Dietary Mutagens and the Risk of Breast Cancer

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In this issue of the Journal, Zheng et al. (1) report a positive association between the preference for well-done red meat and risk of postmenopausal breast cancer. Using color photographs of hamburger, bacon, and beefsteak showing increasing levels of doneness (from extremely rare to very well done), women who selected a cooking preference for ‘‘very well done’’ for each of these foods had a risk nearly five times higher than that for women who consistently selected a preference for rare/medium cooking. Overall consumption of red meat itself had only a weak association with risk, and white meats, including chicken, turkey, and fish, were not statistically significant risk factors regardless of cooking method.

The specific findings to meat preparation tends to rule out saturated fat as the causative factor and is consistent with the possibility that mutagens, including heterocyclic amines, formed during high-temperature cooking of meats may be mammalian carcinogens in humans.

The browned and charred surface of meats contains a hash of laboratory carcinogens. Among these are the heterocyclic amines, formed through chemical reactions involving amino acids. The formation of heterocyclic amines requires high temperatures, such as are found in radiative or conductive cooking (e.g., grilling or frying) but not as a rule in indirect convection (e.g., roasting) or boiling (e.g., poaching or steaming) methods (2). These substances are capable of inducing tumors in a number of species (2) and are reportedly among some of the most powerful mutagenic agents, based on the Ames test (3).

Heterocyclic amines involving creatinine as a precursor are numerically most important. Among these, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) predominates, accounting for approximately one half of the total heterocyclic amine intake in the U.S. diet. Five compounds, i.e., PhIP, 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx), 2-amino-3-methylimidazo[4,5-f]quinoxaline (IQ), and 2-amino-9H-pyrido[2,3-b]indole (AaC), make up approximately two thirds of the total intake (4). Based on animal bioassay data, the relative mutagenic potency of these compounds varies by a factor of more than 20, with IQ and DiMeIQx at the high end, PhIP and AaC at the low end, and MeIQx at an intermediate level of potency (4). Thus, the absolute concentration of specific heterocyclic amines in foods must be weighed against their individual potential for genetic damage when they are evaluated as potential human carcinogens. Major dietary sources of these compounds vary from population to population depending on a number of factors, including cultural mores and meat availability. In a study of female registered nurses (5), the major predictor of PhIP in the diet was grilled or broiled chicken, whereas the chief source of DiMeIQx was pan-fried steak.

In the study by Zheng et al. (1), the absence of an association for chicken and fish is unexpected assuming that heterocyclic amines are causal in breast cancer, since these meats in some data contain among the highest levels of heterocyclic amine compounds. Exposure from chicken would depend heavily on whether the meat was cooked with the skin and if the cooked skin was actually eaten. Not taking these factors into account may have obscured associations for chicken in the authors’ data.

Meat and meat-cooking preferences have been investigated in previous studies of breast cancer, and a few studies have found suggestive associations. Those that have examined intensity of cooking have tended to show positive associations (6–8), although this is not a universal finding (9). In a prospective study from Finland (6), there was a statistically significant el-
evation in risk of breast and other hormone-dependent cancers with increasing consumption of fried meats but not meat cooked by other methods. A case–control study in Uruguay (8), where breast cancer rates are notably high for a developing country and per capita meat consumption exceeds that of the United States, showed a consistent pattern of excess risk for fried and broiled red meat, but not for boiled meat or fish or poultry, which were inversely related to the risk. Other lines of evidence undermine the claim of a major effect of meat or meat cooking on breast cancer risk. For example, consumption of monounsaturated fat, which in the U.S. diet is derived primarily from red meat, is unrelated to the risk of incident breast cancer in prospective studies (10).

The findings of Zheng et al. (1) should be interpreted with caution, given some potentially important limitations. Information on meat cooking was gathered after the diagnosis of breast cancer in the case subjects; thus, the study was vulnerable to differential recall between case and control subjects. In a study of recall bias within the Nurses’ Health Study (11), of all food groups and nutrients assessed, the strongest evidence of recall bias was found for the consumption of red meat, although this finding was not replicated in a similar study (12). Zheng et al. argue that bias in recall related to cooking preference would, if anything, run in the opposite direction, given the widely publicized health hazards of eating undercooked meats. Still, the format of the questionnaire and the pictorial displays showing varying degrees of meat blackening (as opposed to redness of the flesh) would leave little doubt concerning the hypotheses under study.

An additional and related issue was the rather poor response rates among the case subjects (60%). Better response rates among the control subjects (75%) undoubtedly resulted from the restriction among the control subjects to respondents to the 1992 follow-up questionnaire, which may have selected for a more compliant and possibly more health-conscious group of women as controls. (No similar restriction was placed on case subjects, who needed only to have answered the baseline questionnaire in 1986.)

A final comment relates to the results shown in Table 4 of the study by Zheng et al. (1). Rare-to-medium cooking of meats produces only small amounts of mutagen; thus, no dose–response gradient for level of intake would be expected in the rare/medium category, as was observed. However, among those potentially exposed through their preference for highly cooked or overcooked meat, the actual consumption of the food should predict risk, which was not demonstrated in these data. (The relative risk comparing the highest to lowest tertile for intake was 1.17 [3.01/2.57].) This suggests either considerable mismeasurement error in reported intake of cooked meats or that other influences, such as recall bias, may have contributed to the meat preference associations.

The present results are certain to encourage a flurry of epidemiologic research into the role of heterocyclic amines in breast cancer. There is evidence of extensive variability in the intake of these substances within populations, which should make it possible to identify associations if they exist. So far, no studies have validated questionnaire-based heterocyclic amine consumption with a biomarker of carcinogenicity such as DNA adducts, and the optimal set of questions for quantifying exposure is not established and may vary from population to population. The exposure of interest is the actual consumption of the offending foods, yet in these results doneness preference was more important. This implies that reporting of intake according to cooking type may be difficult for most people, indicating the need for large, carefully done studies enhanced by visual aids or biomarkers of heterocyclic amine intake such as urinary metabolites of these compounds. There is evidence that red meat consumption is a risk factor for colon cancer, particularly among those individuals who are rapid acetylators in the metabolism of heterocyclic amines as determined by their genotype for the enzyme N-acetyltransferase 2 (13,14). Acetyltransfer status has not been associated with breast cancer overall (15,16), although it may modify risk associated with cigarette smoking (15), a source of heterocyclic amine exposure. One study (9) did not find a statistically significant interaction of meat consumption with acetylator status in breast cancer, although more research in this area is needed.

In summary, these data demonstrate an association of breast cancer with the preference for well-done meat. No association was observed for the actual consumption of these foods, the relevant exposure. This inability to connect a direct measurement of exposure to risk weakens any assertions regarding causality that may be drawn from these data. Pending more conclusive research, public awareness should be aimed at the known risks associated with undercooking meats, which include serious illness and even death in susceptible persons.

REFERENCES

(11) Giovannucci E, Stampfer MJ, Colditz GA, Manson JE, Rosner BA, Long-


