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.

JEFF BOYD
STEVEN A. NAROD

REFERENCES


NOTES

Affiliations of authors: J. Boyd, Departments of Surgery and Human Genetics, Memorial Sloan-Kettering Cancer Center, New York, NY. S. A. Narod, Centre for Research on Women’s Health, Women’s College Hospital, University of Toronto, Canada.

Correspondence to: Jeff Boyd, Ph.D., Depart-
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.

REPRESENTATION

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></td>
<td></td>
<td>=Median age, %*</td>
</tr>
<tr>
<td>Controls (n = 46)</td>
<td>37</td>
<td>33 (7/21)</td>
</tr>
<tr>
<td>Borderline ovarian cancer (n = 35)</td>
<td>42</td>
<td>19 (3/16)</td>
</tr>
<tr>
<td>Invasive ovarian cancer (n = 174)</td>
<td>58</td>
<td>52 (46/89)</td>
</tr>
<tr>
<td>Age &lt;45 y (n = 33)</td>
<td>39</td>
<td>50 (9/18)</td>
</tr>
<tr>
<td>Age &gt;65 y (n = 53)</td>
<td>71</td>
<td>56 (15/27)</td>
</tr>
</tbody>
</table>

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


NOTES

Affiliations of authors: R. E. Buller (Division of Gynecologic Oncology, Department of Obstetrics and Gynecology and Department of Pharmacology), A. K. Sood, T. Lallas, T. Buekers, J. S. Skilling (Division of Gynecologic Oncology), Department of Obstetrics and Gynecology, The University of Iowa Hospitals and Clinics, Iowa City.

Correspondence to: Richard E. Buller, M.D., Ph.D., Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, 200 Hawkins Dr., #4630 JCP, Iowa City, IA 52242-1009 (e-mail: richard-buller@uiowa.edu).

REFERENCES

(1) Buller RE, Sood AK, Lallas T, Buekers T, Skilling JS. Association between nonrandom...