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# Aromatase polymorphisms and breast cancer risk

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## Keywords

Aromatase, CYPD19, polymorphism

# Introduction

The role of oestrogens in the development of breast cancer, and oestrogen exposure in risk of the disease, is well accepted. In principle low penetrance genes involved in oestrogen biosynthesis could increase breast cancer risk. One such gene is CYPD19, which encodes the enzyme P450 aromatase. Polymorphic sites in this gene have been correlated with breast cancer risk, with some variation in results between different studies in different countries.

# Aims

To study possible associations between common polymorphisms in the CYPD19 gene and breast cancer risk in the British population.

# Comments

There is much speculation about the existence and importance of polymorphisms or low penetrance genes that may increase the risk of the carrier's developing cancer. This study fails to find any risk associated with common alleles of CYPD19, which encodes P450 aromatase, within a British population. Nevertheless such studies are important, especially if they go on to indicate regional variation in the preponderance of important alleles. Whether further evidence of these or other aromatase gene polymorphisms will be more conclusive in defining risk remains to be seen.

# Methods

Subjects were selected from both prospective (288 patients) and retrospective (384 patients) series and matched to the same number of anonymous controls from the EPIC study (Day N *et al*: EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. *Br J Cancer* 1999;**80**[suppl]:95-103).

Genotyping was performed by PCR, gel electrophoresis, single strand conformational polymorphism and sequence analysis.Results were statistically analysed.

# Results

Eight alleles of the [TTTA]n repeat in intron 4 were observed, including a [TTTA]7 repeat associated with a TCT deletion (50 bp upstream). In sequence analysis of 17 cancer samples (34 alleles) no Arg264Cys polymorphism in exon 7 was found. A novel G to T change (105 bp upstream of exon 7, T allele frequency 0.45) in intron 6 was discovered, as was an extra A (89 bp upstream of exon 7, all samples).

Linkage disequilibrium demonstrated a strong linkage between [TTTA]7 and the TCT deletion and between the intron 6 G to T polymorphism and the [TTTA]n tract. Subsequently three common haplotypes account for 98% of all those seen.

No significant differences between genotype distributions were found between cases and controls. None of the previously reported associations with breast cancer risk were found for alleles studied in this series. This was also true if postmenopausal cases only (>55 years) were studied.

A meta-analysis of four studies of the [TTTA] repeat alleles showed borderline (non-significant) evidence of an increased risk associated with [TTTA]12 and [TTTA]n on allele 2. A significant risk was seen for carriers of the [TTTA]10 allele. However, this allele is quite rare (0.6%) and there is evidence of heterogeneity between studies.

# Discussion

Variants of the CYPD19 gene that effect oestrogen biosynthesis are attractive candidates for alleles affecting breast cancer risk. However, the only variant known to result in an amino acid change (exon 7 Arg264Cys) is not related to breast cancer risk in Japan and is rare in the British population studied here (although the sample size does not allow study of low penetrance genes). Other reported variant alleles are unlikely to directly affect aromatase activity.Although linkage disequilibrium found between two polymorphisms in intron 4 and one in intron 6 results in three common haplotypes, none of these was associated with breast cancer risk. It is possible that other polymorphisms that are not in linkage disequilibrium with the [TTTA]n repeat are related to risk.

This study fails to confirm risks previously reported for [TTTA] repeat alleles. The [TTTA]10 repeat demonstrated to carry a significant risk in meta-analysis is very rare and unlikely to have any impact on public health.

These results do not exclude the possibility that other common variants of CYPD19 exist that do effect oestrogen metabolism and breast cancer risk.

## References

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