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Title: Age-dependent association of common polymorphisms in conjugation enzyme genes with breast cancer risk.

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Genes for enzymes that catalyze conjugation reactions involving sulfation (*SULT1A1*), methylation (*COMT*) or glucuronidation (*UGT1A7*) may influence breast carcinogenesis by regulating levels of metabolic intermediates that can act as mutagenic precursors, DNA damaging agents or promoters of ductal epithelial cell growth. Common SNPs in *SULT1A1* (G→A, Arg²¹³His), *COMT* (A→G, Val¹⁵⁸Met), and *UGT1A7* (AA→CG, Arg¹³¹Lys) cause non-synonymous amino acid substitutions that alter enzymatic activity and may influence breast cancer risk. The possible association of these functional polymorphisms with risk was examined in a large study of 6,778 Caucasian women, consisting of 2,321 breast cancer cases and 4,457 cancer-free controls. In overall analyses, only *COMT* was marginally associated with increased breast cancer risk. However, age-stratified analyses using three age groupings (30-44, 45-54 and ≥ 55) identified several statistically significant associations. An age-dependent reversal in risk associations was clearly observed for *SULT1A1* where carriers of the A-allele were at decreased risk (OR = 0.8, p = 0.01) in the younger group and increased risk (OR = 1.2, p = 0.05) in the older group. Similarly for *UGT1A7*, CG-carriers exhibited increased risk in the younger group (OR = 1.2, p = 0.02) and decreased risk (OR = 0.8, p = 0.01) in the older group. *COMT* G-carriers were at increased risk (OR = 1.3, p = 0.01) in the younger group and this tapered to no significant associations in the middle and older groups. Further analyses done in decade increments identified significant risk associations for polymorphisms in all of these genes at certain ages. Examining these results from the perspective of activity levels, higher activity genotypes were associated with increased risk at the younger ages, leveled out to no association at middle age and were associated with decreased risk at older ages. Thus, these conjugation enzyme gene polymorphisms exhibit strong age-dependent associations with breast cancer risk. The observed impact of age on association of these polymorphisms with risk offers a potential explanation for the difficulties encountered in repeating association results in smaller case-control studies.