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Variants in estrogen-biosynthesis genes *CYP17* and *CYP19* and breast cancer risk: a family-based genetic association study

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Abstract

Background Case-control studies have reported inconsistent results concerning breast cancer risk and polymorphisms in genes that control endogenous estrogen biosynthesis. We report findings from the first family-based association study examining associations between female breast cancer risk and polymorphisms in two key estrogen-biosynthesis genes *CYP17* (T→C promoter polymorphism) and *CYP19* (TTTA repeat polymorphism).

Methods We conducted the study among 278 nuclear families containing one or more daughters with breast cancer, with a total of 1123 family members (702 with available constitutional DNA and questionnaire data and 421 without them). These nuclear families were selected from breast cancer families participating in the Metropolitan New York Registry, one of the six centers of the National Cancer Institute's Breast Cancer Family Registry. We used likelihood-based statistical methods to examine allelic associations.

Results We found the *CYP19* allele with 11 TTTA repeats to be associated with breast cancer risk in these families. We also found that maternal (but not paternal) carrier status of *CYP19* alleles with 11 repeats tended to be associated with breast cancer risk in daughters (independently of the daughters' own genotype), suggesting a possible *in utero* effect of *CYP19*. We found no association of a woman's breast cancer risk either with her own or with her mother's *CYP17* genotype.

Conclusion This family-based study indicates that a woman's personal and maternal carrier status of *CYP19* 11 TTTA repeat allele might be related to increased breast cancer risk. However, because this is the first study to report an association between *CYP19* 11 TTTA repeat allele and breast cancer, and because multiple comparisons have been made, the associations should be interpreted with caution and need confirmation in future family-based studies.

Keywords: breast cancer, cyp17, cyp19, estrogen biosynthesis genes, family-based design

Introduction

Cumulative exposure to circulating estrogen is considered to be of primary importance in breast cancer etiology. Estrogen biosynthesis, cellular binding and metabolism involve many steps, and the genes controlling these steps may contribute to inherent variability in breast cancer susceptibility. Endogenous estrogen is produced predominantly in the ovarian theca cells in premenopausal women and in the breast stromal adipose cells in postmenopausal women. The present study focuses on *CYP17* and *CYP19*, two key genes that control the biosynthesis of estradiol and estrones from their lipid precursors and are expressed in these cells. CYP17 controls two successive early steps of endogenous estrogen biosynthesis by converting pregnenolone and progesterone to precursors of androgen and estrogen. CYP19, also known as aromatase, controls the terminal step of estrogen biosynthesis by converting 19-

FGAP = Family Genetic Analysis Program; FS = founder statistic; MNYR = Metropolitan New York Registry; NFS = nonfounder statistic; PCR = polymerase chain reaction; TDT = transmission disequilibrium test.