Detailed Deletion Mapping of Chromosome 17q in Ovarian and Breast Cancers: 2-cM Region on 17q21.3 Often and Commonly Deleted in Tumors

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ABSTRACT

Using 11 restriction fragment length polymorphism markers, we examined loss of heterozygosity on the long arm of chromosome 17, where one or more genes responsible for hereditary breast and ovarian cancers may be present, in sporadic forms of 94 ovarian and 246 breast cancers. Loss of heterozygosity was observed in 33 of 84 (39.3%) ovarian and in 88 of 214 (41.1%) breast cancers that were informative with at least one marker. Detailed deletion mapping of chromosome 17q in these cancers identified two distinct, commonly deleted regions. One was located between 17q12 and 17q21.3 and the other between 17q25.1 and 17q25.3. In breast cancers, the proximal commonly deleted region was between two loci defined by markers C117-701 and C117-730 at 17q21.3, which are 2.4 cm apart. This segment overlaps the region that includes the putative gene for hereditary breast and ovarian carcinomas. The results suggest that at least two tumor suppressor genes associated with sporadic ovarian and breast cancers are present on chromosome 17q and that one of them may be the same gene that is responsible for the hereditary form.

INTRODUCTION

The number of patients with breast and ovarian cancers, which are common malignancies in women, is increasing in many countries. We previously reported frequent allelic losses on chromosomes 4p, 6p, 7p, 8q, 12, 16q, 17q, and 19p in ovarian cancers (1), and chromosomes 3p, 11p, 13q, 16q, 17p, and 17q in primary breast cancers (2, 3). Because 17q alleles are lost frequently in both types of tumor, and this chromosomal arm appears to contain the gene responsible for hereditary forms of breast and ovarian cancers (4-13), 17q is considered to contain one or more genes that play a significant role during development and/or progression of primary cancer in both of these tissues.

As a first step toward identification of such gene(s), we have attempted to identify a region that is commonly deleted in a large number of tumors. To that end, we have screened loss of heterozygosity in sporadic forms of 96 ovarian and 246 breast carcinomas with 11 RFLP markers on the long arm of chromosome 17 and have constructed a deletion map of 17q. This map indicates that two distinct regions are commonly deleted in both types of cancer, and one of them overlaps the region already identified as containing a gene associated with hereditary forms.

MATERIALS AND METHODS

Materials. Tumor tissues were obtained at the time of surgery from 94 patients with ovarian cancer and 246 patients with primary breast cancer.

RESULTS

LOH on Chromosome 17q in Ovarian Cancer. The frequencies of LOH at each of 11 RFLP loci are listed in Table 1. A total of 84 tumors were informative for at least one locus, and 33 (39.3%) of them showed LOH for at least one locus on chromosome 17q. Fig. 1a shows examples of Southern blot analyses that revealed partial deletions of chromosome 17q in three tumors. Tumors A40 and B6 lost one allele at the CI17-730 locus, while A40 retained both alleles at a more distal locus (CI17-507) and B6 retained alleles at a more proximal locus (CI17-316). On the other hand, tumor C12 retained heterozygosity at the CI17-516 locus, although one allele at CI17-710 was lost. The results of LOH analyses of 17q in eight tumors showing partial or interstitial deletions are summarized schematically in Fig. 2a. Two distinct regions commonly deleted in ovarian carcinomas were identified; one was a region between CI17-316 (17q12-q21.1) and CI17-507 (17q21.3) and the other was distal to CI17-516 (q25.1).

We compared the frequency of LOH with age of onset (postmenopausal or premenopausal) and with histopathological types. Although no difference in the frequency of LOH was observed among tumors with respect to the premenopausal or postmenopausal stage of the
Table 1 Loss of heterozygosity on chromosome 17q in ovarian and breast cancers

<table>
<thead>
<tr>
<th>Probe</th>
<th>Chromosomal location</th>
<th>Enzyme</th>
<th>No. of patients tested</th>
<th>Allelic losses/informative cases (%)</th>
<th>No. of patients tested</th>
<th>Allelic losses/informative cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C17-316</td>
<td>q12-21.1</td>
<td>MspI</td>
<td>Serous 15</td>
<td>2/2 (100.0) 0/1 (0.0) 0/0 (0.0) 1/9 (11.1)</td>
<td>85</td>
<td>11/37 (29.7)</td>
</tr>
<tr>
<td>CI17-592</td>
<td>q21.1</td>
<td>EcoRI</td>
<td>14</td>
<td>13 (92.3) 1 (7.7) 0/0 (0.0) 2/4 (50.0)</td>
<td>62</td>
<td>8/18 (44.4)</td>
</tr>
<tr>
<td>CI17-701</td>
<td>q21.3</td>
<td>TaqI</td>
<td>24</td>
<td>14 (58.3) 13 (52.0) 0/0 (0.0) 2/5 (40.0)</td>
<td>232</td>
<td>48/138 (34.8)</td>
</tr>
<tr>
<td>CI17-730</td>
<td>q21.3</td>
<td>TaqI</td>
<td>29</td>
<td>15 (51.7) 14 (48.3) 0/0 (0.0) 2/5 (40.0)</td>
<td>237</td>
<td>36/96 (37.5)</td>
</tr>
<tr>
<td>CI17-507</td>
<td>q21.3</td>
<td>MspI</td>
<td>22</td>
<td>14 (63.6) 11 (49.1) 0/0 (0.0) 2/5 (40.0)</td>
<td>74</td>
<td>7/25 (28.0)</td>
</tr>
<tr>
<td>CI17-533</td>
<td>q21.3</td>
<td>TaqI</td>
<td>22</td>
<td>13 (59.1) 16 (72.7) 0/0 (0.0) 2/5 (40.0)</td>
<td>230</td>
<td>25/93 (26.9)</td>
</tr>
<tr>
<td>CI17-7</td>
<td>q22</td>
<td>PstI</td>
<td>21</td>
<td>8 (38.1) 9 (45.2) 0/0 (0.0) 1/3 (33.3)</td>
<td>87</td>
<td>14/41 (34.1)</td>
</tr>
<tr>
<td>CI17-489</td>
<td>q23</td>
<td>MspI</td>
<td>26</td>
<td>13 (50.0) 11 (42.3) 0/0 (0.0) 3/8 (37.5)</td>
<td>75</td>
<td>10/31 (32.3)</td>
</tr>
<tr>
<td>CM1066</td>
<td>q23</td>
<td>TaqI</td>
<td>28</td>
<td>13 (46.4) 10 (33.3) 0/0 (0.0) 2/10 (20.0)</td>
<td>79</td>
<td>12/49 (24.5)</td>
</tr>
<tr>
<td>CI17-516</td>
<td>q25.1</td>
<td>TaqI</td>
<td>29</td>
<td>14 (48.3) 14 (46.4) 0/0 (0.0) 2/21 (9.5)</td>
<td>84</td>
<td>9/31 (29.0)</td>
</tr>
<tr>
<td>CI17-710</td>
<td>q25.3</td>
<td>TaqI</td>
<td>18</td>
<td>13 (72.2) 10 (55.6) 0/0 (0.0) 3/7 (42.9)</td>
<td>80</td>
<td>13/45 (28.9)</td>
</tr>
</tbody>
</table>

**DISCUSSION**

We have described a detailed analysis of LOH at loci on chromosome 17q in ovarian and breast cancers, and have constructed deletion maps of tumors. Two distinct, commonly deleted regions were identified in primary tumors from either of these tissues, implying that two tumor suppressor genes for ovarian and breast cancers may be present on chromosome 17q. One of these genes lies between loci 17p13 and 17q11.1, while the other is an interval at 17q21.3 between two loci defined by markers C17-701 and CI17-730; this segment corresponds to the region indicated by deletion mapping of ovarian cancers, but it is smaller.

Linkage analysis based on genotypes of 40 CEPH 3 generation families (16, 17) provided an estimated genetic distance of 2.4 cM between two markers CI17-701 and CI17-730, implying a physical distance of 2000–3000 kilobases. Because this region is suspected of containing a gene responsible for the early-onset type of familial breast cancer, we compared the frequencies of LOH among tumors developed in premenopausal versus postmenopausal patients. As shown in Table 2, no significant difference could be attributed to menopausal status.
DELETION ON CHROMOSOME 17 IN OVARIAN AND BREAST CANCERS

A

Fig. 2. Schematic representation of partial deletions on chromosome 17q in ovarian (A) and breast (B) cancers. Top abscissa, case numbers; left ordinate, probe names; LOH; retention of both alleles; vertical bars on the right of each mapping panel, two commonly deleted regions.

Table 2 Correlation of LOH at chromosome 17q21.3 with menopausal status

<table>
<thead>
<tr>
<th>Status</th>
<th>Frequency of LOH at chromosome 17q21.3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ovarian cancer</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>7/20 (35.0)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>49/120 (40.8)</td>
</tr>
</tbody>
</table>

Table 3 LOH on chromosome 17q21.3 in serous versus nonserous ovarian carcinoma

<table>
<thead>
<tr>
<th>Histological type</th>
<th>LOH on 17q21.3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Loss</td>
</tr>
<tr>
<td>Mucinous</td>
<td>4</td>
</tr>
<tr>
<td>Serous</td>
<td>15</td>
</tr>
<tr>
<td>Clear cell</td>
<td>1</td>
</tr>
</tbody>
</table>

* Calculated by Fisher's exact test.

CI17–516 and CI17–710 at 17q25.1–25.3. The other locus, lying between CI17–701 and CI17–730 at 17q21.3 in breast cancers, falls within a larger region commonly deleted in ovarian cancers (between CI17–316 and CI17–507 at 17q12–21.3). The two loci flanking this 2.4-cM proximal common region of deletion have shown close genetic linkage in 40 CEPH families to loci that are tightly linked to the putative tumor suppressor gene responsible for familial ovarian and breast cancers (4–13). Hence, it is likely that this region contains a gene responsible for both sporadic and familial forms of breast and ovarian cancers. However, although linkage has been demonstrated only in families with early-onset type of breast cancer, we saw no difference in the frequency of LOH in this region among sporadic tumors developed in premenopausal or postmenopausal patients.

In ovarian cancers, a significant difference in the frequency of LOH at 17q21.3 was observed among three histopathological groups; i.e., tumor of the serous type showed LOH more often than did mucinous or clear cell types. These results are similar to those we reported earlier for chromosome 6q, where LOH was frequently observed in the serous type but not in other histological types of ovarian cancers (1, 18). We suggest that these three types of tumor may have different etiological mechanisms and that tumor suppressor genes on 6q and 17q may be associated specifically with development or progression of the serous type of ovarian carcinoma.

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REFERENCES


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