High-Risk Lesions in High-Risk Women: A High-Risk Formalin-Based Biology!

TO THE EDITOR: We have reviewed three recent independent series reporting on benign breast disease and preinvasive lesions in prophylactic mastectomies from high-risk women (Table 1). Hypothesis regarding specific breast cancer progression in BRCA1 mutation carriers is portrayed.

Benign breast disease is of major interest in breast pathology. Many terms are used to refer to it: premalignant lesions, precursor lesions, risk marker lesions. It is still a matter of debate among pathologists and basic science researchers whether such lesions are directly connected to the subsequent invasive cancers seen in a patient. Actually, patients with such high-risk lesions are at higher risk for developing invasive breast cancer. On another hand, high-risk women are defined by the presence of a major familial cancer history, suggesting the transmission of germline mutations including breast cancer susceptibility genes, such as BRCA1 and BRCA2, or other yet unknown genes. Women with such genetic predisposition, particularly BRCA mutation carriers, are at high risk for developing invasive breast cancers. Three recent series have tried to assess this high-risk relation between somatic breast lesions and germline mutations. Are high-risk lesions more prevalent in BRCA mutation carriers, therefore explaining the higher risk observed in those patients? Or should this higher risk be explained by other, yet unrecognized biomarkers specific to BRCA mutation carriers? Three pathology-based series

Robert J. Motzer
Memorial Sloan-Kettering Cancer Center, New York, NY

Author’s Disclosures of Potential Conflicts of Interest
The author indicated no potential conflicts of interest.

REFERENCES

DOI: 10.1200/JCO.2004.99.322

Table 1. Comparison Table of the Three Series: Materials, Methods, and Results Summaries

<table>
<thead>
<tr>
<th>BRCA mutation carriers, n</th>
<th>University of Nijmegen</th>
<th>Memorial Sloan-Kettering Cancer Center</th>
<th>Mayo Clinic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal breast cancer history in BRCA mutation carriers, n</td>
<td>11 (42% of 26, data extracted)</td>
<td>17</td>
<td>28</td>
</tr>
<tr>
<td>Controls, n</td>
<td>No control group presented</td>
<td>48</td>
<td>74</td>
</tr>
<tr>
<td>Controls definition</td>
<td>Data for 23 high-risk patients with no BRCA mutations could be extracted from Table 1</td>
<td>Selected autopsy cases as non-Hispanic white women with no personal history of breast cancer</td>
<td>Without a known family history of breast carcinoma</td>
</tr>
<tr>
<td>Pathology review</td>
<td>No details</td>
<td>One pathologist</td>
<td>Two pathologists, blind for status</td>
</tr>
<tr>
<td>Sampling, slides per case v control</td>
<td>19 (mean number for all subjects)</td>
<td>14.1 v 9.2*</td>
<td>7.2 v 8.1†</td>
</tr>
<tr>
<td>Hyperplasia with no atypia, cases v controls</td>
<td>Not evaluated</td>
<td>Not evaluated</td>
<td>5% v 26%*</td>
</tr>
<tr>
<td>ADH, BRCA v sporadic</td>
<td>Grouped under high risk</td>
<td>38% v 4%*</td>
<td>4% v 2%†</td>
</tr>
<tr>
<td>ALH, BRCA v sporadic</td>
<td>lesions 43% v 83% (BRCA)</td>
<td>13% v 0%*</td>
<td>Grouped under lobular neoplasia</td>
</tr>
<tr>
<td>LCIS, BRCA v sporadic v non-BRCA, data extracted</td>
<td>4% v 2%†</td>
<td>0% v 5%†</td>
<td></td>
</tr>
<tr>
<td>DCIS, BRCA v sporadic</td>
<td>13% v 0%*</td>
<td>0% v 0%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; LCIS, lobular carcinoma in situ; DCIS, ductal carcinoma in situ.
*Statistically significant.
†No statistical significance.
have recently tried to answer this question by evaluating the prevalence of high-risk lesions in BRCA patients who underwent unilateral prophylactic mastectomy (PM) when personal history of breast cancer was present, or bilateral PM when there was not yet any known personal breast cancer history. Among high-risk lesions, ductal carcinoma-in-situ (DCIS) confers an 8- to 10-fold increase in relative risk for a given patient. First pathology reports on therapeutic mastectomies have shown a lower prevalence of DCIS component associated with invasive cancers in BRCA mutation carriers, suggesting that BRCA cancers arose de novo from breast epithelium without a preinvasive component [1,2]. In addition, epidemiologic studies suggested lower prevalence of BRCA mutations in patients with DCIS [3]. The more recent series based on prophylactic mastectomies, reporting on preinvasive disease, are of interest since all three agreed on the specific cancer progression in BRCA mutation carriers.

The study from the Nijmegen University (Nijmegen, the Netherlands) [4] selected 67 patients at high hereditary risk, from whom 44 had a BRCA mutation (38 BRCA1 and six BRCA2), who underwent unilateral (26 patients) and bilateral (41 patients) PM. Fifty-seven (57%) patients presented one or more high-risk lesions, comprising lesions such as atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma-in-situ, and DCIS. High-risk lesions were encountered in older patients, who were less likely to have had a previous oophorectomy and had less chance of being a BRCA mutation carrier. Nineteen (43%) BRCA mutation carriers had high-risk lesions, from whom 13 had unilateral PM and six had bilateral PM (data extracted). Among BRCA mutation carriers with high-risk lesions, 20% had previous oophorectomy compared to 42% who did not, stressing the hormonal dependence between ovaries and breast parenchyma. The grouping of such different lesions in the high-risk category is somehow questionable, since the clinical management, the pathology and biology of atypical ductal hyperplasia, lobular neoplasm (atypical lobular hyperplasia and lobular carcinoma-in-situ), and DCIS are extremely different. DCIS was seen on prophylactic mastectomies in 9% of BRCA mutation carriers, and in 26% of patients with no mutations (data extracted). Of note is that neither clinical exams, nor imaging studies including magnetic resonance imaging, were able to detect DCIS. Therefore, prophylactic surgery offered to BRCA patients might be more efficient than surveillance, as suggested by another study [5]. The Dutch authors observed that the occurrence of these high-risk lesions is higher than what was reported in the literature, and explained it by their extensive sampling of breast specimens. As they pointed out, a major limitation of their study is the absence of a control group, which is an essential condition for studying the pathophysiology of the cancer progression in BRCA mutation carriers.

The study [6] from the Memorial Sloan-Kettering Cancer Center (New York, NY) examined breast materials from 24 BRCA mutation carriers who underwent prophylactic mastectomies (71% had previous breast cancer) at their institution between 1987 and 2001, and from 48 controls (with no personal history of breast cancer) extracted from an autopsy registry (performed between 1978 and 1983). There was higher incidence of almost all labeled benign breast lesions (most of which could be grouped under the nonproliferative fibrocystic changes spectrum) in BRCA mutation carriers compared to the autopsy cases. High-risk ductal and high-risk lobular lesions were more frequently encountered in breast tissue from BRCA patients. Thirteen percent of those patients had DCIS compared to none of the controls. The findings of lower prevalence of high-risk lesions in the autopsy group could result from different confounding biases. There were significant differences in the number of slides per breast (14 slides for BRCA mutation carriers versus nine slides for controls), specimens handling, surgical (in a hereditary setting, someone would be very careful in grossing breast tissue) versus autopsy procedures (where sampling is less directed). Also, the groups’ epidemiologic characteristics differed in their ethnic background and personal breast cancer history (the control cases could all be considered as having had bilateral PM).

The report from the Mayo Clinic explored two groups; one underwent unilateral PM after a therapeutic mastectomy for breast cancer, while the second one underwent bilateral PM [7]. Overall, there were 180 high-risk patients, including 39 BRCA mutation carriers and 325 sporadic controls, who were matched by age at diagnosis and date of surgery. There was no difference in slides number between cases and controls. They observed lower prevalence of proliferative fibrocystic changes (moderate and florid hyperplasia with no atypia) in BRCA mutation carriers compared to the remaining hereditary and sporadic patients. The same trend was observed in prophylactic mastectomies from BRCA patients with or without a personal history of breast cancer, as well as in patients with BRCA1 mutations or BRCA2 mutations compared to their respective controls. Reporting their findings from therapeutic mastectomies, authors from the Mayo Clinic (Rochester, MN) have confirmed earlier data regarding the higher grade of invasive cancers in BRCA mutation carriers; nevertheless, they reported similar prevalence of DCIS among BRCA cancers and remaining cancers, emphasizing the presence of an in situ component in BRCA carcinogenesis.

Although slight differences are seen among those three reports, especially in the materials sections and in the ways cases and controls were matched, they present converging data. BRCA cancer progression goes through morphologically recognizable steps, hyperplasia, and in situ cancer.

As surgical pathology is an instant formalin-fixed paraffin-embedded picture of cancer progression, the presence of a lower prevalence of high-risk lesions may be explained by an accelerated tumorigenesis, and a quick transition of a
clone into putative intermediate steps to invasive disease rather than the de novo occurrence of invasive cancer (Fig 1). The high-grade and highly proliferative invasive breast cancers seen in BRCA mutation carriers militate for this hypothesis of a quick passage of a tumor clone through cancer progression steps [2]. Although the biology and the pathology of breast cancers related to BRCA1 or BRCA2 mutations show various differences, all three reports have brought together data from BRCA1 and BRCA2 related breast parenchyma. This was probably done because of sample size issues. Starting from these first data, we believe that it is the time for large collaborative multi-institutional studies exploring benign breast disease in hereditary patients. The latter ones, at higher risk for developing invasive cancers, should benefit from an adapted and adjusted clinical and radiologic surveillance in order to detect early lesions and first events. Experimental pathology could help in identifying molecular biomarkers stratifying patients with high-risk lesions identified by the means of surgical pathology in two groups, some to be closely followed at major risk for subsequent invasive cancer, and others that are at lower risk for it. Prophylactic surgery might be, in some settings, a reasonable option to be proposed to those high-risk patients with high-risk lesions until more clinical trials and molecular data would show other procedures to be more beneficial.

Camilo Adem
Department of Anatomic Pathology, Pitié Salpêtrière Hospital, and Division of Genetic Oncology, Curie Institute, Paris, France

Robert B. Jenkins
Division of Laboratory Genetics, Mayo Clinic, Rochester, MN

Frédérique Capron
Department of Anatomic Pathology, Pitié Salpêtrière Hospital, Paris, France

In Reply: Adem et al review three studies on breast pathology in patients with hereditary breast cancer. They conclude that the available data support their previous claim that breast cancer progression from benign breast disease to invasive cancer is more rapid in BRCA mutation carriers [1]. They list the following arguments: 1) A low prevalence (2-2.5%) of high-risk lesions in prophylactically removed breasts from BRCA1-mutation carriers, and 2) a high incidence of cancer in BRCA-mutation carriers. This model may be true. On the other hand, our study [2] and the Memorial Sloan-Kettering Cancer Center study [3] found a much higher prevalence of high-risk lesions (43% and 46%, respectively). Both these studies used more extensive breast tissue sampling protocols and therefore achieved higher sensitivity. Thus, the hypothesis that BRCA mutation carriers have a higher prevalence of high-risk lesions cannot be discarded. In fact, our data and that from the Memorial Sloan-Kettering Cancer Center study seem to favor increased incidence of lesions over rapid progression [2,3]. We agree that future studies are required to resolve whether progression or incidence of high-risk lesions is more important or whether other factors are involved. We note that irrespective of the underlying biologic model, the data argue...