family history was a strong risk factor for ER-negative status (4). Family history in this study may have been a surrogate for the presence of a BRCA1 mutation, because these women are more likely to develop ER-negative breast cancers than those who do not carry BRCA1 mutations (5). Another study showed that smokers and ex-smokers have a higher likelihood of ER-negative tumors than do never smokers (6). There is also evidence that African American women are more likely than white women to develop ER-negative tumors (7)—whether this reflects screening biases or true biologic factors is unclear.

Although these identified non-genetic risk factors appear to be very non-specific and the precise biologic mechanism associated with ER-negative status is not known, we would be interested in seeing whether Veronesi et al. (1) could use their large dataset to identify a population at high risk for ER-negative breast cancer. Proof that anthropometric, or other measured factors, can identify these women would be useful in helping to exclude women who are not suitable for interventions with selective estrogen receptor modulators, and would identify a cohort for consideration for preventive intervention with non-estrogen-related compounds.

RUPA NARASIMHADVARA
MICHAEL N. POLLAK
WILLIAM D. FOULKES

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In their recent paper, Veronesi et al. (1) reported that women, divided into two groups according to their risk of developing breast carcinomas, respond differently to the preventive effect of tamoxifen. In addition to the impressive reduction of tumors obtained with tamoxifen among women in the high-risk group, the study gives important epidemiologic information: 1) hormone replacement therapy (HRT) appears to be a risk factor for breast carcinoma only for women at high risk, suggesting that an early hormone exposure (early menarche, nulliparity, late age at first pregnancy, intact ovarian function) predisposes these women to an additional risk resulting from subsequent hormone exposure. By contrast, among women at low risk for breast carcinoma, HRT did not seem to be associated with a substantially increased risk. 2) For most of the risk factors analyzed in these hysterectomized patients, Veronesi et al. (1) report odds ratios that are notably higher than those reported in the general population (2). If not a result of the relatively low number of patients analyzed, the impact of hormone exposure might be a result of a particularly low risk among this hysterectomized group. Accordingly, considering all the tumors, the frequency of estrogen receptor (ER)-negative tumors is higher than expected, suggesting a baseline protection of ER-positive tumors. Moreover, in contrast
with a previous report indicating a prevalence of ER-positive tumors in high-risk patients (3), the study by Veronesi et al. (1) showed that the frequency of ER-positive tumors is similar among the low- and high-risk subgroups.

The finding that tamoxifen does not protect women at low risk from ER-positive tumors indicates that other parameters negatively regulate hormone responsiveness in this subgroup of women. Overexpression of the HER2 oncogene has been associated with hormone independence (4). We recently showed that the frequency of HER2-overexpressing breast carcinomas changes in patients according to their hormonal risk category, suggesting that HER2-overexpressing breast carcinomas are not protected by hormone-related factors (5). An additional analysis of this series of about 2000 primary carcinomas indicated that, in patients identified at low risk (i.e., those who have more than three children and late menarche), 42% of tumors were HER2-positive compared with 21% in patients identified at high risk (less than three children and early menarche). It would be relevant to know the distribution of HER2-positive tumors in the various groups in the prevention trial by Veronesi et al. (1). In fact, the lack of efficacy of tamoxifen among women in the low-risk group might be related to a higher frequency of HER2-overexpressing tumors, which are less sensitive to hormones. Furthermore, inhibition of incidence of a breast cancer subset (i.e., hormone-responsive) by the treatment might counterbalance an increase of incidence of another subset (i.e., the HER2-positive), giving an overall null effect of the treatment. A detrimental effect of tamoxifen observed in an experimental model of HER2 transgenic mice was the result of an effect on occult tumors (6); however, tamoxifen administration before tumor onset was found to protect against HER2-positive tumors. Thus, the information regarding HER2 status of the tumors from the trial by Veronesi et al. (1) should help in understanding the action of tamoxifen.

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Affiliations of Authors: S. Ménard, P. Casalini, E. Tagliaabue, S. M. Pupa, A. Balsari, Molecular Targeting Unit, Dept. of Experimental Oncology, Istituto Nazionale Tumori; and Institute of Pathology, University of Milan, 20133 Milan, Italy.

Correspondence to: Sylvie Ménard, Ph.D., Molecular Targeting Unit, Dept. of Experimental Oncology, Istituto Nazionale Tumori, Via Venezian 1, 20133 Milan, Italy (e-mail: sylvie.menard@istitutotumori.mi.it).

RESPONSE

We concluded our recent publication (1) by noting that the effect of tamoxifen in chemoprevention appeared to be restricted to women predicted to be at high risk of the hormone-dependent form of the disease. We identified a subgroup of women in the Italian Randomized Trial of Tamoxifen at high risk of estrogen receptor (ER)-positive breast cancer on the basis of baseline measurements and emphasized that these results require confirmation from other trials before the clinical and public health implications are clear (1). We still believe this to be the case.

Narasimhadevara et al. make some interesting points; notably, that we did not attempt to identify a subgroup at high risk of ER-negative breast cancer. When we investigated the role of the hormonal variables as risk factors, none of the variables in Table 1 of our original article (1) (i.e., use of hormone replacement therapy, height, ovary function, age at menarche, age at first birth) were statistically significantly associated with the risk of ER-negative breast cancer in the study cohort. Only breast cancer in a first-degree relative (odds ratio = 2.6, 95% confidence interval = 0.8 to 8.1) approached statistical significance. We agree that ER-negative breast cancer is a very important form of breast cancer and one that deserves a great deal of attention, especially in terms of prevention, both primary prevention and chemoprevention. However, it is counter intuitive to expect hormonal interventions with agents such as tamoxifen and other SERMs (selective estrogen receptor modulators) to have an impact on the risk of this form of the disease.

It must be clear when reading Menard et al., particularly the opening paragraph, that when we referred to “high risk” (1), we were referring to the high risk of hormone-dependent breast cancer and not high risk of breast cancer per se. When Menard et al. state that the frequency of ER-negative tumors was higher than expected, the statement should be interpreted with caution. In our study, 30% of the breast tumors in women receiving the placebo were ER-negative. This frequency may be different from that in a general population.

<table>
<thead>
<tr>
<th>Table 1. Number and proportion of HER2-overexpressing tumors per number of breast tumors in the various subgroups of patients in the Italian Tamoxifen Chemoprevention Trial</th>
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<tbody>
<tr>
<td>Low-risk group (%)</td>
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<tr>
<td>Estrogen receptor tumors</td>
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<tr>
<td>Receptor-negative</td>
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<td>Receptor-positive</td>
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because half of the women in our study had a bilateral oophorectomy before baseline (1). The higher proportion (40%) of ER-negative tumors in women receiving tamoxifen may reflect the ability of tamoxifen to prevent ER-positive tumors. In women in the placebo arm of our study, which is the only arm that can be compared with population-based studies, the cumulative incidence of ER-positive tumors was about four times higher for those in the high-risk group than for those in the low-risk group. The proportion of ER-positive tumors in the placebo arm was also higher in the high-risk group (73%) than in the low-risk group (66%) (1).

The evidence that tamoxifen protects against ER-positive breast cancer in a subset of subjects is quite compelling (2), but tamoxifen is still ineffective in subjects at low risk of developing the disease. There are many potential mechanisms that could be proposed to explain such a lack of effect, and Menard et al. have chosen to focus on one of these. In our study, we observed a higher proportion of tumors that over-expressed HER2 in the low-risk group than in the high-risk group, supporting the hypothesis of Menard et al. (Table 1).

We continue to obtain a better understanding of the impact of tamoxifen in the chemoprevention setting and are starting to have a better indication of where to search for potential mechanisms. Of course, the great challenge in breast cancer prevention remains the ER-negative form of the disease, where alternatives to the hormonal approach are needed, and with some urgency.

UMBERTO VERONESI
PATRICK MAISONNEUVE
NICOLE ROTMENZ
ANDREA DECENSI
GIUSEPPE VIALE
PETER BOYLE

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Affiliations of authors: U. Veronesi, P. Maisonneuve, N. Rotmensz, A. Decensi, G. Viale, P. Boyle, Divisions of Senology, Chemoprevention and Pathology and Department of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy; G. Viale, University of Milan, Milan, Italy.

Correspondence to: Professor Peter Boyle, Ph.D., Department of Epidemiology and Biostatistics, European Institute of Oncology, via Ripamonti 435, 20141 Milan, Italy (e-mail: director.epi@ieo.it).

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