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Isochromosome 5p, A Novel Recurrent Abnormality in Breast Cancer: Is it a Common Abnormality in Cancer?

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Abstract. *Background: The detection of recurring genetic changes in breast cancer can be extremely difficult. The tumors display very complex structural chromosomal rearrangements the origin of which are often very difficult to estsablish. The identification of recurrent chromosomal changes is a useful strategy for understanding tumorigenesis and specific chromosomal associations. Isochromosome i(5p) is a frequent finding in several types of cancer but it has been rarely described in breast cancer. The aim of the present study was to investigate the presence of i(5p) in primary breast tumors. Materials and Methods: Sixteen cases of breast cancer were cytogenetically studied by direct culture of cancerous cells and G-banding technique. We focused on structural aberrations of chromosome 5 in order to identify the presence of i(5p) in breast cancer. Results: All the cases presented complex chromosomal changes with hyperploidization and various unidentified marker chromosomes being the prominent finding. Among 16 cases studied 6 cases presented an i(5p). No other structural abnormalities of chromosome 5 could be identified. Conclusion: The presence of i(5p) in breast tumors suggests that this chromosomal abnormality plays an important role in the development of breast cancer. Isochromosome 5p needs to be further molecularly analyzed as a candidate region for the isolation of genes related to carcinogenesis. Moreover, the fact that i(5p) has been described in several different tumor types suggests that there are no fundamental tissue-specific differences in the genetic mechanisms leading to tumorigenesis.*

Cytogenetic studies of breast cancer have been hampered by technical difficulties and the complexity of karyotypes. The detection of recurring genetic changes in breast tumors can be extremely difficult. The tumors display complex karyotypes with polyploidization and structural chromosomal rearrangements the origin of which are often very difficult to establish. Despite the advantages of molecular cytogenetic techniques, conventional cytogenetics continue to be a valuable tool in cancer cytogenetics detecting the presence of non-random chromosomal breakpoints and facilitating the identification of genes implicated in tumorigenesis (1-5). The presence of isochromosomes is a frequent finding in several types of cancer (6-9). In a previous cytogenetic stydy, i(5p) was described as a novel recurrent abnormality in ovarian cancer (7). Isochromosome i(5p) is also a frequent finding in bladder cancer and carcinomas of the cervix uteri but it has been rarely described in breast cancer (8, 10, 11). The aim of the present study was to investigate the presence of i(5p) in primary breast tumors using the G-banding technique.

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Materials and Methods

The G-banding technique was employed to review primary breast tumors cytogenetically in our laboratory. Sixteen cases were examined, the cytogenetic findings of which have not been previously published. None of the patients had received either chemotherapy or radiotherapy prior to the cytogenetic study. Further clinical data regarding tumor biological behavior or disease outcome were not available for the cases studied. A small portion of each resected tumor was directly processed for cytogenetic evaluation. The material from the primary tumor was first converted into a cell suspension by mincing the tissue with scalpels. Cancerous cells derived from the tumors were immediately placed into direct culture in Mc Coy's 5A medium supplemented with fetal calf serum and colchicine. The cell suspension was incubated for 90 minutes at 37˚C, then exposed to hypotonic treatment and fixation. The preparations were processed by the trypsin-giemsa banding technique. As many cells as possible were analyzed in each case and not fewer than 15. An abnormal clone was defined as two or more cells with the same structural anomaly. Chromosomal aberrations were designed according to the International System for Human Cytogenetic Nomenclature (ISCN 1995) (12). Since in our previous study (7), i(5p) was described as a novel recurrent chromosomal abnormality in ovarian cancer, the presence of an i(5p) abnormality in breast cancer was investigated. The study was approved by the local Ethical Committee.

Results

All the cases presented complex karyotypes with hyperploidization and various unidentified marker chromosomes being the prominent finding. We focused on structural aberrations of chromosome 5 in order to identify the presence of i(5p) in breast cancer. Among 16 cases studied, 6 cases presented an i(5p) (Figure 1). No other structural abnormalities of chromosome 5 were identified.

Discussion

Breast cancer is the most prevalent malignant disease in women worldwide. Carcinogenesis is a multistep process characterized by genetic changes that influence key pathways involved in cell growth and development. Over the past three decades, advances in cytogenetics and molecular genetics have increased substantially our ability to detect genetic changes in cancer cells and to assess their role in cancer development and progression. Conventional cytogenetics have revealed complex unbalanced chromosomal abnormalities in breast adenocarcinomas. Despite the complexity of changes, i(1q), i(6p), translocations of 1q and 16p, deletions of 1p, 3p, 6q, 11q and 17p have emerged as recurrent abnormalities. Moreover, comparative genomic hybridization (CGH) data have shown the most common genomic imbalances in breast cancer to be gains of 1q, 8q, 17q, 20q and losses of 8p, 13q, 16q and 18q (5,13-14).

The presence of isochromosomes is a frequent finding in several types of cancer and in a few of the cases studied, they have been described as the sole anomaly (15-16). Regarding i(5p), studies have shown that it is a frequent finding in bladder cancer and carcinomas of the cervix uteri (8,10-11,17). Furthermore, in a previous cytogenetic study, i(5p) was described as a novel recurrent abnormality in ovarian cancer (7). However, i(5p) has rarely been described in breast cancer. To the Author's knowledge, only four breast cancer cases with i(5p) and complex karyotypes have been described to date (8,18-19). In the present study, the presence of i(5p) in primary breast tumors using the G-banding technique was investigated in 16 cases. i(5p) was observed in 6 cases. Thus, the present data support the notion that i(5p) may be a novel recurrent abnormality in breast cancer.

The formation of isochromosomes and their possible role in cancer development remains unknown. These chromosomal abnormalities may represent either primary, pathogenetically essential, changes or secondary evolutionary aberrations. Regarding i(14q), Strefford *et al*. (20) reported that i(14q) may be important for bladder carcinogenesis. Although the molecular events underlying the production of isochromosomes in cancer are unknown, the breakpoints could involve specific cancer-related genes contributing to carcinogenesis. Regarding carcinomas of the cervix uteri, in which i(5p) is a frequent abnormality, loss of heterozygosity for the loci on 5p has been reported, possibly suggesting that loss of tumor suppressor genes on 5p may be of importance in cervical carcinomas. On the other hand, the formation of an i(5p) in cancer could result in gene duplication having a similarly important role in carcinogenesis (10, 21).

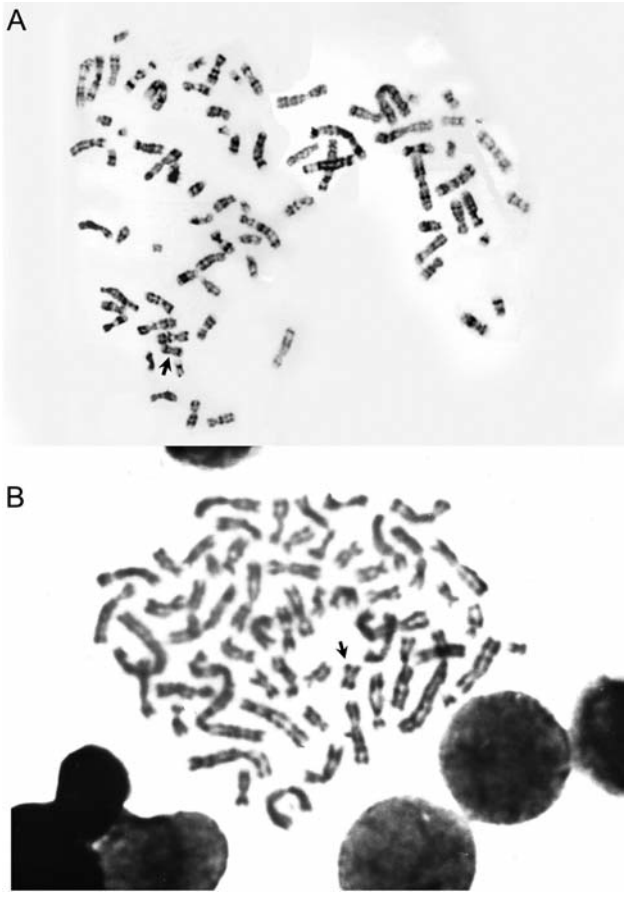

Figure 1. *A, B. Metaphases from two cases of primary breast tumors; arrows indicate i(5p).*

The chromosomal changes in some carcinomas may be recurrent but they usually lack diagnostic specificity. However, the detection of recurrent chromosomal breakpoints in cancer is of major importance contributing to the identification of genes important in carcinogenesis. Therefore, the presence of i(5p) in breast tumors might suggest that it plays an important role in the development of breast cancer and needs to be further molecularly analyzed as a potential candidate region for the isolation of genes related to carcinogenesis. Moreover, the fact that i(5p) has been observed in several different tumor types might support the concept that genetic mechanisms leading to initiation or progression of neoplasia are common within tumors of different tissue origin.

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