Letters to the Editor

Hormone-Metabolizing Genotypes: An Alternate Interpretation

To the Editors: In a recent article by Rebbeck et al. (1), the authors reported that a pairwise combination of two sets of genotypes: CYP1A1*2C and SULT1A1*2, and CYP1A2*1F and SULT1E1 A were each associated with breast cancer etiology. Although the article was otherwise excellent and from a distinguished laboratory, they narrowly interpreted or perhaps misinterpreted their results as being consistent with a role for the formation of catechol estrogens by CYP1A1 and CYP1A2 and the detoxification of estrogens and catechol estrogens by SULT1A1 and SULT1E1, the latter of which can be oxidized to catechol quinones that form low levels of primarily depurinating DNA adducts with relatively low mutagenic potential.

First of all, SULT1A1 has little or no activity for these hormones at physiologic concentrations (2). Second, the authors have overlooked an alternate hypothesis that has considerable support in the literature. The most mass-abundant food-borne heterocyclic amine, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), which is a known mammary carcinogen in rodents and has been specifically implicated as a breast cancer risk factor in the Iowa Womens’ Health Study (3), is initially bioactivated by CYP1A2 or detoxified by CYP1A1 (4), and then finally activated by SULT1A1 and SULT1E1 (5, 6) to form a stable DNA adduct that is found at high levels in human breast epithelium (7, 8). CYP1A2 is a major cytochrome P450 in the liver that generates high levels of the circulating N-hydroxy metabolite. CYP1A1 is expressed primarily in extrahepatic tissues, and whereas it can form N-hydroxy-PhIP, it forms primarily the detoxified 4'-hydroxy-PhIP. Both SULT1A1 and SULT1E1 are present in the breast and can convert N-hydroxy-PhIP absorbed from the circulation to reactive metabolites that form a C8-deoxyguanosine-DNA adduct with high mutagenic potential. Thus, as found in this study (1), CYP1A1*2C (high inducibility) and SULT1A1*2 (low activity) would represent important detoxification events, whereas CYP1A2*1F (high inducibility) and SULT1E1 A (normal activity) would represent at-risk genotypes.

Accordingly, the article may have been better titled “Pairwise combinations of PhIP metabolism genotypes in postmenopausal breast cancer etiology” instead of “Pairwise combinations of estrogen metabolism genotypes in postmenopausal breast cancer etiology”.

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References
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