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 CI17-701 and CI17-730 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 breast and ovarian 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, 17q, 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.
Tumor 761 had lost one allele at the CI 17-701 locus but retained the deletion map indicated two distinct regions that were commonly exact test). We have also examined the correlation between LOH of CI 17-710 locus. The results of LOH analyses of the 35 tumors show allele at CI17-710 had been lost. On the other hand, tumor 853 had tumor 807 retained heterozygosity at the CI 17-516 locus, while one heterozygosity at a more distal locus. Tumor 189 retained both alleles which revealed partial or interstitial deletions of chromosome 17q. Partial deletions on chromosome 17q in ovarian and breast cancers are summarized in Fig. 2b. 88 (41.1%) showed LOH at one or more loci on chromosome 17q and the clinical stage of the patients, but no significant correlation was observed (data not shown).

LOH on Chromosome 17q in Primary Breast Cancer. Among 246 primary breast tumors examined with the same 11 RFLP markers on chromosome 17q, 214 were informative for at least one locus, and 246 primary breast tumors examined with the same 11 RFLP markers was observed (data not shown).

patients (Table 2), the difference in the frequency of LOH among three histological types was significant (Table 3); 15 (60%) of 25 serous types showed LOH with at least one marker, while four of 14 mucinous types or one of 12 clear cell types revealed LOH (serous versus mucinous, P = 0.060; serous versus clear cell, P = 0.003 by Fisher’s exact test). We have also examined the correlation between LOH of 17q and the clinical stage of the patients, but no significant correlation was observed (data not shown).

LOH on Chromosome 17q in Primary Breast Cancer. Among 246 primary breast tumors examined with the same 11 RFLP markers on chromosome 17q, 214 were informative for at least one locus, and 88 (41.1%) showed LOH at one or more loci on chromosome 17q (Table 1). Fig. 1b shows examples of Southern blots of tumor DNAs which revealed partial or interstitial deletions of chromosome 17q. Tumor 761 had lost one allele at the CI17-701 locus but retained heterozygosity at a more distal locus. Tumor 189 retained both alleles at the CI17-701 locus but had lost one allele at the CI17-730 locus; tumor 807 retained heterozygosity at the CI17-516 locus, while one allele at CI17-710 had been lost. On the other hand, tumor 853 had lost one allele at the CI17-516 locus but retained heterozygosity at the CI17-710 locus. The results of LOH analyses of the 35 tumors showing partial or interstitial deletions on 17q are summarized in Fig. 2b. The deletion map indicated two distinct regions that were commonly deleted: one was between CI17-516 (17q25.1) and CI17-710 (17q25.3), the same distal region of deletion detected in ovarian cancer; the other was an interval at 17q21.3 between two loci defined by markers CI17-710 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 (lod score of 33.7), 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.

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 defined by...
DELETION ON CHROMOSOME 17 IN OVARIAN AND BREAST CANCERS

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; O, 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>6/17 (35.3)</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>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Loss</td>
<td>Retained</td>
</tr>
<tr>
<td>Mucinous</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Serous</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Clear cell</td>
<td>1</td>
<td>11</td>
</tr>
</tbody>
</table>

* Calculated by Fisher's exact test.

C117–516 and C117–710 at 17q25.1–25.3. The other locus, lying between C117–701 and C117–730 at 17q21.3 in breast cancers, falls within a larger region commonly deleted in ovarian cancers (between C117–316 and C117–507 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 might 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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