CORRESPONDENCE

Re: Italian Randomized Trial Among Women With Hysterectomy: Tamoxifen and Hormone-Dependent Breast Cancer in High-Risk Women

Veronesi et al. *(1)* report findings from the large-scale Italian Randomized Trial of Tamoxifen. Their results show that the risk-reducing effects of tamoxifen on high-risk women with breast cancer are most marked for estrogen receptor (ER)-positive tumors. Women at high risk were defined as being ER-positive tumors on the basis of a number of reproductive and hormonal criteria: height of greater than 160 cm, no oophorectomy, menarche by age 13 years, no full-term pregnancy before age 24 years. This group comprised 702 women (13.0%) of the total cohort (n = 5395). The results demonstrate that the criteria used to identify the high-risk cohort are valuable, especially in identifying women who may develop ER-positive tumors. These women are particularly suitable for enrollment into chemoprevention studies that interrupt estrogen pathways.

When comparing the results seen in the placebo group, high-risk women in the ER-positive group (cumulative incidence ≈4.2% after 9 years, 11 events) showed an approximately 4.4-fold increased incidence of breast cancer over the low risk ER-positive group (cumulative incidence ≈0.9%, 18 events). High-risk women in the ER-negative group (cumulative incidence ≈1.1%, four events) showed only an approximately 2.2-fold increase over low-risk women (cumulative incidence ≈0.5%, nine events).

The criteria were not designed to identify women at high risk of ER-negative breast cancer, and do not do so. Nevertheless, women who develop ER-negative breast cancers represent a very important group: these women have a worse prognosis than those who develop ER-positive cancers *(2).* In contrast to studies of ER-positive breast cancers *(3),* there are few epidemiologic studies that identify risk factors for ER-negative breast cancers. One study showed that 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 nonspecific 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.

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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 independency *(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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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 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

	Low-risk group (%)		High-risk group (%)	
Estrogen receptor tumors	Placebo	Tamoxifen	Placebo	Tamoxifen
Receptor-negative	2/9 (22)	5/11 (45)	0/4 (0)	0/1 (0)
Receptor-positive	3/17 (18)	5/15 (33)	1/11 (9)	0/1 (0)

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.

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It is a pleasure to acknowledge the participation of the Italian women who took part in this study and all the members of the Italian Tamoxifen Study Group. The study was funded in part by grants from the CNR, the Italian Association for Research on Cancer, the American–Italian Cancer Foundation, and from the Italian League Against Cancer.