PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

*BRCA2*overexpression in breast cancer

ArticleInfo		
ArticleID	:	3637
ArticleDOI	:	10.1186/bcr-1999-66615
ArticleCitationID	:	66615
ArticleSequenceNumber	:	57
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	3
ArticleHistory	:	RegistrationDate : 1999–10–5 OnlineDate : 1999–10–5
ArticleCopyright	:	Current Science Ltd1999
ArticleGrants	:	
ArticleContext	:	1305811

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Keywords

BRCA2, breast carcinoma, quantitative RT-PCR, sporadic tumours

Introduction

Germ-line mutations in the breast cancer susceptibility gene *BRCA2* appear to be responsible for around 20% of hereditary breast cancers. Like *BRCA1*, *BRCA2* is not frequently mutated in sporadic breast carcinomas, although high frequencies of loss of heterozygosity (LOH) at these loci point to a role in the pathogenesis of these tumours, possibly by a mechanism other than structural mutation.

Aims

To investigate *BRCA2* gene expression in sporadic breasttumours by quantitative reverse transcriptase polymerase chain reaction(RT-PCR).

Comments

The roles of the breast cancer susceptibility genes *BRCA1* and *BRCA2* in sporadic breast carcinomas are unclear. Only a small percentage of sporadic breast tumours appear to carry somatic mutations in the *BRCA2* gene, despite the fact that 30-40% of sporadic breast cancers show LOH at this locus. The idea that there is another critical gene at 13q12-q13 remains plausible, and *BRCA2* may be inactivated by a mechanism other than somatic mutation. The data presented here indicate a role for *BRCA2* in the pathogenesis of sporadic breast tumours associated with overexpression, although the mechanisms by which this tumour suppressor gene exerts a positive effect on cell proliferation remain to be determined. The thought that up-regulation of *BRCA2* may be a protective response, and *BRCA2* expression status may have prognostic significance, is deserving of further investigation.

Methods

Primary breast tumours from 127 patients were analysed, and classified by standard clinicopathological and biological factors. *BRCA2* mRNA expression was characterised by quantitative reverse transcriptase (RT)-PCR. LOH analysis was also carried out with four polymorphic microsatellite DNA marker loci flanking *BRCA2* on chromosome 13q12-q13.

Results

BRCA2 mRNA expression showed wide variation in the tumour samples analysed. Fourteen tumours (11%) showed underexpression, and 25 (20%) showed overexpression. *BRCA2* mRNA overexpression correlated significantly with histopathological grade III, and was mainly attributed to nuclear pleomorphism and mitotic index. No other links between *BRCA2* expression and clinicopathological and biological factors were found to be statistically significant. No relationship was observed between LOH at 13q12-q13 and *BRCA2* mRNA expression.

Discussion

In this series of 127 primary breast cancers, both underexpression and overexpression of *BRCA2* mRNA was observed. The overexpression of *BRCA2* demonstrated here was linked with histopathological grade III, suggesting a role in the aggressiveness of breast tumours. In particular, *BRCA2* overexpression correlated with the extent of genetic changes in tumours (nuclear pleomorphism) and the proliferation rate (mitotic index). This *in vivo* data is consistent with *in vitro* results showing an up-regulation of *BRCA2* mRNA in rapidly proliferating cells. Disruption of *BRCA2* expression was not due to the loss of one allele as determined by LOH experiments, suggesting the possibility of another key tumour suppressor gene at the 13q12-q13 locus that plays an important role in breast cancer.

References

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