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Loss of heterozygosity in fibrocystic change

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Keywords

Apocrine metaplasia, breast cancer, fibrocystic change, loss of heterozygosity

Introduction

The morphological entities classed as fibrocystic change of the breast are common in women, and evidence of their relationship to breast cancer is equivocal. Different authors have reported that fibrocystic change may either be a risk factor, a precursor, or have no association with subsequent malignancy. The findings of loss of heterozygosity (LOH) in benign breast epithelium associated with normal terminal duct lobular units (TDLUs) and premalignant proliferative lesions have raised questions regarding the significance of this phenomenon in breast development, and the relationship of these lesions to breast tumorigenesis.

Aims

To characterize the frequency of LOH in fibrocystic change and to investigate genetic relationships between benign and malignant breast disease.

Comments

Apocrine metaplasia in the breast is controversial. Some hypotheses regarding a possible relationship between apocrine epithelium and carcinoma have been proposed. The apocrine epithelium may be a precursor of malignant transformation; it may reflect a response to the same stimulus which promotes carcinoma or it could indicate an instability of the breast epithelium, which causes the development of alterations with a higher propensity for cancer. The findings here that foci of apocrine metaplasia may share a genetically altered precursor cell with an associated carcinoma provide intriguing and contentious evidence that, occasionally, a direct progression from apocrine metaplasia to carcinoma may occur.

Methods

Cases of fibrocystic change (n = 32) were studied for LOH at 14 chromosomal loci. Individual foci of epithelial cells, representing normal TDLUs, ductal hyperplasia, adenosis and apocrine metaplasia, were isolated from surrounding tissue by microdissection, resulting in a total of 90 specimens. In all cases, there was no concurrent carcinoma present. A further 14 cases of invasive carcinoma with adjacent apocrine metaplasia were also studied.

Results

LOH was observed in 6 out of 27 normal TDLUs, 4 out of 23 adenosis, 4 out of 21 hyperplasias, and 10 out of 19 apocrine metaplasias. LOH in at least one microdissected specimen was seen in 21 of the 32 cases. Seven of the cases with invasive carcinoma with apocrine metaplasia showed LOH with at least one marker, and also shared LOH between the apocrine metaplasia and the associated carcinoma.

Discussion

Allelotyping data revealed that even in normal breast epithelium, and in the absence of cancer, LOH can be detected in approximately 20% of specimens. The distribution of LOH events among the 90 specimens studied can be interpreted as evidence for nonrandom occurrence of LOH. In particular, LOH was detected at a high frequency in apocrine metaplasia. The finding of cases of invasive carcinoma associated with apocrine metaplasia showing identical LOH at one or more loci provides suggestive evidence for a common precursor cell containing genetic abnormalities which can develop into both lesions.

References

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