control subjects were included in the study.

**Anonymization of Samples**

The specimens used for genetic analyses of the case patients and control subjects included in the study were taken from stored, frozen buffy coats obtained from blood samples that were collected at baseline from the BCPT participants. These samples were stored at the Northwest Lipid Research Laboratory in Seattle, Washington. DNA was extracted from all samples at the Molecular Diagnostic Laboratory of the University of Seattle, using standard techniques.

While the DNA was being extracted, the NSABP Biostatistical Center created a data file that contained the key demographic and outcome data for all the case patients and control subjects included in the study population. This file was provided to an independent statistician who developed a new set of participant identification numbers to replace those used by the NSABP to identify the women in the data file and their buffy coat specimens. The independent statistician had sole access to the key that linked the NSABP identification number to the new identification number. Once the DNA extraction was completed, the independent statistician relabeled the DNA specimens with the new identification number. Then the relabeled specimens were sent to the Yale University School of Medicine for genotyping; the independent statistician replaced the NSABP study number in the data file with the new DNA specimen number, the key linking the NSABP and new DNA specimen numbers was destroyed, and the data file was returned to the NSABP Biostatistical Center. Thus, before genotyping took place, there was no longer a link between the old NSABP number and the new DNA specimen number. When the Yale University School of Medicine completed the genotyping, their findings for each DNA specimen number were provided to the NSABP Biostatistical Center, and the information on mutation status was added to the delinked data file.

**Assaying for FVL and PT20210 Mutations by Multiplex Polymerase Chain Reaction**

Multiplex polymerase chain reaction (PCR) was performed on genomic DNA from each sample. Approximately 500 ng of each of the DNA samples was subjected to multiplex PCR in a 25-μL reaction volume containing 1 μL of 5 mM dNTPs, 2.5 μL 10× buffer, 0.125 μL of Taq polymerase (5 U/μL) (Invitrogen, Carlsbad, CA), and 100 ng of Factor V Leiden oligomers: sense: 5′-TGCCCACTTTACCAAGACCA-3′ (NM-001302.2 [1588–1609]); antisense: 5′-CTTGAAGGAAATGCCCCATT-3′ (AY364535.1 [38701–38681]); and 100 ng of each of the PTII oligomers: sense: 5′-CTCTAGAAACAGTGCTTAACA-3′ (AF478696.1 [21217–21236]); antisense: 5′-ATAGCATGGAGCATTGAA-3′ (AF478696.1 [21561–21543]).
PCR was conducted with a PTC-0200 DNA Engine (MJ Research, Waltham, MA) using the following conditions: 95 °C for 2 minutes, followed by 35 cycles of PCR at 94 °C for 60 seconds, 53 °C for 30 seconds, and 67 °C for 1 minute, and finally a 67 °C incubation for 3 minutes. The amplified PCR products were next digested with MnlI and HindIII enzymes (Invitrogen) at 37 °C overnight. Digested DNA samples were resolved by electrophoresis in a 1.5% agarose gel, and the separated DNA was visualized by ethidium bromide staining. Mutations were identified by the presence of the predicted restriction fragment length polymorphisms associated with FVL and PT20210 (16).

Statistical Analysis

Average annual rates of thromboembolic events were calculated by dividing the number of observed events by the number of observed event-specific person-years of follow-up. P values for tests of differences between the treatment groups for annual rates were determined with the exact method, assuming that the events came from a Poisson distribution and conditioning on the total number of events and person-years at risk (17). Event rates in the two treatment groups were compared by using relative rates and 95% confidence intervals (CIs). Confidence intervals for relative rates were determined assuming that the events followed a Poisson distribution, conditioning on the total number of events and person-years at risk. Cumulative incidence rates by follow-up time were determined, accounting for competing risks due to death (18), and P values for comparison of curves by treatment were determined by the method of Pepe (19).

To assess differences between relevant populations for demographic characteristics, mean values or categorized distributions of pertinent variables were determined and compared. Differences in mean values of age and body mass index (BMI; height in kilograms divided by the square of the height in meters) were assessed using the Student t test. Differences in dichotomized proportions by smoking status, aspirin use, diabetes history, and race were assessed using Fisher’s exact test.

Logistic regression was used to assess the association of mutations with thromboembolic events. Estimates of the odds ratios (ORs) of the associations comparing the risk of disease among those with and without mutations were determined from the coefficients estimated from modeling employing the partially conditional inference procedures of the statistical package LogXact (20). The 95% confidence intervals for the odds ratios were determined from this modeling by using the exact method. Adjustment for BMI was accomplished in the regression by including a dichotomized parameter representing the categories of non-obese (BMI ≤ 29.9 kg/m²) and obese (BMI ≥ 30.0 kg/m²) women.

All analyses using treatment group are based on the treatment assigned at the time of randomization. All reported P values are two-sided. Results were considered to be statistically significant if the P value was less than .05 or if the 95% confidence interval for the relative rates did not include 1.0.

RESULTS

Assessment of Risk of Thromboembolic Events in the Entire BCPT Cohort

Case patients with thromboembolic events and annual rates of these events in the entire BCPT cohort were grouped by age and treatment (Table 1). In the placebo group, 28 women experienced thromboembolic events; six of these women experienced a pulmonary embolism and 22 a deep vein thrombosis. In the tamoxifen group, 53 women experienced thromboembolic events; 18 of these women experienced a pulmonary embolism and 35 a deep vein thrombosis. The relative risk of thromboembolic events in the tamoxifen group compared with the placebo group was 1.90 (95% CI = 1.18 to 3.12). When the analysis was stratified by age group, the difference between tamoxifen and placebo was statistically significant only among those who were aged 50 years or older. In the group aged 50 years and older, 19 women in the placebo group experienced thromboembolic events compared with 40 in the tamoxifen group (RR = 2.01, 95% CI = 1.19 to 3.85).

We next determined the cumulative incidence of pulmonary embolism and deep vein thrombosis over follow-up time (Fig. 1). The increased rate of development of thromboembolic events associated with tamoxifen therapy became apparent 6 months after the initiation of treatment. The curves did not continue to diverge further after 3 years of follow-up. We also compared the annual rates of all thromboembolic events by year of follow-up (Fig. 2). These data also suggest that the excess risk of thromboembolic events associated with tamoxifen treatment occurred within the first 3 years after the initiation of therapy. The rate of thromboembolic events in the tamoxifen group during this period was relatively stable, at approximately 2.5 per 1000 per year.

Table 1. Thromboembolic events among women in the BCPT by age at entry*

<table>
<thead>
<tr>
<th>Type of thromboembolic event by age at entry (y)</th>
<th>No. of events</th>
<th>Annual incidence per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Pulmonary embolism ≤49</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>≥50</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Deep vein thrombosis ≤49</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>≥50</td>
<td>14</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>35</td>
</tr>
<tr>
<td>Total thromboembolic events ≤49</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>≥50</td>
<td>19</td>
<td>40</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>53</td>
</tr>
</tbody>
</table>

*BCPT = National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial; RR = relative risk; CI = confidence interval.
Nested Case-Control Study of FVL and PT20210 Mutations

DNA quantities sufficient for genotyping were extracted from 76 of the 81 BCPT participants who experienced thromboembolic events. Of the five specimens that were insufficient, three were from women who experienced a deep vein thrombosis and two were from women who experienced a pulmonary embolism. Complete sets of four control subjects were identified for 67 of these 76 case patients with available DNA. Only three control subjects could be identified for each of the remaining nine case patients. Thus, the study population for assessment of FVL and PT20210 included 76 case patients with thromboembolic events and 295 control subjects. Ninety percent of the selected control subjects were age-matched within 2 years of the age of the case patient, and 96% were matched within 3 years. Ninety-four percent of the selected control subjects matched the case patient within 2 months of treatment duration, and 95% matched within 3 months.

Case patients and control subjects had similar characteristics, except for BMI (Table 2). Of the 76 case patients, 54 women experienced a deep vein thrombosis and 22 a pulmonary embolism. The mean age at entry of women included in the genetic evaluation was 57 years. Approximately 95% of the population was white, and approximately 13% of the women identified themselves as current smokers at the time they entered the BCPT. These characteristics were matching factors and, as expected, there was no statistically significant difference between the case patient and control groups for these characteristics. Approximately 19% of the population reported using aspirin regularly at study entry, and only 4% reported a history of diabetes; there were no differences between the case patient and control groups for either of these factors. The only noteworthy statistically significant difference between the case patients and control groups was the mean BMI (mean ± standard deviation, 30.0 kg/m² ± 7.7 for the case patients versus 27.1 kg/m² ± 5.6 for the control subjects; \(P<.001\)).

Nine of the 76 case patients and 20 of the 295 control subjects had FVL or PT20210 mutations (Table 3). Three women had mutations of both FVL and PT20210 (one case patient, two control subjects); 18 had only an FVL mutation (seven case patients, 11 control subjects); and eight had only a PT20210 mutation (one case patient, seven control subjects). Sixteen of the women with mutations were in the placebo group (five case patients and 11 control subjects), and 13 were in the tamoxifen group (four case patients and nine control subjects). The odds ratio for mutation, comparing the risk of thromboembolic events for those with a mutation and that for those without a mutation, was estimated from logistic regression to be 1.90 (Table 4). That is, the risk of thromboembolic events for those with mutation was calculated to be 90% higher than the risk of...
thromboembolic events for those without a mutation. However, the increase was not statistically significant (95% CI = 0.72 to 4.76). Because there was a statistically significant difference in the mean BMI of the case patients and control subjects (Table 2), and because this variable is associated with the risk of thromboembolic events, an odds ratio adjusted for BMI was also determined. Although the BMI-adjusted odds ratio for risk of thromboembolic events was higher than the unadjusted odds ratio, it too was not statistically significant (OR = 2.17, 95% CI = 0.77 to 5.81). BMI was statistically significantly associated with thromboembolic events; the risk of thromboembolic events for obese women was more than 3.5-fold that for non-obese women. The unadjusted odds ratio for BMI was 3.69 (95% CI = 2.09 to 6.65); the mutation-adjusted odds ratio for the association between BMI and risk of thromboembolic events was 3.78 (95% CI = 2.13 to 6.86).

To assess the possibility of an interaction between treatment and mutation status for the risk of thromboembolic events, treatment-specific estimates of the odds ratio for thromboembolic events were determined in separate models for each treatment group (Table 4). The results of treatment-specific modeling were similar to those found for modeling the total population. BMI was associated with risk of thromboembolic events in both treatment groups (unadjusted for mutation status, placebo: OR = 4.42, 95% CI = 1.57 to 13.57; and tamoxifen: OR = 3.38, 95% CI = 1.68 to 7.00). For both treatment groups, neither the unadjusted nor the BMI-adjusted odds ratios for mutation status were statistically significantly different. Although the point estimates for each group were at the same level of magnitude, the confidence intervals overlapped substantially, indicating a lack of interaction between treatment and mutation status for the risk of thromboembolic events (BMI-adjusted, placebo: OR = 2.25, 95% CI = 0.48 to 9.79; and tamoxifen: OR = 2.10, 95% CI = 0.42 to 8.71). Because there was only one case patient with pulmonary embolism with a mutation, and only two case patients with thromboembolic events with a PT20210 mutation (Table 5), modeling using specific types of thromboembolic events (pulmonary embolism and deep vein thrombosis) as the response variable or the specific type of mutation (FVL and PT20210) as model terms was not performed.

DISCUSSION

This study affirmed that an increased rate of venous thromboembolic events was associated with tamoxifen. However, there was no relationship among the use of tamoxifen, the development of venous thromboembolic events, and the presence of FVL and PT20210 genetic abnormalities. Women in the BCPT were not cancer patients but at risk for the malignancy. Thus, they had a lower risk for thromboembolic events than did patients with documented cancer.

The precise mechanism of hypercoagulability in cancer patients is unclear, although there are many theories for the phenomenon, including the liberation of tumor-associated thromboplastins, the effects of pharmacologic agents such as chemotherapy and hormonal drugs, the presence of foreign material such as indwelling intravenous lines, inactivity and recumbence, obesity, infections, and surgical procedures. Primary hematologic causes include defects of coagulation proteins, both inherited and acquired.

In the BCPT, the overall relative rate of thromboembolic events in the tamoxifen group compared with that in the placebo group was 1.9. This frequency is similar to that noted with hormone replacement therapy (21). Based on cumulative and annual rate data, the incidence of thromboembolic events in the BCPT was noted with tamoxifen only during the first 3 years and not in the fourth and fifth years of treatment. The reason for this temporal pattern is uncertain, but it is consistent with findings for thromboembolic events with oral contraceptive use and hormone replacement therapy (22,23).
Predisposing factors for the development of thromboembolic events among potential subjects in a breast cancer prevention study include age, BMI, smoking, diabetes, avoidance of aspirin, race, family history of thromboembolic events, surgical procedures, previous history of thromboembolic events, preexisting but unknown abnormalities of hypercoagulability factors, and the use of tamoxifen. Subjects with a history of thromboembolic events were excluded from the BCPT, and a history of smoking, diabetes, or aspirin use was similar in the group that had thromboembolic disease and the matched control subjects. One feature that distinguished the thromboembolic events group from the matched control subjects was that the thromboembolic events group had a higher BMI. However, adjusting for this factor did not change findings regarding the association of thromboembolic events with tamoxifen exposure, thromboembolic events with genetic mutation, or the lack of interaction between mutation and tamoxifen for thromboembolic events.

The assessment of inherited and acquired abnormalities of the coagulation system usually requires many laboratory tests. In our previous retrospective report of BCPT subjects who developed thromboembolic events, several coagulation abnormalities were found, including a higher incidence of antithrombin deficiency. Antithrombin deficiency is an abnormality with a high degree of relative risk for first episode clotting. When treatment and placebo participants were analyzed for coagulation factor abnormalities in our retrospective study, there was no statistically significant difference between the two groups. Our previous finding of more subjects with antithrombin deficiency than we anticipated may be explained by another study of BCPT participants, which analyzed the effects of tamoxifen and placebo on the levels of antithrombin, protein S, and protein C. In 111 study subjects, tamoxifen was associated with lower levels of antithrombin and protein S after 6 months of therapy, whereas there were no changes with placebo. This finding suggests that a relationship exists between tamoxifen and the metabolism of these hypercoagulability factors.

For this report, FVL and PT20210 were the only inherited factors that we studied. Of the 76 BCPT participants who developed thromboembolic events and for whom stored cells were available, genetic mutations were found in nine (11.8%), a frequency similar to that found in groups of subjects undergoing investigation for hypercoagulability. Four of these women had been taking tamoxifen and five placebo, demonstrating no statistical evidence of an additive effect of the drug to genetic mutations on the rate of thromboembolic events. The data were also adjusted for BMI; once again, there was no statistical evidence to indicate any interaction. A lack of association of FVL and PT20210 with thromboembolic events and tamoxifen was also noted in another breast cancer prevention trial.

These data suggest a lack of benefit in screening for FVL and PT20210 in women considering taking tamoxifen for breast cancer prevention. Obviously, greater assurance of this conclusion would require more studies of the other factors associated with hypercoagulability. Many clinicians remain concerned about the use of tamoxifen, oral contraceptives, and hormone replacement therapy by women who are known to be carriers of thrombophilic mutations. Oncologists have consistently offered tamoxifen as treatment for women with breast cancer despite these concerns, so long as there is no previous history of clotting. Within the last few years, the use of aromatase inhibitors, which are associated with a lesser incidence of clotting, has offered oncologists another possible breast cancer treatment option.

Concerns about hypercoagulability and the use of tamoxifen for breast cancer prevention are still being debated. Many clinicians use tamoxifen because of the drug’s proven benefits in decreasing the incidence of both invasive and noninvasive breast cancer, and for bone support; others withhold it because of concerns about hypercoagulability regardless of the presence or absence of thrombophilic mutations. No controlled studies have provided definitive guidelines for the use of this drug with regard to hypercoagulability. However, neither the BCPT nor the earlier retrospective examination provides support for the pretreatment assessment of hypercoagulability factors in asymptomatic women who are about to receive tamoxifen as a cancer preventative.

The findings of this and several other studies support an association between thromboembolic events and tamoxifen use. In the BCPT, tamoxifen treatment increased the risk of thromboembolic events 1.9-fold. When the increased risk of thromboembolic events associated with tamoxifen use is evaluated over time from initiation of therapy, the tamoxifen effect is apparent for the first 3 years of treatment but not thereafter. In addition to describing the characteristics of thromboembolic events risk seen in the BCPT, this study sought to describe the nature of associations that may exist among thromboembolic events risk, tamoxifen use, and the presence of FVL and PT20210 mutations. Although the number of women in the study who had mutations was small and statistical significance was not demonstrated, the relative risk of thromboembolic events associated with the presence of FVL and PT20210 mutation was similar in magnitude to that seen for the relative risk of thromboembolic events with tamoxifen use. Furthermore, when these women were evaluated by treatment group, the relative risks of thromboembolic events associated with mutation were similar, indicating that tamoxifen treatment does not interact with mutations to result in an additive effect.

Table 5. Distribution of thromboembolic disease case patients by type of thromboembolic event, type of mutation, and treatment group among women in the BCPT*

<table>
<thead>
<tr>
<th>Mutation status and type</th>
<th>Deep vein thrombosis</th>
<th>Pulmonary embolism</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mutation</td>
<td>Placebo (n = 22)</td>
<td>Tamoxifen (n = 32)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>15</td>
<td>23</td>
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<td>1</td>
<td>1</td>
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<td></td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*BCPT = National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial.
with tamoxifen. This lack of interaction was confirmed statistically. As has been demonstrated previously, a statistically significant association between the risk of thromboembolic events and BMI was also evident in this population; however, adjustment for this variable did not affect the relationship of thromboembolic events risk noted for tamoxifen treatment or for genetic mutations. Finally, the findings from this report suggest that screening subjects for FVL and/or PT20210 would not be a useful approach with which to identify and exclude from prevention therapy a subset of individuals overly predisposed to thromboembolic events while taking tamoxifen.

**REFERENCES**


**Notes**

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