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Title: Age dependent association of common polymorphisms in estrogen metabolism genes with breast cancer risk.

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The majority of epidemiological factors used to clinically evaluate breast cancer risk are influenced by endogenous estrogen exposure. Estrogen and its related metabolites affect breast carcinogenesis by serving both as promoters of ductal epithelial cell growth and mutagenic precursors. Common polymorphisms (SNPs) in several genes, *COMT* (A→G, rs4680), *CYP1A1* (T[m1]→C[m2], rs4646903), *CYP17* (T[A1]→C[A2], rs743572) and *SULT1A1* (G→A, rs928861), that significantly impact estrogen metabolism have been associated with breast cancer risk in some studies, but the associations of these polymorphisms with risk remain unclear. In the present study, associations of these four SNPs in estrogen metabolism genes were examined in a single large case-control study of 4,556 Caucasian women, consisting of 1,530 breast cancer cases and 3,026 cancer-free controls. In overall unadjusted analyses, only the *CYP17* C/C genotype was significantly associated with breast cancer risk (OR = 1.2, p = 0.05). When analyses were adjusted for personal history measures (PHMs) significant association with breast cancer risk was observed for carriers of the *COMT* G allele (OR = 1.2, p = 0.02), but the *CYP17* association no longer reached significance (p = 0.08). Age stratified (30-44, 45-54 and ≥ 55) analyses identified significant associations in all four SNPs in the youngest age group (*COMT* [G/*], OR = 1.4, p = 0.02; *CYP17* [C/C]; OR = 1.3, p = 0.05; *CYP1A1*[C/*], OR = 0.7, p = 0.04; *SULT1A1* [A/*], OR = 0.7, p = 0.001). Interestingly, carrying the *SULT1A1* A allele was associated with decreased risk in the younger group (OR = 0.7, p = 0.001) and increased risk in the older age group (OR = 1.3, p = 0.01). Overall these data suggest that the impact on breast cancer risk for these polymorphisms is strongly influenced by age and their influence on risk may shift with the hormonal and metabolic changes that occur over a lifetime. A logistic regression based model incorporating only these four SNPs provided a 2.7-fold stratification of risk between the upper and lower deciles in women ages 30-44. Addition of PHMs to this model improved the stratification of risk to 5.8-fold. Thus, the four SNPs examined in this study are informative for evaluating breast cancer risk in the younger age group.