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Breast-Cancer Predisposition in Multiple Endocrine Neoplasia Type 1

TO THE EDITOR: Multiple endocrine neoplasia type 1 (MEN1) is caused by germline mutations in the MEN1 tumor-suppressor gene and is typically characterized by parathyroid adenomas, duodenopancreatic neuroendocrine tumors, and pituitary adenomas. Recent studies in animals suggest that MEN1 is involved in breast-cancer initiation. Through its encoding of menin, a coregulator of estrogen receptor α, MEN1 has been implicated in breast-cancer progression.

To clarify the role of MEN1 in human breast cancer, the International Breast Cancer in MEN1 Study Group assessed the incidence of breast cancer in the Dutch longitudinal MEN1 database, which includes more than 90% of Dutch patients with MEN1. (Study group members are listed in the Supplementary Appendix, available with the full text of this letter at NEJM.org.) In 190 female patients with MEN1, the relative risk of invasive breast cancer was 2.83 (P<0.001), with a standardized incidence ratio of 2.14 (95% confidence interval [CI], 1.18 to 3.86) (Table S1 in the Supplementary Appendix). The mean (±SD) age at diagnosis of mostly luminal-type breast cancer was 48.0±8.8 years, as compared with an age of 60 to 65 years in the general population.

Three of the 12 Dutch breast-cancer patients with MEN1 had a history of hyperprolactinemia. Risk ratios for other major cancers were not elevated (Table S1 in the Supplementary Appendix).

We validated the observations in three independent cohorts from the United States, Tasmania, and France that included a total of 675 female patients with MEN1. In a comparison of breast-cancer prevalence and incidence with corresponding data from the respective national cancer registries, the risk ratios were 2.40 in the United States (P=0.11), 2.31 in Tasmania (P=0.22), and 2.33 in France (P=0.03). (The comparisons were not significant in the United States and Tasmania because of the small numbers of patients in these cohorts.) The standardized incidence ratio in the combined verification cohorts was 1.96 (95% CI, 1.33 to 2.88), and the average age at diagnosis was 51 years.

Nuclear localization of menin was reduced by more than 50% in 8 of 10 breast-cancer samples obtained from Dutch patients with MEN1 on immunohistochemical staining with the use of menin antibody A300-105A (Bethyl Laboratories) (Table 1). Subsequent analysis on DNA sequencing or multiplex ligation-dependent probe amplification revealed loss of heterozygosity at the MEN1 locus in 3 of 9 tumors. Reduced menin

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at Diagnosis (yr)</th>
<th>Histologic Analysis</th>
<th>Tumor–Node–Metastasis (TNM) Stage</th>
<th>Estrogen Receptor</th>
<th>Progesterone Receptor</th>
<th>HER2</th>
<th>Menin Expression</th>
<th>Loss of Heterozygosity at MEN1 Locus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>Ductal</td>
<td>T1N1M0</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>Ductal</td>
<td>T3N1M0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>Ductal</td>
<td>T1N0M0</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>Ductal</td>
<td>T1N1M0</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>Lobular</td>
<td>T1N0M0</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>6</td>
<td>53</td>
<td>Ductal</td>
<td>T1N0M0</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>45</td>
<td>Micropapillary</td>
<td>T1N1M0</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>42</td>
<td>Ductal†</td>
<td>T1N0M0</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>33</td>
<td>Ductal</td>
<td>T1N1M0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>10</td>
<td>46</td>
<td>Ductal</td>
<td>T1N0M0</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>ND</td>
</tr>
</tbody>
</table>

* A plus sign indicates positivity, and a minus sign negativity. HER2 denotes human epidermal growth factor receptor 2, and ND not determined.
† This patient had a tumor in each breast.
staining was found in only 4 of 88 control breast tumors on a tissue microarray (P<0.001 by Pearson's chi-square test). All studies were conducted in accordance with regulations of the local institutional review board.

In conclusion, female patients with MEN1 are at increased risk for breast cancer. Loss of menin expression and loss of heterozygosity at the MEN1 locus in a subgroup of patients suggest a mammary-cell autonomous effect in MEN1-related breast cancer. Our observations indicate that MEN1 mutations are involved in human breast carcinogenesis. Further research will clarify the relevance of MEN1 function for patients with nonfamilial breast cancer. Intensified breast-cancer screening at a relatively young age should be considered in female patients with MEN1.

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