Looking Farther Afield

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BERing the Burden of Risk

Base excision repair (BER) is important in maintaining genomic stability through the repair of damage induced through oxidative stress. There are at least four BER genes (*MYH*, *OGG1*, *MIM*, and *MTH1*) that act in concert to repair 8-oxoguanine–associated DNA damage. Of these, biallelic germ line mutations in *MYH* (*MUTYH*) have been identified in patients with hereditary polyposis (1). It remains to be determined, however, whether heterozygous or homozygous mutations in the *BER* gene family modify risk of colorectal cancer in the general population. Farrington et al. (2) evaluated BER germ line mutations in a population-based case-control study of colorectal cancer in Scotland. In addition to questionnaire data collected on diet, family history, and lifestyle, DNA from 2,239 cases and 1,845 age- and sex-matched controls was examined to identify individuals that carried variant *BER* alleles. The investigators used a two-stage approach. Initially, they screened for the two most commonly reported variants in *MYH* (Y165C and G382D). For subjects who were heterozygous at one of these loci, additional screening was done for *OGG1* and *MTH1* variants. All variants were confirmed with sequencing. Newly identified variants were evaluated in at least 340 control chromosomes to rule out common polymorphisms. Remaining variants underwent bioinformatic analysis to determine the potential functional significance of the coded protein. One newly identified variant in this study, *MUTYH* nucleotide 9,639A→G, was subsequently evaluated for functional relevance and was shown to affect splicing in an *in vitro* assay. For all mutations, population genotype relative risks and penetrance were calculated. Eight (0.36%) of the cases were homozygous for G382D and three cases were compound heterozygotes for Y165C/G382D (no case was homozygous for Y165C). One additional case, heterozygous for G382D, manifested the nucleotide 9,639A→G mutation, which results in a mutant G382D transcript. There were no biallelic mutations in the controls. A total of 45 cases and 28 controls had monoallelic (heterozygous) *MUTYH* mutations. Overall, biallelic *MUTYH* mutations carried a 93-fold increased risk (95% confidence interval, 42-213). Biallelic *MUTYH* carriers experienced almost complete penetrance by age 60 years, yet 36% of these cases had no coexisting adenomatous polyps. For monoallelic *MUTYH* carriers, a 68% increased risk (95% confidence interval, 1.1-3.0) was observed for individuals over the age of 55 years. This translates into a population attributable risk of about 1%.

This is an elegantly done study that uses the tools of both epidemiology and biology to test the hypothesis. The authors were relatively circumspect in their conclusion and acknowledge the limitation of relatively low allele frequencies that may hamper selection of cancer susceptibility genes (particularly when there is no *a priori* hypothesis behind selection). The results of this study raise an interesting ethical issue: When does the line between major susceptibility loci and genetic polymorphisms become blurred? Or should we avoid this crude dichotomous classification of risk alleles and move to a more complex nosology (3)? As polymorphisms are identified that have important functional significance, it is plausible that a few may be linked with a higher PAR for certain diseases. When this occurs, it will be necessary to consider the societal and ethical implications that surround genetic susceptibility testing in unaffected populations. For example, in this study, it is possible that at least some of the *MUTYH* monoallelic control carriers will develop colorectal cancer. If this were to occur, the authors may have greatly underestimated the population attributable risk.

A Fish Out of Water Is Better than a Pig in a Poke

High meat intake has been associated with an increased risk of colon cancer in several studies (4). Some studies have implicated red meat (including high-temperature cooked meats), whereas others have implicated processed meats. In contrast, fish consumption has been inversely associated with colon cancer, although less consistently, whereas poultry has shown no relation (reviewed in ref. 5). Norat et al. (5) evaluated the potential association between meat and fish consumption and colon cancer using data from the prospective European Prospective Investigation into Cancer and Nutrition study. This study includes over 500,000 men and women ages 35 to 70 years recruited from 10 European countries during 1992 and 1998. Questionnaires were completed on lifestyle, diet, and medical history. For this analysis, 478,040 were included. Meats were grouped into red meat, processed meat, and poultry. Fish included fresh, canned, salted, and smoked fish. Follow-up was primarily based on population cancer registries, and began at the date of enrollment and ended at the date of diagnosis of colorectal cancer, death, or last complete follow-up. A total of 1,329 participants developed colorectal cancer, of which 95% were histologically verified. Increased red and processed meat intake was associated with an increased risk of colorectal cancer (hazard ratio, 1.57; 95% CI, 1.13-2.17) for highest to lowest consumption, although this was slightly attenuated after adjustment for other covariates. Additional analyses revealed that highest consumption of processed meats (hazard ratio, 1.42; 95% confidence interval, 1.09-1.86) and particularly, pork (P_{trend} = 0.03) was associated with an increased risk. Fish intake was associated with a decreased risk (hazard ratio, 0.69; 95% confidence interval, 0.54-0.88) for highest to lowest intake. Poultry consumption was not associated with risk. These associations (higher risk for red and process meat intake and lower risk for fish intake) persisted even after mutual adjustment in the same model. Taken together, the absolute risk of developing colorectal cancer within 10 years for an individual 50 years of age was 1.71% for high red and processed meat consumers and 1.28% for low consumers. Similarly, the absolute risk was 1.28% and 1.86% for high and low fish consumers, respectively. Because the methods of meat preparation vary greatly among the participating countries, these observations might not be due to cooking methods. The authors speculate that heme found in meats can stimulate endogenous *N*-nitroso compound formation (6), which is associated with carcinogenesis. Further, the inverse association with fish consumption may point to the protection provided by ω-3 fatty acids.

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This is the most convincing cohort study to date to examine these relationships. There are a number of well-designed feeding studies that are examining biomarkers of health risk connected with either fish consumption or meat consumption. Perhaps, such feeding studies will help find the agents underlying these observed associations.

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