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CGH of invasive breast cancer

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Keywords

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Introduction

Comparative genomic hybridization (CGH) provides a powerful method for identifying DNA copy number changes. Recently it has been shown that ductal carcinoma *in situ* (DCIS) is a genetically advanced lesion in which differences in morphology are mirrored by the variability of the associated genetic alterations. However, little is known about genetic changes and their correlation with specific morphological subtypes in invasive breast cancer.

Aims

To establish a model for the possible progression from the different subtypes of DCIS to invasive breast cancer.

Comments

This is a very good paper that adds further evidence to the hypothesis that breast cancer develops through several different genetic pathways. The frequent presence of 16q losses in low grade but not high grade breast tumours suggests a sequential progression is rather unlikely. Furthermore, the presence of 16q loss in low grade lesions suggests it may have a role in the very early manifestation of breast carcinogenesis.

Methods

Fresh frozen tissues from 77 cases of breast carcinoma were investigated. They comprised 40 invasive ductal, 14 lobular, 6 tubular, 9 tubulo-lobular and 8 mucinous carcinomas. Oestrogen and progesterone

status was determined using immunohistochemistry. For each case 10 tissue sections were cut and DNA was extracted using proteinase K digestion followed by phenol-chloroform extraction. For CGH analysis the tumour DNA was labelled by a standard nick-translation reaction with biotin-16-dUTP. Labelled DNA fragments were purified by applying column chromatography. Digital image analysis and karyotyping were then performed. Furthermore fluorescence *in situ* hybridization (FISH) was carried out on three grade 3 invasive ductal carcinomas with 16q losses using probes specific for centromere 11 and 11q13.

Results

DNA copy number changes were present in most breast cancers with an average of 6.7 aberrations per case (range 0-20). The most frequent changes were losses of 8p, 13q and 16q and gains of 1q, 3q, 8q, 1q and 20q. Amplifications were detected in 25 (32%) cases, most frequently at 11q13, 17q12 and 20q13. Grade 1 well differentiated carcinomas averaged 3.6 aberrations per case and amplifications were detected in 18%. The most frequent changes identified were at 1q (55%), 8q (27%) and 16q (45%). Tubular and tubulo-lobular carcinomas had a similar average number of aberrations, rate of amplifications and losses and gains of 16q and 1q respectively. The grade 2 tumours contained an average of 6.4 aberrations with 25% showing amplifications. The chromosome regions most commonly affected were 1q (65%), 3q (25%), 8p (25%), 8q (21%), 13q (20%) and 16q (55%). The poorly differentiated grade 3 tumours averaged 8.4 aberrations per case, 38% revealing amplifications. The most frequent chromosomal alterations were losses of 8p (46%) and 13q (31%) and gains of 1q (88%), 3q (34%), 8q (73%), 17q (46%) and 20q(31%).FISH analysis on three grade 3 ductal carcinomas with 16q losses demonstrated aneuploidy and in one case amplification of 11q13. Losses at 16q were predominantly found in hormone-positive tumours whereas oestrogen receptor-negative tumours showed gains of 1q,3q,8q,17qand 20q and losses of 13q.

Discussion

The existing classification of invasive breast cancer is reflected by specific combinations of quantitative and qualitative genetic changes. In addition, the distinct subtypes of breast cancer show genetic alterations that are similar to those observed in DCIS subtypes classified according to nuclear grade and cell polarisation. Losses of 16q and gains of 1q are associated with well differentiated DCIS and invasive carcinoma, whereas gains of 11q13 and 17q12 are associated with poorly differentiated DCIS and invasive carcinoma.

References

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