Letters to the Editor


Letter

Stephen S. Hecht
University of Minnesota Cancer Center, Minneapolis, Minnesota 55455

The paper by Chen et al. (1) proposes to test the hypothesis that individuals with reduced levels of CYP2D6 (debrisoquine 4-hydroxylase) activity will have a lower risk of anogenital cancer associated with exposure to the tobacco-specific nitrosamine NNK.1 NNK is a potent carcinogen associated with tobacco-induced cancers in humans. Their rationale is that CYP2D6 can metabolically activate NNK to intermediates that bind to DNA and initiate carcinogenesis. Therefore, individuals with lower activity will have lower risk. In my opinion, this hypothesis is weak because CYP2D6 is an ineffective catalyst of NNK metabolic activation.

The role of CYP2D6 in NNK metabolic activation has been investigated directly in three studies. In the first, Crespi et al. (2) showed that a B-lymphoblastoid cell line stably expressing CYP2D6 cDNA activated NNK to a mutagen, but the activity was substantially less than that of similar cell lines expressing CYP2A3 and CYP1A2 and was similar to a cell line expressing CYP2E1. In a second study, the metabolism of NNK was investigated using cell lysate protein from HepG2 cells in which 12 human CYP forms—1A2, 2A6, 2B7, 2C8, 2C9, 2D6, 2E1, 2F1, 3A3, 3A4, 3A5, and 4B1—were expressed (3). CYP1A2 had, by far, the highest activity; that of CYP2D6 was the same as control HepG2 cells. In the third study, a new cell line containing two CYP2D6 transcriptional cassettes and having 3-fold higher CYP2D6 activity than that used in the first study was used to analyze NNK metabolism and mutagenicity (4). NNK mutagenicity was again observed, but the turnover number for NNK metabolism was relatively low, leading the authors to conclude that “one would expect a minor role for CYP2D6 in human hepatic metabolism of NNK.” Collectively, these studies demonstrate that CYP2D6 is a relatively poor catalyst of NNK metabolic activation. Currently, available evidence indicates that human CYP1A2, 2A6, 3A4, and 2E1 are substantially better catalysts of NNK metabolic activation than CYP2D6 (5).

The relationship between CYP2D6 activity and lung cancer is inconsistent and inconclusive, based on a large number of published studies (6). The study of Chen et al. (1) indicates that there is no relationship between CYP2D6 activity and anogenital cancer. These findings do not detract from the potential importance of NNK in tobacco-induced cancer at these sites because CYP2D6 is not an effective catalyst of NNK metabolic activation.

References


Reply

Chu Chen, Linda S. Cook, Xiao-Yan Li, Sarah Hallagan, Margaret M. Madeleine, Janet R. Daling, and Noel S. Weiss

Fred Hutchinson Cancer Research Center, Seattle, Washington [C. C., M. M. M., J. R. D., N. S. W.]; University of Calgary, Calgary, Alberta, Canada [L. S. C.]; Brigham and Women’s Hospital, Boston, Massachusetts 02115 [X.-Y. L.]; and University of Washington, Seattle, Washington [S. H., N. S. W.]

We believe that it was reasonable for us to have investigated the possibility that differences in CYP2D6 genotype could be associated with differences in risk of anogenital tumors (1)—and for others to have done similar studies of lung tumors—even with the knowledge that CYP1A2, 2A6, 2E1, and 3A4 have been shown to activate NNK1 to a greater or equal extent than CYP2D6 in B-lymphoblastoid (2, 3) and HepG2 (4) cell lines. This is because: (a) The relative importance of metabolism of NNK by the liver versus that by the anogenital tissues is unknown at this time. Because of the short half-lives of NNK metabolites, metabolism of NNK in target tissue might be quantitatively important. (b) The relative concentrations of CYP2D6, 1A2, 2A6, 2E1, and 3A4 in anogenital tissues are unknown at present, making it difficult to predict the relative importance in NNK activation of these enzymes.

We agree with Hecht’s conclusion that our “findings do not detract from the potential importance of NNK in tobacco-

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1 The abbreviation used is: NNK, 4-(methylamino)-1-(3-pyridyl)-1-butanone.

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induced cancer” (5). We tried to say as much in our article (1), i.e., that “… enzymes other than CYP2D6, such as CYP2A6 and CYP2E1, are capable of metabolizing nitrosamines” and that, our findings notwithstanding, it is likely that “tobacco-specific nitrosamines play a role in the etiology of anal and vulvar cancers.” Unfortunately for us, it has been easier to identify this hypothesis involving other P450 enzymes than it has been to convince a reluctant study section that we should be awarded funds to test it.

References


Stephen S. Hecht


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