EDITORIAL

Loss of Heterozygosity in Breast Cancer: Cause or Effect?

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In an excellent report in this issue of the journal, Ali and colleagues describe the loss of heterozygosity of genes on the short arm of chromosome 3 (3p) in human breast cancer (1). They localize the region of interest to 3p at the loci of c-erbAβ and c-erbA2—members of the steroid/thyroid hormone receptor family. Deletions on 3p have also been found in small cell lung cancer (2-4) and in renal cell carcinoma (5,6) and are consistent with a model of tumor-suppressor genes as a cause for both inherited and sporadic forms of particular cancers (7). It is not surprising that genetic abnormalities were found by Ali and associates, since Trent's excellent review of cytogenetic alterations in human breast cancer (8) indicates that most breast cancers have cytogenetic abnormalities, particularly on chromosomes 1, 3, 6, 7, and 11. Indeed, in previous publications, Ali and co-workers (9) and other investigators (10) have described the loss of heterozygosity of several genes on chromosome 11 in primary breast tumors, and their findings have been consistent with the cytogenetic abnormalities reviewed by Trent.

The important issue is whether the described loss of heterozygosity is causative in the development of breast cancer, a progression change in a fraction of breast cancers, or merely an incidental deletion occurring in abnormal mitoses. Two reports (4,11) have shown that the random loss of a chromosome in a specific tumor type had occurred in 5%-25% of the tumor DNA samples examined. However, one suspects that when the rate of loss of heterozygosity rises above this background level, the chromosomal deletion is significant. For example, the 3p deletion is universal in small cell lung cancer (2-4) and appears in approximately 85% of renal cell carcinomas (5,6).

Ali et al. found loss of alleles on 3p in 25 of 84 heterozygous individuals. Discounting individuals whose DNA is not informative (not heterozygous) for 3p markers between DNF1552 and RAF1, the percentage of breast cancers showing 3p deletion would be much less than 50%. Allele loss for chromosome 13 in small cell lung cancer, however, shows a gradient of loss peaking at the retinoblastoma susceptibility locus (Naylor S: unpublished observations), and damage to the RB-1 locus is characteristic of small cell lung cancer (12,13) (Hansel CH, Naylor SL: unpublished observations). Similarly, allele loss from chromosome 17p in colorectal carcinoma peaks at the p53 locus, which has been clearly mutated in the few tumors examined (14). Allele loss in excess of 50% from chromosome 17p in breast cancer has been reported (15,16). Consequently, an apparently low frequency of allele loss could become a very significant loss as appropriate probes are developed. Alternatively, one can envision that loss of any growth regulatory gene might give the tumor an advantage, even if it is not specific.

A causal relationship between certain genetic deletions and the development of breast cancer is suggested by study results from Anderson and colleagues (17), who looked at loss of heterozygosity on chromosome 1p34-p36. This loss was most frequent in patients with a strong family history of breast cancer (60%), diagnosis before age 45 (70%), or multiple tumors or foci (50%). Furthermore, a genetic study in 17 families with familial occurrence of breast and ovarian cancers (18) supports a causative role of chromosome 1p.

A similar claim has been made for loss of heterozygosity of 1q23-q32 (19).

Other chromosomes implicated in the pathogenesis of breast cancer include chromosome 13. Lundberg et al. (20) studied 10 cases of ductal breast cancer. They observed two cases of specific loss of heterozygosity at three distinct loci along the length of chromosome 13; one case of loss of alleles on chromosomes 2, 13, 14, and 20; and one case of loss of heterozygosity on chromosomes 5 and 13. Subsequent studies examining the retinoblastoma gene on chromosome 13 in breast cancer patients (21,22) revealed deletions or alterations in a significant number of primary tumors.

In view of the evidence of cytogenetic lesions in breast cancer and the development of specific gene probes for such a variety of chromosomes, what should we conclude regarding the causal relationship of these genetic abnormalities and the development of breast cancer? One suspects that if appropriate probes were used for each chromosome, abnormalities would be found in most chromosomes. In fact, this appears to be the case in colorectal carcinoma.

Vogelstein and associates (11) comprehensively studied polymorphic DNA markers from every nonacrocentric autosomal arm in 56 paired colorectal carcinomas and adjacent normal colonic mucosa specimens. They found that allelic deletions were remarkably common, that one allele of each polymorphic marker tested was lost at least in some tumors, and that some tumors lost more than one-half of the parental alleles tested. In addition to allelic deletions, new DNA fragments not present in normal tissue were identified in some carcinomas. And finally, patients with more than the median percentage of allelic deletions had a considerably worse prognosis.

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Thus, the increased burden of multiple genetic changes can influence the behavior of colorectal carcinomas. A major implication of this study is that the large number and variety of genetic losses in established carcinoma tissue are such that it may be presumptuous to assume a causal role in breast cancer development for any one low-frequency chromosomal loss of heterozygosity. Highly focused genetic linkage studies of familial breast cancer are required to identify the genes that are causal in the development of breast cancer.

References


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