Buller et al. (1) suggest a novel mechanism for genetic susceptibility to ovarian cancer. In our view, the data presented are puzzling and do not support a new model for susceptibility to ovarian cancer. There are two models under which germline mutation of an X-chromosome tumor suppressor may contribute to cancer predisposition through nonrandom X-chromosome inactivation (NXCI). In one model, approximately 30% of females (authors’ data) undergo NXCI for reasons unrelated to a cancer predisposing allele, and some fraction of these carry a mutant tumor suppressor allele that manifests when the normal allele undergoes NXCI. In the second model, cells with the mutant allele present on the active X chromosome have a proliferative advantage over cells with a normal active allele during tissue morphogenesis, resulting in apparent increased rates of NXCI. This model implies that the mutant cancer susceptibility allele occurs fre-
frequency in the population studied. The suggestion that the association of NXCI with germline BRCA1 mutation could in part explain why there are increases in prostate cancer, and colon cancer in addition to breast and ovarian cancer in hereditary breast and ovarian cancer families” is without foundation.

Because we cannot accept that a model involving an X-linked tumor suppressor gene is a viable explanation for the observed association of NXCI with ovarian cancer, other explanations are sought. Postnatal alterations in lymphocyte X-inactivation patterns may result from cancer chemotherapy or aging. As Brown reminds us in an editorial (3), the apparent prevalence of NXCI increases with age, from 10% in neonates to more than 45% in elderly women. Borderline tumors occur at a generally younger age than invasive ovarian cancers, yet Buller et al. did not control for age differences in their analysis. Other possibilities include gene-specific methylation of the androgen receptor as a result of the aging process (4), in which case androgen receptor methylation as a surrogate for NXCI may be inappropriate, and alterations of DNA methylation with storage, which was not controlled for in this study.

Notes

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RESPONSE

Narod and Boyd (1) have challenged our proposed model of an X-linked tumor suppressor gene invoked to explain the association between nonrandom X-chromosome inactivation and ovarian cancer. They have suggested alternative explanations but focused narrowly on a model wherein the germline mutation of an X-linked tumor suppressor gene contributes to hereditary cancers. We would reiterate from our published article (1) that there are two ways in which an X-linked tumor suppressor gene contributes to ovarian cancer. The first way provides a subset of sporadic ovarian cancers that are rendered null at the X-linked tumor suppressor gene locus by virtue of nonrandom X-chromosome inactivation and concomitant loss of the active allele. The calculated odds ratio of 2.3 suggested by Narod and Boyd does not conflict with this model. A second mechanism relates to hereditary ovarian cancer. In this case, a germline mutation of the X-linked tumor suppressor gene associated with nonrandom X-chromosome inactivation does not require loss of heterozygosity. We would accept it as a rare event. Unless the authors’ own data (2) have been revised, they and others are unable to explain all cases of hereditary breast and ovarian cancers on the basis of germline BRCA1 and BRCA2 mutations. Thus, the existence of a putative yet elusive BRCA3 gene must be invoked. Where better to hide than on the X chromosome? Until very recently, the X chromosome could be considered a genetically privileged hiding site because of the paucity of markers for high resolution mapping and linkage analysis. Indeed, a putative hereditary prostate cancer susceptibility tumor suppressor gene has only recently been mapped to the X chromosome (3).

Narod and Boyd have clearly misinter-}

1508 CORRESPONDENCE}

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expressed between the two probands. Thus, it is impossible to conclude which X chromosome is active. One can only say that the X-linked tumor suppressor gene is not the AR gene itself. Narod and Boyd are correct that male-to-male transmission is incompatible with X linkage. However, the hereditary breast and ovarian cancers in Family 15 are explained by the germline BRCA1 mutation, as shown in the caption to Fig. 5 of our article. Thus, an X-linked tumor suppressor gene is not required for this family. Nonetheless, nonrandom X-chromosome inactivation may still contribute to the penetrance of disease. These data suggest that nonrandom X-chromosome inactivation may be autosomally determined. Hence, our conclusion that nonrandom X-chromosome inactivation is “complex.”

Finally, Narod and Boyd were critical of our failure to control for age. Table 1 shows a breakdown of nonrandom X-chromosome inactivation based upon the study group with attention to age at diagnosis (1). Nonrandom X-chromosome inactivation is independent of age and dependent on health status. Women who develop invasive ovarian cancer are more likely to demonstrate nonrandom X-chromosome inactivation regardless of age at diagnosis. Further investigation of the phenomenon of nonrandom X-chromosome inactivation and its relationship to ovarian cancer and cancer in general are warranted.

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Table 1. Comparison of frequency of nonrandom X-chromosome inactivation by study group and age at analysis

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean age at sampling, y</th>
<th>Frequency of nonrandom X-chromosome inactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n = 46)</td>
<td>37</td>
<td>Median age, %* 33 (7/21) 28 (7/25)</td>
</tr>
<tr>
<td>Borderline ovarian cancer (n = 35)</td>
<td>42</td>
<td>Median age, %* 19 (3/16) 37 (7/19)</td>
</tr>
<tr>
<td>Invasive ovarian cancer (n = 174)</td>
<td>58</td>
<td>Median age, %* 52 (46/89) 55 (47/85)</td>
</tr>
<tr>
<td>Age &lt;45 y (n = 33)</td>
<td>39</td>
<td>Median age, %* 50 (9/18) 53 (8/15)</td>
</tr>
<tr>
<td>Age &gt;65 y (n = 53)</td>
<td>71</td>
<td>Median age, %* 56 (15/27) 58 (15/26)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses = cases with nonrandom X-chromosome inactivation divided by total informative cases for specified age interval.