Tamoxifen and the Factor V Leiden Mutation

Jack Cuzick

Correspondence to: Jack Cuzick, PhD, Cancer Research UK Centre for Epidemiology, Mathematics and Statistics, Wolfson Institute of Preventive Medicine, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, UK (e-mail: j.cuzick@qmul.ac.uk).

Both tamoxifen and the factor V Leiden (FVL) mutations are well-established risk factors for thromboembolic events (TE). Tamoxifen has been shown to increase risk by two- to fourfold in both adjuvant and preventive trials (1). The FVL mutation is well-established as a risk factor for TE in the general population, with a three- to sixfold relative risk compared with persons without the mutation (2), and it also confers risk in persons in whom excess estrogen stimulation has occurred, such as in women using hormone replacement therapy or high-dose oral contraceptives and in pregnant women (3). Thus, it came as a surprise that among women who took tamoxifen in two major breast cancer prevention trials, FVL carriers carried no excess risk of thromboembolism, despite the fact that tamoxifen itself was a clear and strong risk factor (4,5). In fact for the International Breast Cancer Intervention Study-I (IBIS-I) prevention trial, among 35 women with an available blood sample who developed a TE (29 of whom received tamoxifen), none were positive for the FVL mutation as compared with eight (5.0%) of the 159 matched control women (6). In addition, none of the women with a TE had the prothrombin G2010A mutation, which is also known to lead to an increased risk of TE (7), as opposed to three women in the control group (1.9%). Similar results were seen in the National Surgical Adjuvant Breast and Bowel Project P1 breast cancer prevention trial (NSABP-P1[BCPT]) (8), in which, again, neither the FVL mutation nor the prothrombin mutation was related to TE risk in tamoxifen users. In this trial, 48 women with a TE were compared with 189 matched controls. Again, tamoxifen was a risk factor for TE, with a relative risk of 1.9 (P = .006).

An analysis in breast cancer patients taking tamoxifen that is presented in this issue by Garber et al. (9) found the prevalence of an FVL mutation to be almost fivefold higher in women who had a TE (18.5%) compared with matched control subjects (4.5%) and strongly supports an effect of FVL mutation on risk of TE among tamoxifen users, at least in the adjuvant setting. From these data, it was not possible to determine whether the effects of tamoxifen and the FVL mutation were multiplicative (ie, did not interact) or whether the effect of FVL was stronger or weaker among tamoxifen users than among women who did not take this drug. The incidence of a serious TE during 5 years of treatment with tamoxifen is about 2.4% in adjuvant trials (10), so based on these data, the risk would be more than 10% among FVL carriers and would be clinically relevant. In the prevention setting, the TE risk is substantially less, that is, about 0.6% during 5 years of active tamoxifen treatment in women older than 50 years and even less in younger women (1).

Why are the results so apparently different in these two contexts? It could still be due to chance. There were 74 case subjects in the tamoxifen arms of the prevention trials and 124 evaluated case subjects here, and an interaction test gives P = .10. An obvious difference is that the women in this study all had breast cancer, and about 50% had also received chemotherapy, which has been found to be a risk factor for TEs in many other studies (11), but curiously not in the presented article. However, why FVL would predict TE in this setting, but not when tamoxifen is used for prevention, remains a mystery.

The issue for breast cancer treatment with tamoxifen is now less important than a few years ago because newer, generally more effective treatments, such as aromatase inhibitors in the postmenopausal setting and luteinizing hormone–releasing hormone agonists in the premenopausal setting, are now available. However, because these newer treatments are not without their own side effects (eg, bone loss and arthralgia), tamoxifen remains a valuable option for some women. In the adjuvant setting, it may be prudent to test for FVL and prothrombin G2010A mutations before starting treatment with tamoxifen. However, the lack of an association between tamoxifen use and TE risk in the prevention trials makes this decision less clear when tamoxifen is used prophylactically. In postmenopausal women, raloxifene is another option for breast cancer prevention, and it does not appear to confer as much risk of TE as tamoxifen (12), but recent evidence also indicates that it is only 75% as effective in preventing breast cancer as tamoxifen (13). Aromatase inhibitors are also being evaluated for breast cancer prevention in high-risk postmenopausal women (14).

Continued follow-up and research on the relationship between the FVL mutation and tamoxifen, especially in the prevention setting, will be the only way to clarify these apparently contradictory findings.

References

7. Poort SR, Rosendaal FR, Reitsma PH, et al. A common genetic variation in the 3’- untranslated region of the prothrombin gene is associated with...


Affiliation of author: Cancer Research UK Centre for Epidemiology, Mathematics and Statistics, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, UK.