Editorial

Dietary Isothiocyanates as Confounding Factors in the Molecular Epidemiology of Colon Cancer


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In this issue, Lin et al. (1) show convincing statistics that subjects exposed to dietary broccoli who have a GSTM1 null phenotype are less susceptible to colon cancer than those who are GSTM1 positive. The expected effect of a GSTM1 null phenotype is greater, not less, susceptibility to cancers due to reduced carcinogen detoxification by GSTM1 (2, 3).

Broccoli reverses this outcome for two reasons: (a) it contains sulforaphane, a cancer chemopreventive isothiocyanate (4) that present evidence indicates both inhibits cytochrome P450 (and therefore carcinogen activation) and induces GSTs, consequently increasing carcinogen detoxification (5–7); and (b) sulforaphane is itself a substrate for GSTs, which may abolish its anticarcinogenic activity (8, 9). Because Lin et al. suggest that their findings are the consequence of reduced conjugation of sulforaphane among GSTM1 null subjects (1), this commentary will attempt to assemble data available relating to this hypothesis to assess its validity.

Their study has an interesting practical outcome because dietary isothiocyanates have rarely, if ever, been taken into account in investigations of the molecular epidemiology of cancer, and it is probable that they have been confounding factors in a number of studies (3) and should be borne in mind in the design of future protocols.

Lin et al. (1) have observed a significant effect of a broccoli diet on susceptibility to colon cancer, even without taking into consideration exposure to specific colon carcinogens. To analyze the processes upon which their findings might be based, it is necessary to select a known colon carcinogen and consider the influence of the broccoli diet and its constituent sulforaphane upon the amounts of N-acetoxy-PhIP leaving the liver. GSTM1 uses sulforaphane as a substrate and, when present, reduces levels of sulforaphane available for the inhibition of the activation of N-acetoxy-PhIP and the induction of its detoxification. The following facts concerning GSTM1-dependent metabolism of isothiocyanates are important for the understanding of the results of the report by Lin et al. (1).

The metabolic reaction is reversible, and the rate and $K_m$ of both conjugate formation and its reversion are greater with GSTM1 than with GSTA1. As a result, GSTM1 converts sulforaphane to the GSH conjugate more rapidly than does GSTA1. Consequently, GSTM1 makes more sulforaphane available for excretion via the GSH pump. In contrast, GSTA1 sequesters the conjugate and catalyzes its reversion to sulforaphane at a slow rate. Sufficient kinetic data for the GSH conjugation of sulforaphane and other chemopreventive analogues such benzyl and

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2 The abbreviations used are: GSTM1, GSTA1, and GSTA2, glutathione S-transferase M1, A1, and A2, respectively; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine; GSH, reduced glutathione; BPDE, benzo[a]pyrene-7,8-diol-9,10-oxide.
phenylethyl isothiocyanates are not available to make a critical kinetic analysis possible (8, 9). However, the present view is that in the GSTM1-positive subject, the conjugation and excretion of sulforaphane is favored, with resulting diminution of chemoprevention. In the GSTM1-null individual, sulforaphane tends to be conserved as GSTA1-sequestered conjugate and converted slowly to the active isothiocyanate. Using benzyl isothiocyanate and GSTA1 as a model system, it has been calculated that at equilibrium ~1% is present as the un conjugated isothiocyanate (9). It is apparent that the targets responsible for control of expression of the enzymes concerned are very reactive and are affected at low doses of isothiocyanate. As mentioned above, studies with human hepatocytes in primary culture show that the major effect is on gene expression (4) rather than directly upon the enzymes.

The findings of reduced risk of colon adenomas among high consumers of broccoli who are GSTM1 null by Lin et al. (1) may explain some of the inconsistencies in studies of the effect of GSTM1 genotypes on susceptibility to cancer (3). The revelation of an unexpected confounding factor in the diet serves to illustrate the extremely complex mechanism and multiple factors involved in carcinogenesis and the important challenges in the field of molecular epidemiology.

References
Dietary isothiocyanates as confounding factors in the molecular epidemiology of colon cancer.

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