Introduction

Epidemiologic studies have implicated exposure to tobacco smoke and high intakes of cooked, broiled, or well-done meats in the increased risk of colorectal cancers (1-4). Microsomal epoxide hydrolase (mEH) is a phase II biotransformation enzyme which detoxifies epoxides, including carcinogens such as polycyclic aromatic hydrocarbons found in cigarette smoke and cooked meats (5). A tyrosine to histidine substitution in exon 3 (Y113H) of the mEH gene decreases in vitro enzyme activity by 40%, whereas a histidine to arginine substitution in exon 4 (H139R) increases in vitro enzyme activity by 25% (6). Smaller epidemiologic studies evaluating the relationship between the mEH polymorphisms and risk of colorectal cancer and its precursors have been inconclusive (7-9). We evaluated the risk of colon cancer associated with both the mEH Y113H and H139R genotypes in a large case-control study.

Materials and Methods

Methods for selection of cases and controls and data collection have been described in detail elsewhere (10-12). Briefly, participants were subjects from the Kaiser Permanente Medical Care Program of Northern California, an eight-county area in Utah, and the metropolitan Twin Cities area of Minnesota. Eligibility criteria have been previously described (10). Controls who had never had a previous colorectal tumor were selected from Kaiser Permanente Medical Care Program membership lists in California; driver’s license lists, random-digit-dialing, or Centers for Medicare and Medicaid Services lists for Utah; and driver’s license or state identification lists in Minnesota. Centers for Medicare and Medicaid Services lists for Utah; and driver’s license lists, random-digit-dialing, or Kaiser Permanente Medical Care Program membership lists for California; driver’s license lists, random-digit-dialing, or

mEH Genotyping. The mEH Y113H, H139R polymorphisms were detected using the 5’ nuclease assay on a 7900HT sequence detection system (Applied Biosystems, Foster City, CA). Primers and probes and PCR core reagents were purchased from Applied Biosystems. The assays were validated by genotyping 100 individuals by both 5’ nuclease assay and RFLP or sequencing. There were no discrepancies between the two assays. Genotyping was done in 20 µL reactions containing 1× Taqman PCR core reagents 4 mmol/L MgCl2, 200 nmol/L primers (Y113H: 5’CTGGAAGAGCACGAGTGG-AGCAGTGGAGATT3’, 5’TGGCTGCGCTTTTTGCAA3’; H139R: 5’TCCACCTGACTGTCTTG3’, 5’TGGAGATGTGGCTGATCTTTAAACACTCTAGAA3’), 100 nmol/L probes (Y113H: VIC-5’TCAACAGATACCCCTACT3’-NFQ; H139H: 6FAM-5’AACAGACACCTCTACT3’-NFQ; H139R: VIC-5’CAGGCCATACCCCGA3’-NFQ; and 3 ng DNA. Amplification cycles were 50°C for 5 minutes, 95°C for 10 minutes, and 40 cycles of 95°C for 15 seconds and 60°C for 60 seconds. Positive controls for all the genotypes and reagent controls were included in each plate. Genotyping of 94 randomly selected samples was repeated for each polymorphism. There were no discrepancies.

Statistical Methods. Unconditional logistic regression models were used. Multivariate adjustment included age, sex, body mass index (kg/m²), vigorous physical activity index (13), regular use of aspirin or nonsteroidal anti-inflammatory drugs, and usual number of cigarettes smoked per day. This study had 90% power to detect an odds ratio (OR) of 1.4 for the main effect comparing homozygous wild-type mEH 113YY with homozygous variant mEH 113HH genotype, and 80% power to detect an OR of 1.4 for the equivalent comparison within the H139R genotype.

Results

Of 4,403 eligible participants with valid data for the study, 3,553 participants with available DNA (1,593 cases and 1,960 controls) were genotyped for both the mEH Y113H and H139K polymorphisms. Characteristics of the study population have been described elsewhere (14). Genotype frequencies for both the Y113H and H139K polymorphic sites were in Hardy-Weinberg equilibrium among the controls and among the cases, and did not vary significantly between cases and controls. Frequencies for both the Y113H and H139K polymorphic sites were in Hardy-Weinberg equilibrium among the controls and among the cases, and did not vary significantly between cases and controls. Frequencies for both the Y113H and H139K alleles (0.27 for cases; 0.32 for controls) and H139K allele (0.17 for cases; 0.22 for controls) are consistent with previously reported genotype frequencies (7, 8, 15-19).

Risks of colon cancer associated with the Y113H and H139K genotypes, combined genotypes, and imputed phenotypes as proposed by Smith and Harrison (19) are summarized in Table 1. Greater usual number of cigarettes smoked increased risk of colon cancer overall, especially when restricted to microsatellite instability-positive colon cancers; however, tests for trend did not identify significant differences by mEH Y113H or H139R genotypes. The risk estimates did not vary significantly when stratified by total

null results in brief

Microsomal Epoxide Hydrolase Polymorphisms Are Not Associated with Colon Cancer Risk

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Cancer Epidemiology, Biomarkers & Prevention 2005;14(5):1350–1. Published on April 13, 2017. DOI: 10.1158/1055-9965.EPI-04-0354

Grant support: NIH research grants CA84998, CA59045, and CA61757 and National Cancer Institute training grant R25 CA94880 (K. Robien).

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Harrison et al. (7), Sachse et al. (9), and Mitrou et al. (8) all found the Y113H genotype to be associated with a decreased risk of colorectal cancer. However, among smokers, Mitrou et al. reported an increased risk of colorectal cancer. Both Sachse et al. (9) and Harrison et al. (7) reported a significant difference in Y113H genotype frequencies between cases and controls, suggesting that Y113H genotype may be a susceptibility factor in the development of colorectal cancer. These findings of an altered risk were not confirmed in our study.
Studies of adenomatous polyps, possible precursors of colorectal cancer, have similarly failed to find an association between mEH genotype and risk of polyps. However, some have observed interactions with smoking and cooked meat by mEH genotype (15, 16, 23, 24).

We conclude that the mEH Y113H and H139R genotypes do not affect risk of colon cancer, and may only be a factor in the development of adenomatous polyps (earlier stages of colon carcinogenesis) under conditions of elevated carcinogen exposure.

Acknowledgments
We thank Juanita Leija for technical assistance with the mEH genotype determinations.

References
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