Re: Estrogen Receptor Status of Primary Breast Cancer Is Predictive of Estrogen Receptor Status of Contralateral Breast Cancer

The recent paper by Swain et al. (1) showing a high degree of concordance between the estrogen receptor (ER) status of first primary and contralateral breast cancers is of considerable biological interest, particularly because gene expression studies have shown that a large number of genes distinguish ER-positive from ER-negative breast cancers (2,3). In the study by Swain et al., only women diagnosed before the age of 50 did not receive tamoxifen. Thus, only in that group of women can the biology of the two breast cancers be truly studied. Notably, concordance was seen in 50 of the 62 pairs of cancers in this group of women (in 19 women, both cancers were ER negative, and in 31 women, both cancers were ER positive), leaving only 12 women (eight women with an ER-negative first cancer and an ER-positive second cancer and four women with an ER-positive first cancer and an ER-negative second cancer) in which the first and second cancers were discordant for ER status. The median time from randomization to contralateral invasive breast cancer was 4.66 years (range = 0.26–10.3 years).

It has been known for several years that, as the age at diagnosis of breast cancer increases, the probability of the tumor being ER positive increases (4). We recently quantified this phenomenon (5). For example, on the basis of the regression slope shown in Fig. 1, the percentage of ER-positive breast cancers in an unselected population increased from 62% at age 35 or younger (95% confidence interval [CI] = 55% to 69%) to 72% (95% CI = 69% to 76%) by age 49. To better understand the interplay of age and common etiologic factors that underlie the two breast cancers, it would be interesting to see how the concordance of ER status of the two cancers changes with time since first breast cancer diagnosis in the dataset analyzed by Swain et al. (1). From both our (5) and previous (6,7) data, I predict that the median interval between the first and second cancers will be shorter for the 19 women in which the two cancers were concordantly ER negative than for the women in which the two cancers were either concordantly ER positive (n = 31) or discordantly ER negative and then ER positive (n = 8). This conjecture is supported by the data from Swain et al. (1), in which only four of 62 (6%) pairs of cancers had a discordant ER-positive first/ER-negative second status, which is against the time trends (i.e., insofar as older women tend to develop ER-positive cancers) presented in Fig. 1. If confirmed, these findings would indicate that temporal factors have to be controlled for when considering concordance data. Moreover, if cancers farther apart in time are less likely to be discordant than synchronous cancers, then this suggests that pairs of first primary and contralateral cancers are composed of several different etiologically unrelated subgroups, although they were previously considered to represent a single group. Conversely, if there is no relationship between the median time interval between the first primary and contralateral breast cancer and the ER status of the two cancers, then this would imply that there is likely to be

![Fig. 1. Change in estrogen receptor status with increasing age at diagnosis in 596 women with invasive breast cancer.](image)

Looking at the figure, it's clear that as the age at diagnosis increases, the percentage of ER-positive tumors also increases. The data are plotted against age at diagnosis (x-axis) for 596 women diagnosed between 1987 and 1997, with invasive breast cancer before the age of 65 years at a single Toronto institution. The ER status of breast tumors (positive or negative), diagnosed at each age shown, was averaged (solid diamonds). ER status determination was based on a biochemical assay, and a level greater than 10 fmol/mg of protein was recorded as positive. Because 31 of 596 women were diagnosed before the age of 35 years, the data were pooled together and the mean percent ER-positive tumors for these women is shown at age 35. The best fitting slope is shown, and the 95% confidence intervals are indicated by dotted lines. $R^2 = 0.30; \alpha = 0.37 (P<.001); \beta = .007 (P = .002)$. The figure is based on data from reference (5).
an unknown, time-insensitive factor that is playing a major role in determining the observed concordance.

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REFERENCES


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RESPONSE

Foulkes presents the hypothesis that the median interval between the primary and contralateral breast cancer of the women in our study (1) will be shorter in women aged younger than 50 years who had concordant estrogen receptor (ER)–negative tumors than in women with concordant ER-positive tumors or those who had discordant tumors. However, among our cohort, the median time to contralateral breast cancer was 5.08 years for women who had concordant ER-negative tumors (n = 19) and 4.76 years (n = 31) for women with concordant ER-positive tumors. Among women in the discordant groups, the median time to a second primary tumor was 4.14 years (n = 8) for women who presented with an ER-negative primary tumor and 2.99 years (n = 4) for women who presented with an ER-positive primary tumor. These results suggest that there is no difference in the time of presentation of concordant contralateral breast cancer according to the ER status of the primary tumor, and that of discordant tumors present at an earlier time, suggesting different etiologies.

To explore the relationship between concordance and time, we divided patients into three groups according to time from diagnosis of the primary tumor to time of diagnosis of the contralateral tumor: less than 3 years (n = 19), from 3 to 6 years (n = 23), and more than 6 years (n = 20). There was no evidence for an association between time of diagnosis and concordance (P = .56 by Fisher’s exact test and P = .63 by linear trend test). In fact, the lowest concordance rate was in the earliest time period, not in the latest. We found similar results in an analysis that was based on five time periods instead of three. Although these very exploratory analyses are intriguing and many speculations can be made, the numbers are very small, and prospective evaluations of these questions along with molecular analyses are critical to clarifying this issue.

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