Cancer

Epidemiology 11: Genetic Epidemiology of Breast, Prostate, and Gynecologic Cancers: Hormone and Carcinogen Metabolism

Polymorphisms in the estrogen metabolism genes CYP17, CYP1B1, CYP1A2, COMT and ER alpha and susceptibility to primary intracranial brain gliomas in women

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DOI: Published April 2004

Proc Amer Assoc Cancer Res, Volume 45, 2004

Abstract

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We evaluated the associations of polymorphisms in genes important in estrogen metabolism with the risk of glioma in women. Several such polymorphisms have been linked to susceptibility to other cancers in women. A 5' variant in *CYP17A1* (-34T>C) may be important in regulating estrogen synthesis. Single nucleotide polymorphisms (SNPs) in *CYP1B1* (L432V) and *CYP1A2* (IVS1-154, A>C) affect metabolism of estrogens to catechol estrogens, which are further oxidized to genotoxic quinones. A SNP-induced amino acid change in *COMT* (V158M) influences enzyme activity of the gene product, which deactivates potentially genotoxic catechol estrogens. A SNP in *ESR1* (IVS1-397, C>T) may affect estrogen binding to ERα, altering gene transcription. We evaluated these polymorphisms as risk factors for glioma in women in the Upper Midwest Health Study, a population-based case-control study of rural residents of four states with high glioma incidence. Cases (n=341) were identified by hospitals, private physicians, and registries. Controls (n=527) were stratified samples of licensed drivers and Medicare enrollees.

Questionnaires elicited occupational and environmental exposures. DNA was isolated from blood from 135 cases and 251 controls and TaqMan methodology used to characterize genotypes. We assumed the genotype homozygous for the at-risk allele was the at-risk genotype. Unadjusted analyses showed no statistically significant associations between polymorphisms and glioma risk: *CYP17A1* CC, 14 % of controls and 16% of cases, odds ratio [OR] 1.1, 95% confidence interval [CI] 0.6-2.0; *CYP1B1* val/val, 19% of controls and 28% of cases, OR 1.6, CI 1.0-2.6; *CYP1A2* AA, 52% of controls and 51% of cases, OR 1.0, CI 0.6-1.5; *COMT* met/met, 29% of controls and 27% of cases, OR 0.9, CI 0.6-1.5; and *ESR1* CC, 22% of controls and 24% of cases, OR 1.1, CI 0.6-1.8. To determine if the polymorphisms were risk factors under specific exposure conditions, participants were stratified by smoking, alcohol use, farm residence/job, post-menopausal status in 1993, hormone replacement therapy if post-menopausal, and estrogenic pesticide exposure. Adjusted odds ratios for *CYP17A1* (-34T>C), *CYP1A2* (IVS1-154, A>C), *COMT* (V158M), and *ESR1* (IVS1-397, C>T) polymorphisms were not elevated. Multivariate logistic regression of all five polymorphisms plus farm status, smoking and alcohol use found a persistent increased risk associated with *CYP1B1* val/val (OR 1.6, CI 0.9-2.8). However, polymorphisms in estrogen metabolism genes do not appear to have a strong association with glioma risk in women. Genes for proteins interacting with other hormones may have a greater effect. Future analyses will include polymorphisms in additional genes encoding enzymes important in carcinogen metabolism, DNA repair, cell cycle control, and immune function, and additional occupational exposures.

American Association for Cancer Research

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April 2004
Volume 64, Issue 7 Supplement
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