Null Results in Brief

Alcohol Dehydrogenase 3 Genotype Is Not Predictive for Risk of Colorectal Cancer[1]

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Introduction

Excess alcohol consumption is associated with higher risk of colorectal cancer (1). A common functional polymorphism in ADH_3,[3] encoding the rate-limiting enzyme converting alcohol to acetaldehyde, has been identified in Caucasian population (2). The ADH_3^{1-1} genotype has more than twice the activity than the ADH_3^{2-2} genotype *in vitro* (2). In epidemiological studies, the fast-metabolizing ADH_3^{1-1} genotype has been associated with increased risk of breast cancer (3), oral cavity, and pharyngeal cancers (4). We hypothesized that this functional polymorphism in ADH_3 would increase the risk of colorectal cancer associated with alcohol consumption.

Materials and Methods

We conducted a nested case control study within the Physicians' Health Study, a double-blind trial of aspirin and β-carotene among 22,071 United States male physicians, of which 93% are Caucasians. Alcohol consumption was derived from baseline questionnaire. Participants were followed through biannual mailed questionnaires. From 1982 to 1995, 211 incident cases of colorectal cancer were identified and confirmed from medical records by the End Point Committee. Men (343) free from diagnosed cancer at the time of case ascertainment were selected as controls who were matched on age ($\pm$1 year) and smoking status (never, past, and current). To increase the statistical power, we included additional 770 control subjects from a separate case control study on myocardial infarction. Together, 211 cases and 1113 controls are included in the study.

Genotyping for ADH_3 was carried out using a PCR-RFLP-based method modified from that of Freudenheim *et al.* (3). Methods for measurement of plasma folate (5) and total homocysteine levels (6) were described previously. Laboratory personnel were blind to case control status.

Analyses yielded nearly identical estimates on case control and combined populations but with greater precision with the latter. Thus, only results from the combined population are reported. Using the most common genotype, ADH_3^{1-1}, as a reference, we calculated RRs and 95% CIs for the association of the ADH_3 genotype with risk of colorectal cancer using unconditional logistic regression adjusting for age, smoking status (never, past, and current), multivitamin use, and aspirin assignment group in the trial. Interaction of alcohol consumption and the ADH_3 genotype was tested by likelihood ratio test. Alcohol consumption was categorized into tertiles based on the distribution of controls with cutoff points: less than or equal to one drink per week, two to four drinks per week, and more than or equal to five drinks per week. Statistical analyses were done using SAS 6.0 statistical package (SAS Institute).

Results

In this population of male physicians, we found no significant differences between cases and controls. In both groups, the distribution of ADH_3 genotype was in agreement with the expected value of Hardy-Weinberg Equilibrium ($P > 0.80$). Compared with the ADH_3^{1-1} genotype, the multivariate-adjusted RR was 0.92 (95% CI: 0.67–1.27) for the ADH_3^{1-2} genotype and 0.83 (95%CI: 0.53–1.31) for the ADH_3^{2-2} genotype (Table 1).

In this population of light drinkers, we observed only a small increase in colorectal cancer risk associated with alcohol consumption (Table 1). Compared with individuals who consumed one drink per week or less, those who consumed two to four drinks per week had a 52% (95% CI: 1.05–2.17) increase in risk, whereas those with five drinks per week or more had a nonsignificant 25% (95% CI: 0.85–1.84) increase in risk. The overall trend for risk associated with alcohol consumption was not significant ($P = 0.23$). The association of cancer risk and alcohol consumption was stronger among individuals with the ADH_3^{2-2} ($P = 0.04$) genotype compared with other genotypes. Using low drinkers with the ADH_3^{1-1} genotype as a reference, low drinkers with the ADH_3^{2-2} genotype had a decreased risk of colorectal cancer (RR: 0.44, 95% CI: 0.16–1.20) whole high drinkers with the ADH_3^{2-2} genotype had an increased risk (RR: 1.63, 95% CI: 0.77–3.45). However, neither modification in risk was significant. The likelihood ratio test for interaction was borderline significant ($P = 0.06$).

Discussion

To the best of our knowledge, this is the first study on the association of ADH_3 polymorphism and risk of colorectal cancer. This prospective study, although moderate in size, has sufficient power (>80%) to detect RR of 1.5 for ADH_3^2 allele (assuming 40% allele frequency) or RR of 1.8 for ADH_3^{2-2}

Revised 9/7/01; accepted 9/24/01.
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[1] Supported by research Grants CA 42182 and CA 87969 from NIH. Dr. Jia Chen was supported by a career development award CA 81750 from the National Cancer Institute.
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[3] The abbreviations used are: ADH_3, alcohol dehydrogenase 3; RR, relative risk; CI, confidence interval.

Table 1 Relationship of alcohol intake and risk of colorectal cancer according to ADH_3 genotype

	Overall	ADH3 Genotype			*P*, trend
		ADH_3^{1-1}	ADH_3^{1-2}	ADH_3^{2-2}	
	RR[a] (95% CI) [No. case, No. control]	RR (95% CI) [No. case, No. control]	RR (95% CI) [No. case, No. control]	RR (95% CI) [No. case, No. control]	
Overall		1.0 (referent) [86, 426]	0.92 (0.67–1.27) [96, 513]	0.83 (0.53–1.31) [29, 174]	0.40
Alcohol consumption (drinks/week)					
≤1	1.0 (referent) [61, 397]	1.0 (referent) [28, 167]	1.09 (0.62–1.91) [28, 162]	0.44 (0.16–1.20) [5, 68]	0.20
2–4	1.51 (1.05–2.17) [84, 369]	1.54 (0.88–2.71) [31, 128]	1.42 (0.84–2.40) [41, 184]	1.38 (0.66–2.90) [12, 57]	0.68
≥5	1.25 (0.85–1.84) [66, 338]	1.31 (0.73–2.35) [27, 127]	1.00 (0.56–1.78) [27, 163]	1.63 (0.77–3.45) [12, 48]	0.94
P, trend	0.25	0.59	0.81	0.04	

[a] RR adjusted for age, smoking status, use of aspirin, and multivitamins.

genotype (assuming 15% genotype frequency). Besides true lack of association, the absence of independent risk associated with the ADH_3 polymorphism may be explained by the limited effect of alcohol, thus, its metabolizing gene on colorectal carcinogenesis. This may also reflect the fact that physicians in this study population only consume moderate alcohol (36% less than or equal to one drink per week), and they are generally well nourished, which may counteract the adverse effects imposed by alcohol on colorectal carcinogenesis.

Despite the absence of independent risk associated the ADH_3 polymorphism, there was an indication of interaction between the ADH_3 genotype and alcohol consumption on risk of colorectal cancer. A dose-response relationship of cancer risk and alcohol consumption was significant only among individuals with the slow ADH_3^{2-2} genotype. However, the reduced risk of colorectal cancer in low drinkers with the ADH_3^{2-2} genotype compared with low drinkers with the ADH_3^{1-1} genotype cannot be easily explained. It may reflect the small sample size of the ADH_3^{2-2} subgroup (29 cases and 173 controls).

In summary, the ADH_3 polymorphism did not confer significant risk of colorectal cancer independently; however, it may modify the association between alcohol consumption and risk of colorectal cancer.

Acknowledgments

We thank the participants of the Physicians' Health Study for their cooperation and participation. We also thank Xiaoyang Liu for programming assistance and Dr. Klaus Lindpaintner for preparation of the DNA.

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