A Functional Polymorphism in Catechol-O-Methyl Transferase Gene Explains Increased Risk of Uterine Leiomyomas in Black Americans

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Introduction: Uterine leiomyomas (fibroids) are the most common tumors in premenopausal women. Numerous clinical and biochemical observations suggest that initiation/promotion of leiomyomas is associated with estrogenic influence. The catechol-*O*-methyltransferase (COMT) enzyme is central in estrogen metabolism pathway. We aimed to investigate whether polymorphisms in COMT gene are associated with increased risk of uterine leiomyomas.

Methods: We identified 186 women with surgically and histologically-confirmed uterine leiomyomas and 142 matched controls with normal uteri. We analyzed the functional polymorphism Val(158)Met in exon III of the COMT gene using PCR/RFLP. The Valine-to-Methionine substitution is associated with a four fold decrease in enzymatic activity.

Results: The COMT Val/Val genotype was associated with significantly increased risk of uterine leiomyoma in all ethnic groups (black, white, and Hispanics). Overall, women with COMT Val/Val genotype were 2.5 times (confidence limits 1.017-6.151) more likely to have uterine leiomyomas than other genotypes. The overall prevalence of Val/Val genotype was significantly higher in black women (47%) than whites (19%) or Hispanics (30%) (P=0.003). Val/Val myometrial cell lines exhibited significantly enhanced response to estrogen in proliferation and ERE-Luceiferase (Luc) reporter assays compared to Met/Met counterparts. Myometrial specimens from Val/Val women demonstrated distinct gene expression of several E2-regulated genes when compared to matched Met/Met tissues including; increased expression of COX2, Cyclin D1, PR-A, PR-B, Bcl2, and decreased expression of Bax, a profile consistent with higher estrogenic milieu. COMT-specific inhibitors arrested growth and attenuated ERE-Luc reporter tranactivation in leiomyoma cells. This effect was mediated, at least in part, by activation of apoptosis and inhibition of cell cycle regulating genes.

Conclusion: These results suggest that COMT Val/Val genotype might be one of the genetic risk factors for uterine leiomyoma development. The higher prevalence of this genotype in blacks might, at least in part, explain the increased occurrence of this tumor among black women.