DNA Methyltransferase and Alcohol Dehydrogenase: Gene-Nutrient Interactions in Relation to Risk of Colorectal Polyps

Audrey Y. Jung,[1] Elizabeth M. Poole,[1,2] Jeanette Bigler,[1] John Whitton,[1] John D. Potter,[1,2] and Cornelia M. Ulrich[1,2]

[1]Cancer Prevention Program, Fred Hutchinson Cancer Research Center and [2]Department of Epidemiology, University of Washington, Seattle, Washington

Abstract

Disturbances in DNA methylation are a characteristic of colorectal carcinogenesis. Folate-mediated one-carbon metabolism is essential for providing one-carbon groups for DNA methylation via DNA methyltransferases (DNMTs). Alcohol, a folate antagonist, could adversely affect one-carbon metabolism. In a case-control study of colorectal polyps, we evaluated three single nucleotide polymorphisms (−149C>T, −283T>C, −579G>T) in the promoter region of the *DNMT3b* gene, and a functional polymorphism in the coding region of the alcohol dehydrogenase *ADH1C* gene, *ADH1C* *2. Cases had a first diagnosis of colorectal adenomatous (*n* = 530) or hyperplastic (*n* = 202) polyps at the time of colonoscopy, whereas controls were polyp-free (*n* = 649). Multivariate logistic regression analysis was used to estimate odds ratios (OR) and corresponding 95% confidence intervals (CI). There were no significant main associations between the *DNMT3b* or *ADH1C* polymorphisms and polyp risk. However, *DNMT3b* −149TT was associated with an increase in adenoma risk among individuals with low folate and methionine intake (OR, 2.00; 95% CI, 1.06-3.78, *P* interaction = 0.10). The *ADH1C* *2/*2 genotype was associated with a possibly elevated risk for adenomatous polyps among individuals who consumed >26 g of alcohol/d (OR, 1.95; 95% CI, 0.60-6.30), whereas individuals who were wild-type for *ADH1C* were not at increased risk of adenoma (*P* interaction = 0.01). These gene-diet interactions suggest that polymorphisms relevant to DNA methylation or alcohol metabolism may play a role in colorectal carcinogenesis in conjunction with a high-risk diet. (Cancer Epidemiol Biomarkers Prev 2008;17(2):330–8)

Introduction

Many studies have described associations between low folate intake and higher incidence of colorectal cancer or colorectal polyps (1, 2). Both epidemiologic and experimental studies have shown the importance of folate-mediated one-carbon metabolism in colorectal carcinogenesis (3). Folate functions as a donor of one-carbon units and has several essential functions, including DNA methylation, nucleotide synthesis, and DNA stability and repair (4-7). Other nutrients, such as methionine, are also important in DNA methylation (8). The folate and methionine cycles (see Fig. 1) are critical for providing methyl groups for DNA methylation (4). DNA methylation of CpG sites in the promoter regions (CpG islands) of genes can result in gene silencing. At the same time, ''genomic DNA methylation,'' which largely reflects methylation at repeat sequences and in satellite regions of the DNA, may be important in providing genomic stability (9).

DNA methyltransferases (DNMTs) catalyze the addition of a methyl group (CH_3) to the 5′ position of a cytosine base at CpG sites after DNA synthesis. Five active forms of DNMTs (DNMT1, DNMT2, DNMT3a, DNMT3b, and DNMT3l) have been characterized. DNMT1 is responsible for the maintenance of DNA methylation, whereas DNMT3a and DNMT3b are responsible for *de novo* DNA methylation (10-12). The biological role of DNMT2 in humans is currently unknown (13). DNMT3b is thought to be the most critical for carcinogenesis, and several polymorphisms in this gene have been described and investigated in relation to neoplastic outcomes (14-21).

The most extensively studied *DNMT3b* polymorphism is the −149C>T variant. This single nucleotide polymorphism has been associated with a decrease in breast cancer risk (21), an increased risk of prostate cancer (17) and lung cancer (15), and of developing hereditary nonpolyposis colorectal cancer earlier in life (19). The −149T allele has been associated with increased promoter activity (16) and two studies have shown decreased promoter methylation patterns among cancer patients with the T allele, although this may be considered contrary to the results of the promoter assay (18, 22).

Two other promoter polymorphisms have also been studied in relation to cancer risk. One, −283T>C is in high linkage disequilibrium with −149C>T. This polymorphism has been associated with decreased risk of lung cancer (14); in the same study, the T allele was associated with decreased promoter activity compared with the C allele. The third polymorphism, −579G>T was

Received 9/18/07; revised 11/21/07; accepted 12/5/07.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Cornelia Ulrich, Cancer Prevention Program, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, M4-B402, Seattle, WA 98109-1024. Phone: 206-667-7617; Fax: 206-667-7850. E-mail: nulrich@fhcrc.org

Copyright © 2008 American Association for Cancer Research.

doi:10.1158/1055-9965.EPI-07-2608

Downloaded from cebp.aacrjournals.org on November 30, 2021. © 2008 American Association for Cancer Research.

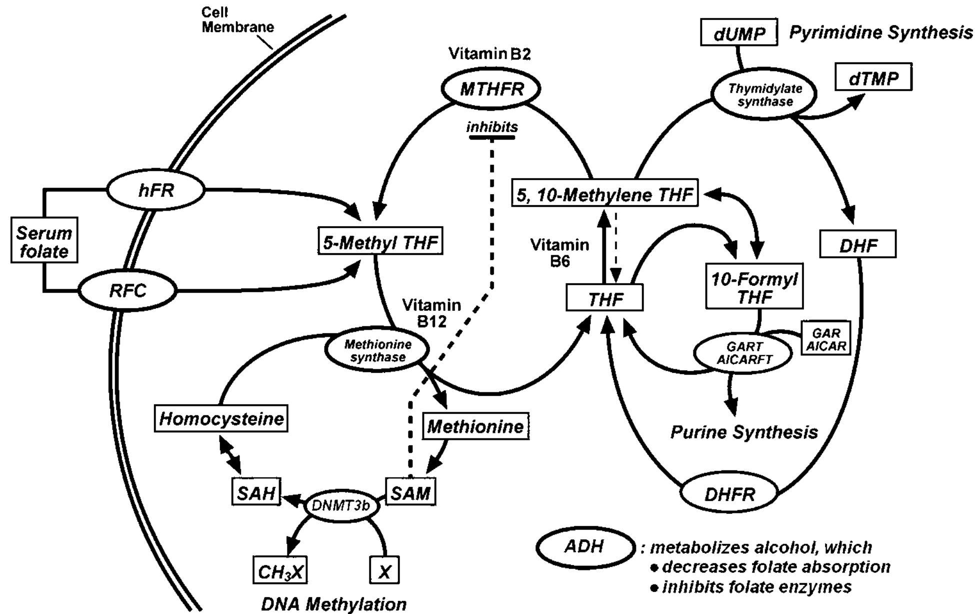

Figure 1. Overview of folate-mediated one-carbon metabolism (simplified). *THF,* tetrahydrofolate; *DHF,* dihydrofolate; *RFC,* reduced folate carrier; *hFR,* human folate receptor; *MTHFR,* 5,10-methylenetetrahydrofolate reductase; *DHFR,* dihydrofolate reductase; *GART,* glycinamide ribonucleotide transformylase; *AICARFT,* 5-amino-imidazole-4-carboxamide ribonucleotide transformylase; *AICAR,* 5-aminoimidazole-4-carboxamide ribonucleotide; *GAR,* glycinamide ribonucleotide; *SAM,* S-adenosylmethionine (AdoMet); *SAH,* S-adenosylhomocysteine (AdoHcy); *dUMP,* deoxyuridine monophosphate; *dTMP,* deoxythymidine monophosphate; *MS,* methionine synthase; *TS,* thymidylate synthase; *ADH,* alcohol dehydrogenase; *DNMT3b,* DNA methyltransferase 3b; *X,* a variety of substrates for methylation.

in complete linkage disequilibrium with the −283T>C polymorphism in the study above (14) and was not associated with changes in promoter activity.

S-adenosylmethionine is the universal donor of methyl groups for a multitude of methyltransferase reactions including DNA methylation (23, 24). The availability of *S*-adenosylmethionine depends on dietary intakes of nutrients such as methionine and B vitamins such as folate, vitamins B_{12}, and B_6 (24, 25). Folate, in the form of 5-methyl-tetrahydrofolate, acts as a methyl donor in the conversion of homocysteine to methionine, in the reaction catalyzed by methionine synthase (Fig. 1; refs. 2, 25). Methionine is subsequently metabolized to *S*-adenosylmethionine. When methionine and choline intake are insufficient, methionine is synthesized endogenously from homocysteine in order to maintain homeostatic levels of *S*-adenosylmethionine (6). Several studies in human and animal models have shown that diets deficient in folate, methionine, and choline could reduce global DNA methylation (5, 6, 26, 27).

In addition to B vitamins and methionine, alcohol intake influences the availability of one-carbon units for DNA methylation. Alcohol antagonizes folate and disrupts many aspects of normal folate transport and metabolism by preventing the release of folate from hepatocytes (28). Moderate-to-high alcohol intake interferes with folate bioavailability (29). Three mechanisms by which excessive alcohol may impede folate bioavailability and metabolism are decreasing dietary folate content, decreasing intestinal absorption of folate, and increasing urinary folate excretion (29). Alcohol affects one-carbon metabolism by inhibiting the methionine synthase reaction causing methionine levels to decrease and homocysteine levels to increase (29, 30). Homocysteine is in equilibrium with *S*-adenosylhomocysteine, a potent product inhibitor of the DNMTs.

Alcohol is oxidized in the liver to acetaldehyde by alcohol dehydrogenase; acetaldehyde is then metabolized to acetate by aldehyde dehydrogenase (31). Many adverse effects of alcohol are attributed to acetaldehyde including increased heart rate, nausea, flush, DNA damage, and possibly, cancer risk (32). Alcohol dehydrogenase is comprised of five subunits encoded on seven genes (33). Variants that influence the conversion of alcohol to acetaldehyde have been described for *ADH1, ADH1B* (also known as *ADH2*), and *ADH1C* (also known as *ADH3*; refs. 34-36). In Caucasians, germ line variants in *ADH1C* are common, whereas variants in *ADH1B* are uncommon (37).

A polymorphism known as *ADH1C* *2 results in a valine substitution at amino acid 350 (I350V); the wild-type amino acid at this position is known as *1. The *ADH1C* wild-type allele (*ADH1C* *1) oxidizes ethanol 2.5 times faster than those encoded by the *ADH1C* variant allele (38). Because of this, it has been hypothesized that fast metabolizers (homozygous for the fast allele of *ADH1C*) of ethanol would have higher levels of acetaldehyde per gram of tissue in the colonic mucosa compared with all other tissues and would therefore be at greater risk for colorectal cancer (36). This polymorphism has been studied for various cancer types, including colorectal cancers (31, 37, 39-41); reviewed in ref. 36 and 42. Most of these analyses investigated the interaction with alcohol intake (31, 33, 37, 39, 41).

Downloaded from cebp.aacrjournals.org on November 30, 2021. © 2008 American Association for Cancer Research.

Gene-nutrient interactions have been repeatedly described for folate-mediated one-carbon metabolism, in which the level of colorectal cancer risk associated with dietary factors depends, in part, on an interaction between exposure and relevant genetic variants (43-46). We investigated three polymorphisms in the *DNMT3b* gene, −149C>T, −283T>C, −579G>T, and a polymorphism in the *ADH1C* gene, *ADH1C* *2 in relation to risk of colorectal adenomas, established precursors of colorectal cancer. In these analyses, we included relevant interactions with one-carbon nutrients such as folate and methionine as well as alcohol intake.

Materials and Methods

Study Subjects. Cases with colorectal adenomatous and/or hyperplastic polyps and polyp-free control subjects were recruited through a large multiclinic private gastroenterology practice in metropolitan Minneapolis. Detailed participant recruitment for this case-control study have been described previously (47). Briefly, patients ages 30 to 74 years, who were scheduled for a colonoscopy between April 1991 and April 1994 were recruited prior to colonoscopy to blind patients and recruiters to the final diagnosis. The study was approved by the internal review boards of the University of Minnesota and each endoscopy site. Written informed consent was obtained. For the present study, the Institutional Review Board of the Fred Hutchinson Cancer Research Center approved all associated activities.

Cases had a first diagnosis of colon or rectal adenomatous (n = 530) or hyperplastic polyps (n = 202) at the time of the colonoscopy. Control subjects were free of polyps at colonoscopy (n = 649). Patients whose colonoscopy did not reach the cecum were ineligible; removed polyps were examined histologically using standard diagnostic criteria (48). The participation rate for all patients who underwent colonoscopies was 68%. Information on the use of nonsteroidal anti-inflammatory drugs, lifestyle factors, anthropometry, demographics, and medical information, including family history of cancer and polyps, was obtained by questionnaire. Dietary intakes over the year prior to polyp diagnosis or reference date was obtained using an adaptation of the Willett semiquantitative food frequency questionnaire, which has been studied previously for validity and repeatability within the Nurses' Health Study cohort (49), the Iowa Women's Health Study cohort (50), and the Health Professionals Follow-up Study cohort (51). In the Iowa Women's Health study, correlation coefficients of this instrument on repeat administration were r = 0.62 for dietary folate, r = 0.67 for vitamin B_{12} intake, and r = 0.99 for alcohol consumption (50). Giovannucci et al. (52) compared food frequency questionnaire values with folate levels measured in red blood cells (an indicator of long-term folate status) and reported correlations of r = 0.55 for women and r = 0.56 for men.

Genotyping. The *DNMT3b* (−149C>T, −283T>C, and −579G>T) and *ADH1C* (*2) polymorphisms were detected by allelic discrimination using a 5′ nuclease assay on a 7900HT sequence detection system (Applied Biosystems). The 5′ nuclease genotyping assays were validated by genotyping 92 individuals using both 5′ nuclease assay and restriction fragment length polymorphism or sequencing. There were no discrepancies between the two assays. The 20 μL genotyping reactions

Table 1. PCR conditions

Polymorphism	PCR	Primers/Probes	(Mg^{2+})	[Primers, Probes]	Amplicon	Cycling
DNMT3b −149C>T	FP	5′TGTTCACTTCCAGTTGTCCTGAA3′	3 mmol/L	200 nmol/L	118 bp	50°C, 2 min, 95°C, 10 min, 40× 95°C, 30 s; 62°C, 60 s
	RP	5′GGACACTCACTGGGCCTTAG3′		200 nmol/L		
	C allele	5′VIC-CAGACCC**C**AGGCCT-3′NFQ		100 nmol/L		
	T allele	5′6FAM-AGACCC**T**AGGCC-TCCA-3′NFQ		100 nmol/L		
DNMT3b −283T>C	FP	5′ GTTCGGGTTGAAAGGAGCC3′	6 mmol/L	200 nmol/L	86 bp	50°C, 2 min, 95°C, 10 min, 45× 95°C, 15 s; 65°C, 60 s
	RP	5′ GAAGCCCTAAGCGGGAGG3′		200 nmol/L		
	T allele	5′VIC-CAAAACCAG**A**CTCCTT-3′NFQ		100 nmol/L		
	C allele	5′6FAM-CAAAACCAG**G**CTCCT-3′NFQ		100 nmol/L		
DNMT3b −579G>T	FP	5′CAAAGGCAAGTGACTTGGAAAA3′	4 mmol/L	200 nmol/L	82 bp	50°C, 2 min, 95°C, 10 min, 45× 95°C, 15 s; 60°C, 60 s
	RP	5′CCAGGATTAGATAGAG-AACGAGTAAAAAA3′		200 nmol/L		
	G allele	5′VIC-AAATCCC**C**GCTGAAA-3′NFQ		100 nmol/L		
	T allele	5′6FAM-TAAATCCC**A**GCT-GAAAC-3′NFQ		100 nmol/L		
ADH1C 1045A>G	FP	5′ CAATGATATTTTCTTC-TTTTCAGGCTTT3′	5 mmol/L	200 nmol/L	109 bp	50°C, 2 min, 95°C, 10 min, 50× 95°C, 15 s; 60°C, 1 min
	RP	5′GCGAAGCAGGTCAAATCCTT3′		200 nmol/L		
	A allele	5′VIC-CATTAATAACAAAT-**A**TTTTACC3′-NFQ		150 nmol/L		
	G allele	5′6FAM-CATTAATAACAAAT**G**-TTTTACCT-3′NFQ		100 nmol/L		

Downloaded from cebp.aacrjournals.org on November 30, 2021. © 2008 American Association for Cancer Research.

contained 1× TaqMan Core Reagents (Applied Biosystems), 0.5 units of AmpliTaq DNA polymerase, 0.2 units of AmpErase UNG, primers, probes, and 4 ng of genomic DNA. Primers, probes, Mg^{2+} concentrations, and cycling conditions are listed in Table 1. Positive controls for all the genotypes as well as two negative controls were included on each plate. For quality control purposes, genotyping for 94 randomly selected samples was repeated. There were no discrepancies. All the genotypes were in Hardy-Weinberg equilibrium.

Statistical Data Analysis. Logistic regression analysis was used to estimate odds ratios (OR) and corresponding 95% confidence intervals (CI) comparing cases (with adenomatous or hyperplastic polyps) to polyp-free controls in association with *DNMT3b* or *ADH1C* genotypes, adjusting for age, sex, body mass index, smoking (pack-years), hormone use (females only), and intakes of fiber, alcohol, total energy, riboflavin, vitamin B_{12}, vitamin B_6, folate, and methionine.

Pairwise linkage disequilibrium between the three *DNMT3b* single nucleotide polymorphisms was calculated using SAS Genetics, and haplotypes were inferred. A generalized estimating equations weighted logistic regression model was used to analyze the haplotype effects, using the haplotype probabilities as weights and clustering the haplotypes for each individual (53). The analyses were adjusted for age, sex, body mass index, smoking (pack-years), hormone use (females only), and intakes of fiber, alcohol, total energy, riboflavin, vitamin B_{12}, vitamin B_6, folate, and methionine.

Results

The characteristics of the study population and risk factors for colorectal polyps in this population have been described previously (47, 54-56) and are shown in Table 2. Those with adenomatous polyps were older than individuals with hyperplastic polyps or polyp-free controls and were more likely to be male. Postmenopausal hormone and nonsteroidal anti-inflammatory drug use have previously been associated with decreased polyp risk in this study population (47, 56).

We investigated three polymorphisms within the promoter region of *DNMT3b*: −149C>T, −283T>C, and −579G>T, and a polymorphism within the coding region of *ADH1C*, *ADH1C* *2. Genotype frequencies among case and control groups are given in Table 2. The pairwise r^2 values between −149C>T and −283T>C, −149C>T and −579G>T, and −283T>C and −579G>T were 0.76, 0.80, and 0.90, respectively.

DNMT3b. ORs associated with the *DNMT3b* variants are given in Table 3. There was no difference in adenoma or hyperplastic polyp risk associated with *DNMT3b* polymorphisms. Stratification by polyp size, age, or sex did not affect risk estimates. Haplotypes of the three *DNMT3b* polymorphisms (−149C>T, −283T>C, −579G>T) were inferred. The most common was the CTG haplotype (i.e., wild-type at all three loci; Table 2.) We observed no associations between polyp risk and *DNMT3b* haplotypes (Table 3).

We evaluated whether the *DNMT3b* associations with adenomas differed by intakes of one-carbon nutrients (Table 4). Folate and methionine are most relevant to the provision of methyl groups for DNMT3b. Individuals with variant *DNMT3b* genotypes and low folate and low methionine intake showed an increased risk of colorectal adenoma (low folate and methionine: folate <268 μg, methionine <1.66 g; medium folate and methionine: folate 268-400 μg, methionine 1.55-2.16 g; high folate and methionine: folate >440 μg, methionine >2.16 g). The −149C>T variant (homozygous variant) was associated with an increase in adenoma risk among individuals with low folate and methionine intake (OR, 2.00; 95% CI, 1.06-3.78); whereas there was no association with −149C>T genotype among those with medium or high intake (*P* interaction = 0.10).

ADH1C. ORs for the association between the *ADH1C* polymorphism and polyp risk are shown in Table 3. There was no statistically significant difference in

Table 2. Main characteristics of the study population

Variables	Adenomatous polyps, *n* (%)	Hyperplastic polyps, *n* (%)	Controls, *n* (%)
Total *N*	530	202	649
Age (y)	58.0 ± 9.7	53.6 ± 9.9	52.9 ± 11.0
Sex			
Male	331 (62.2)	116 (57.4)	251 (38.6)
Female	201 (37.8)	86 (42.6)	399 (61.4)
Folate intake (μg)			
<268	170 (32.4)	62 (31.3)	213 (33.8)
268-440	190 (36.2)	72 (36.4)	203 (32.2)
>440	165 (31.4)	64 (32.3)	215 (34.1)
Methionine intake (g)			
<1.55	165 (31.4)	71 (35.9)	217 (34.4)
1.55-2.16	177 (33.7)	63 (31.8)	197 (31.2)
>2.17	183 (34.9)	64 (32.3)	217 (34.4)
Alcohol intake (g)*			
0	202 (38.6)	64 (32.3)	283 (44.9)
1-7	128 (24.5)	53 (26.8)	185 (29.4)
8-25	122 (23.3)	54 (27.3)	116 (18.4)
>26	71 (13.6)	27 (13.6)	46 (7.3)
DNMT3b −149C>T genotype			
C/C	167 (31.8)	53 (27.3)	216 (34.7)
C/T	250 (47.7)	106 (54.6)	300 (48.2)
T/T	107 (20.4)	35 (18.0)	106 (17.0)
DNMT3b −283T>C genotype			
T/T	186 (35.5)	61 (31.6)	235 (37.8)
T/C	243 (46.4)	105 (54.4)	291 (46.9)
C/C	95 (18.1)	27 (14.0)	95 (15.3)
DNMT3b −579G>T genotype			
G/G	190 (36.1)	60 (31.1)	239 (38.4)
G/T	237 (45.1)	102 (52.9)	288 (46.3)
T/T	98 (18.7)	31 (16.1)	95 (15.3)
ADH1C genotype			
*1/*1	177 (34.0)	74 (38.3)	220 (35.4)
*1/*2	251 (48.3)	86 (44.6)	299 (48.1)
*2/*2	92 (17.5)	33 (17.1)	103 (16.6)
DNMT3b haplotype† (−149C>T, −283T>C, −579G>T)			
CCG	1.2	0.7	1.2
CCT	0.2	0.3	0.6
CTG	53.8	52.7	56.6
CTT	0.5	0.8	0.4
TCG	0.1	0.1	0.1
TCT	39.8	40.3	36.9
TTG	3.8	4.1	3.7
TTT	0.6	1.0	0.6

NOTE: The pairwise R^2 for the three polymorphisms were 0.76 between −149C>T and −283T>C, 0.80 between −149C>T and −579G>T, and 0.90 between −283T>C and −579G>T.

*Alcohol intake was assessed in grams per day.

†Percentages rather than total *N* are reported for haplotypes because they are inferred rather than determined.

Downloaded from cebp.aacrjournals.org on November 30, 2021. © 2008 American Association for Cancer Research.

Table 3. Association between *DNMT3b* and *ADH1C* polymorphisms and risk of adenomatous and hyperplastic polyps

Polymorphism	Controls (*n*)	Adenomas		Hyperplastic polyps	
		Cases (*n*)	OR (95% CI)	Cases (*n*)	OR (95% CI)
DNMT3b genotypes					
−149C>T					
C/C (ref.)	216	167	1.00 (ref.)	53	1.00 (ref.)
C/T	300	250	0.93 (0.69-1.26)	106	1.24 (0.82-1.86)
T/T	106	107	1.28 (0.88-1.87)	35	1.33 (0.78-2.28)
−283T>C					
T/T (ref.)	235	186	1.00 (ref.)	61	1.00 (ref.)
T/C	291	243	0.93 (0.69-1.24)	105	1.34 (0.90-1.98)
C/C	95	95	1.21 (0.82-1.78)	27	1.12 (0.63-1.98)
−579G>T					
G/G (ref.)	239	190	1.00 (ref.)	60	1.00 (ref.)
G/T	288	237	0.92 (0.69-1.23)	102	1.33 (0.89-1.97)
T/T	95	98	1.27 (0.87-1.87)	31	1.38 (0.80-2.40)
DNMT3b haplotypes*					
CTG (ref.)	56.6	53.8	1.00 (ref.)	52.7	1.00 (ref.)
TCT	36.9	39.8	1.09 (0.93-1.27)	40.3	1.12 (0.92-1.37)
Rare	6.5	6.3	1.03 (0.84-1.24)	7.0	0.90 (0.68-1.17)
ADH1C					
1/1 (ref.)	220	177	1.00 (ref.)	74	1.00 (ref.)
1/2	299	251	1.15 (0.86-1.55)	86	0.88 (0.59-1.30)
2/2	103	92	1.23 (0.83-1.81)	33	1.04 (0.62-1.73)

NOTE: Multivariate adjustment for age, sex, smoking (pack-years), alcohol, hormone use (females only), body mass index, caloric intake, fiber intake, folate intake, methionine intake, vitamin B_{12} intake, vitamin B_6 intake, and riboflavin intake.
*Percentages rather than total *N* are reported for haplotypes because they are inferred rather than determined.

adenoma or hyperplastic polyp risk associated with the *ADH1C* *2 genotype. However, after stratification by alcohol intake, we observed that individuals with the *ADH1C* *2/*2 genotype were at an increasing risk with increasing alcohol consumption (for >26 g alcohol per day, OR, 1.95; 95% CI, 0.60-6.30). This was a pattern for the *2 genotype, whereas those who were wild-type had no increase in risk as alcohol consumption increased. We tested for a difference of slopes (i.e., trend interaction) within each genotype group and found a significant difference between both variant genotypes and the *1 genotype (Table 5, overall *P* interaction = 0.03; *P* interaction = 0.03 for *1/*2 versus *1/*1 and 0.02 for *2/*2 versus *1/*1).

Discussion

The results of this study indicate that polymorphisms in *DNMT3b* and *ADH1C* may not be associated with risk of colorectal adenoma, but that they may interact with

Table 4. *DNMT3b* genotype, combined folate, and methionine intake and risk of adenomatous polyps

DNMT3b Polymorphism	Combined folate and methionine intake*					
	Low			Medium or high		
	Controls (*n*)	Cases (*n*)	OR (95% CI)	Controls (*n*)	Cases (*n*)	OR (95% CI)
−149C>T						
C/C (ref.)	83	57	1.00 (ref.)	125	107	1.32 (0.78-2.21)
C/T	111	88	1.12 (0.68-1.83)	181	160	1.10 (0.67-1.81)
T/T	36	40	2.00 (1.06-3.78)	68	66	1.32 (0.75-2.34)
			P interaction = 0.10			
−283T>C						
T/T (ref.)	90	67	1.00 (ref.)	138	116	1.14 (0.69-1.87)
T/C	108	86	1.02 (0.63-1.65)	174	155	0.99 (0.61-1.60)
C/C	32	32	1.47 (0.76-2.84)	61	62	1.25 (0.71-2.19)
			P interaction = 0.47			
−579G>T						
G/G (ref.)	90	70	1.00 (ref.)	141	116	1.07 (0.65-1.74)
G/T	108	82	0.93 (0.58-1.50)	172	154	1.98 (0.61-1.58)
T/T	33	34	1.55 (0.82-2.96)	60	63	1.22 (0.70-2.14)
			P interaction = 0.51			

NOTE: Multivariate adjustment for age, sex, body mass index, caloric intake, alcohol, dietary fiber intake, hormone use (females only), smoking (pack-years), vitamin B_{12} intake, vitamin B_6 intake, and riboflavin intake.
*Tertiles were first created for folate and methionine separately using 1 for low (folate <268 μg, methionine <1.55 g), 2 for medium (folate 268-440 μg, methionine 1.55-2.16 g), and 3 for high (folate >440 μg, methionine >2.16 g). Folate and methionine tertile scores were added to create a combined folate and methionine variable with values ranging from 2 to 6. These combined scores were then divided as follows: combined folate and methionine intake was considered low if the score was 2 or 3, medium if the score was 4, and high if the score was 5 or 6.

Downloaded from cebp.aacrjournals.org on November 30, 2021. © 2008 American Association for Cancer Research.

Table 5. *ADH1C* genotype, alcohol intake, and risk of adenomatous polyps

ADH1C Polymorphism	Alcohol intake (g)											
	0			1-7			8-25			>26		
	Controls (*n*)	Cases (*n*)	OR (95% CI)	Controls (*n*)	Cases (*n*)	OR (95% CI)	Controls (*n*)	Cases (*n*)	OR (95% CI)	Controls (*n*)	Cases (*n*)	OR (95% CI)
1/1	92	84	1.00 (ref.)	68	36	0.62 (0.35-1.09)	41	30	0.76 (0.39-1.48)	16	24	1.09 (0.38-3.08)
1/2	130	86	0.75 (0.48-1.17)	83	65	1.00 (0.61-1.65)	51	56	1.12 (0.62-2.01)	22	43	2.25 (0.72-7.01)
2/2	48	25	0.61 (0.32-1.15)	29	25	1.15 (0.58-2.28)	14	21	1.71 (0.74-3.96)	10	19	1.95 (0.60-6.30)
						P interaction = 0.03						

NOTE: Multivariate adjustment for age, sex, body mass index, caloric intake, dietary fiber intake, hormone use (females only), smoking (pack-years), vitamin B_{12} intake, vitamin B_6 intake, riboflavin intake, methionine intake, and folate intake.

nutrients in the one-carbon metabolism pathway to affect adenoma risk. Specifically, we found evidence that increasing alcohol intake may be more important among slow alcohol metabolizers. Additionally, we found that polymorphisms in *DNMT3b* may be associated with adenoma risk only in the context of low folate and methionine intake.

DNMT3b. Our results suggest that the −149C>T transition in *DNMT3b* was associated with an increased risk of adenomas among those with the −149TT genotype in combination with low folate and methionine intake. We found no association between the −283T>C polymorphism or the −579G>T polymorphism and polyp risk. The −149T allele has previously been associated with reduced levels of gene methylation in normal and tumor tissue compared with the C allele (18, 22); thus, the combination of low intake of one-carbon metabolism nutrients and the −149T allele may result in hypomethylation of genomic DNA, a state that has been observed for multiple cancer types (57-65). However, in another study, the −149T allele was associated with increased promoter activity (16), indicating that the function of the −149C>T polymorphism has not been fully elucidated. It may, like many other tumor processes, be dependent on stage of progression.

Overexpression of *DNMT3b* has been found in tumors (66), although evidence has been equivocal (67). Many tumor suppressor genes and other regulatory genes are hypermethylated in colorectal cancer (11, 68). Moreover, Toyota et al. showed that CpG island methylation and subsequent silencing of the *CHFR* gene depended on the activity of DNMT3b (69). Conversely, in another study, DNA hypermethylation of the CpG islands of human colorectal tumor-suppressor genes was not associated with overexpression of *DNMT3b* in 25 cases of colon cancer (70). Concurrent with promoter hypermethylation, genomic hypomethylation is common in cancers and suggests a second possible mechanism for associations with cancer risk. Hypomethylation in these non-promoter regions of DNA may cause genomic instability (62), although some studies do not support this mechanism (71).

Nutrition throughout life influences DNA methylation because the one-carbon metabolism, which is highly dependent on dietary methyl donors and cofactors, provides methyl groups for all biological methylation reactions (8). Dietary methionine and choline provide a major source of one-carbon units, and folic acid, vitamin B_{12}, and pyridoxal phosphate are cofactors in one-carbon metabolism, thus nutritional deficiencies or surpluses could induce DNA hypomethylation or DNA hypermethylation, respectively. Studies have shown that nutritional supplementation during early development could increase methylation at specific genes and cause permanent changes in gene expression (72). Mouse studies have shown that nutritional supplementation, particularly folate and methionine supplementation in adults, can increase methylation at specific genes. In a prospective, randomized trial, subjects who received folate supplementation had increased genomic DNA methylation, and decreased p53 strand breaks compared with those receiving placebo (73). Others found that folate supplementation was associated with decreased DNA hypomethylation in rectal mucosa in patients with colonic adenomas (74). Additionally, diets deficient in folate have been shown to induce genomic DNA hypomethylation in animal models (26, 75) and in humans (76, 77).

Two recent studies have reported associations between polymorphisms in the *DNMT3b* gene and colon cancer risk. Hong et al. investigated the −579G>T polymorphism and observed a statistically significantly decreased risk of adenomas for the combined GT and GG genotypes in younger Korean patients (20). In another study, Jones et al. reported that hereditary nonpolyposis colorectal cancer patients carrying one or two copies of the *DNMT3b* −149C>T variant T allele developed colorectal cancer significantly earlier than those patients homozygous for the wild-type gene in a population of mismatch repair gene mutation carriers (19).

Several other cancer types have been associated with the −149C>T polymorphism. The TT or combination CT and TT genotypes have been associated with increased risk of lung cancer (15, 16) and prostate cancer (17), but with decreased risk of or no association with breast cancer (21, 78). However, none of the studies referenced above took one-carbon metabolism nutrients into account; which is a critical component of these studies given the existing evidence for gene-nutrient interactions in folate-mediated one-carbon metabolism.

Downloaded from cebp.aacrjournals.org on November 30, 2021. © 2008 American Association for Cancer Research.

ADH1C. We observed no overall association between the *ADH1C* *2 polymorphism and polyp risk. However, we observed a statistically significant interaction between this polymorphism and alcohol intake. The *2/*2 genotype was associated with increased risk of cancer among those with the highest alcohol intake. The *2 allele is associated with ~2.5-fold lower enzyme activity (36). We had hypothesized that the highest risk would be found among those with the highest alcohol intakes and who were wild-type for *ADH1C* because these people would have the highest levels of acetaldehyde, a toxic alcohol metabolite, in their systems. Our findings contradict this hypothesis, possibly indicating that there are other mechanisms by which alcohol may influence cancer risk.

Alcohol intake has been inconsistently associated with increased risk of colorectal cancer (79). Alcohol has several procarcinogenic effects, including the production of acetaldehyde during metabolism, the production of reactive oxygen species, and antagonism of folate and other one-carbon metabolism nutrients (36). The lack of consistently elevated risks between alcohol intake and colorectal cancer risk may be due to the failure to take genetic variability in genes related to alcohol metabolism, such as the alcohol dehydrogenases and the aldehyde dehydrogenases, into account.

Few studies have examined the potential associations between *ADH1C* genotype and risk of colorectal neoplasia in relation to alcohol and/or folate intake. To our knowledge, three studies, in addition to ours, have been done (31, 37, 39). Giovannucci et al. reported on 375 adenoma cases and 727 controls from the Health Professionals Follow-up Study that high intakes of alcohol (at least two drinks daily) are associated with an increased risk of colorectal adenomas, particularly among those with the *ADH1C* *2/*2 genotype. Additionally, they observed that the interaction between alcohol and *ADH1C* genotypes was stronger among those with low folate intake (37). However, in the same study population (211 cases of colorectal cancer and 1,104 controls), Chen et al. found that, although the association between colorectal cancer risk and alcohol consumption was stronger among individuals with the *ADH1C* *2/*2 genotype compared with other genotypes, the *ADH1C* polymorphism did not confer a significant risk of colorectal cancer independently (39). Conversely, in a study of 433 adenoma cases and 436 controls from the Netherlands, the risk of adenomas was highest among subjects who had the *ADH1C* *1/*1 genotype and were in the upper tertile of alcohol consumption. They described stronger associations between alcohol consumption and colorectal adenomas in carriers of the *ADH1C* *1/*1 genotype than those with other *ADH1C* genotypes (31).

Our results are consistent with the results of Giovannucci et al. Furthermore, their study and ours showed that alcohol was not appreciably related to the risk of colorectal adenoma among those with the *ADH1C* *1/*1 genotype, but the highest level of consumption was associated with a higher risk among individuals with the *ADH1C* *1/*2 genotype. However, in the study by Giovannucci et al., the majority of participants underwent sigmoidoscopy, rather than full colonoscopy (52), indicating that there could be undiagnosed colon polyps in the upper portions of the colon among controls. Similarly, the study by Tiemersma et al. also included participants who had had either sigmoidoscopy or colon X-ray as a method for identifying polyps (18% of cases and 40% of controls; ref. 31). All participants in the present study underwent full colonoscopy; thus, reducing the chance that undiagnosed colon polyps were present among control participants and thus reducing misclassification and subsequent bias of ORs towards the null.

This study has several limitations. First, intakes of one-carbon metabolism nutrients and alcohol were collected via food frequency questionnaire and thus may not be accurate measures of true intakes. However, the food frequency questionnaire was administered prior to polyp diagnosis, and thus, any misclassification is likely to be nondifferential with respect to case status and the associations observed here would be underestimates of the true associations between one-carbon nutrients, alcohol, and polyp risk. Similarly, because alcohol consumption was generally low in this study population, we were limited in our ability to evaluate the combined effects of deficient one-carbon nutrient intake and high alcohol intake. The mechanism for increased polyp risk associated with *ADH1C* may be related to the effects of alcohol on folate absorption and metabolism; stronger interactions may be observed in populations with higher alcohol intake. Second, we limited our analyses to genetic variation in two genes related to methylation and alcohol metabolism, rather than considering the joint effects of several genes in these pathways. However, we chose genes and polymorphisms that are likely to be functionally relevant. Future studies of these pathways should consider multiple genes/variants together.

Additionally, we did not have access to polyp tissue in this study; thus, we were unable to directly measure aberrant methylation patterns, somatic mutations (such as *APC*), or microsatellite instability. Information on these molecular characteristics would help to more clearly delineate biological mechanisms of adenoma development.

In summary, we report here that intakes of one-carbon metabolism nutrients and alcohol may interact with genetic polymorphisms in genes related to DNA methylation and alcohol metabolism. These results add further to the data showing that folate-related gene-nutrient interactions play an important role in the risk of colorectal neoplasia.

References

1. Potter JD. Methyl supply, methyl metabolizing enzymes and colorectal neoplasia. J Nutr 2002;132:2410–2S.
2. Duthie SJ, Narayanan S, Sharp L, Little J, Basten G, Powers H. Folate, DNA stability and colo-rectal neoplasia. Proc Nutr Soc 2004; 63:571–8.
3. Choi SW, Mason JB. Folate and carcinogenesis: an integrated scheme. J Nutr 2000;130:129–32.
4. Duthie SJ, Narayanan S, Brand GM, Grant G. DNA stability and genomic methylation status in colonocytes isolated from methyl-donor-deficient rats. Eur J Nutr 2000;39:106–11.
5. Duthie SJ. Folic acid deficiency and cancer: mechanisms of DNA instability. Br Med Bull 1999;55:578–92.
6. James SJ, Pogribny IP, Pogribna M, Miller BJ, Jernigan S, Melnyk S. Mechanisms of DNA damage, DNA hypomethylation, and tumor progression in the folate/methyl-deficient rat model of hepatocarcinogenesis. J Nutr 2003;133:3740–7S.
7. Powers HJ. Interaction among folate, riboflavin, genotype, and cancer, with reference to colorectal and cervical cancer. J Nutr 2005;135:2960–6S.

Downloaded from cebp.aacrjournals.org on November 30, 2021. © 2008 American Association for Cancer Research.

8. Waterland RA. Assessing the effects of high methionine intake on DNA methylation. J Nutr 2006;136:1706–10S.
9. Chen RZ, Pettersson U, Beard C, Jackson-Grusby L, Jaenisch R. DNA hypomethylation leads to elevated mutation rates. Nature 1998;395:89–93.
10. Laird PW. The power and the promise of DNA methylation markers. Nat Rev Cancer 2003;3:253–66.
11. Jones PA, Baylin SB. The fundamental role of epigenetic events in cancer. Nat Rev Genet 2002;3:415–28.
12. Okano M, Bell DW, Haber DA, Li E. DNA methyltransferases Dnmt3a and Dnmt3b are essential for *de novo* methylation and mammalian development. Cell 1999;99:247–57.
13. Hsieh CL. The *de novo* methylation activity of Dnmt3a is distinctly different than that of Dnmt1. BMC Biochem 2005;6:6.
14. Lee SJ, Jeon HS, Jang JS, et al. DNMT3B polymorphisms and risk of primary lung cancer. Carcinogenesis 2005;26:403–9.
15. Shen H, Wang L, Spitz MR, Hong WK, Mao L, Wei Q. A novel polymorphism in human cytosine DNA-methyltransferase-3B promoter is associated with an increased risk of lung cancer. Cancer Res 2002;62:4992–5.
16. Wang L, Rodriguez M, Kim ES, et al. A novel C/T polymorphism in the core promoter of human *de novo* cytosine DNA methyltransferase 3B6 is associated with prognosis in head and neck cancer. Int J Oncol 2004;25:993–9.
17. Singal R, Das PM, Manoharan M, Reis IM, Schlesselman JJ. Polymorphisms in the DNA methyltransferase 3b gene and prostate cancer risk. Oncol Rep 2005;14:569–73.
18. Teodoridis JM, Hall J, Marsh S, et al. CpG island methylation of DNA damage response genes in advanced ovarian cancer. Cancer Res 2005;65:8961–7.
19. Jones JS, Amos CI, Pande M, et al. DNMT3b polymorphism and hereditary nonpolyposis colorectal cancer age of onset. Cancer Epidemiol Biomarkers Prev 2006;15:886–91.
20. Hong YS, Lee HJ, You CH, et al. DNMT3b 39179GT polymorphism and the risk of adenocarcinoma of the colon in Koreans. Biochem Genet 2007;45:155–63.
21. Montgomery KG, Liu MC, Eccles DM, Campbell IG. The DNMT3B C → T promoter polymorphism and risk of breast cancer in a British population: a case-control study. Breast Cancer Res 2004;6:R390–4.
22. Kawakami K, Ruszkiewicz A, Bennett G, et al. DNA hypermethylation in the normal colonic mucosa of patients with colorectal cancer. Br J Cancer 2006;94:593–8.
23. Wagner C. Biochemical role of folate in cellular metabolism. Folate in health and disease. New York: Marcel Dekker; 1995.
24. Ghoshal K, Li X, Datta J, et al. A folate- and methyl-deficient diet alters the expression of DNA methyltransferases and methyl CpG binding proteins involved in epigenetic gene silencing in livers of f344 rats. J Nutr 2006;136:1522–7.
25. Nijhout HF, Reed M, Anderson D, Mattingly J, James SJ, Ulrich CM. Long-range allosteric interactions between the folate and methionine cycles stabilize DNA methylation rate. Epigenetics 2006;1:81–7.
26. Kim YI. Folate and carcinogenesis: evidence, mechanisms, and implications. J Nutr Biochem 1999;10:66–88.
27. Kim YI. Nutritional epigenetics: impact of folate deficiency on DNA methylation and colon cancer susceptibility. J Nutr 2005;135:2703–9.
28. Hillman RS, Steinberg SE. The effects of alcohol on folate metabolism. Annu Rev Med 1982;33:345–54.
29. Mason JB, Choi SW. Effects of alcohol on folate metabolism: implications for carcinogenesis. Alcohol 2005;35:235–41.
30. Halsted CH, Villanueva JA, Devlin AM, et al. Folate deficiency disturbs hepatic methionine metabolism and promotes liver injury in the ethanol-fed micropig. Proc Natl Acad Sci U S A 2002;99:10072–7.
31. Tiemersma EW, Wark PA, Ocke MC, et al. Alcohol consumption, alcohol dehydrogenase 3 polymorphism, and colorectal adenomas. Cancer Epidemiol Biomarkers Prev 2003;12:419–25.
32. Boffetta P, Hashibe M. Alcohol and cancer. Lancet Oncol 2006;7:149–56.
33. Peters ES, McClean MD, Liu M, Eisen EA, Mueller N, Kelsey KT. The ADH1C polymorphism modifies the risk of squamous cell carcinoma of the head and neck associated with alcohol and tobacco use. Cancer Epidemiol Biomarkers Prev 2005;14:476–82.
34. Bosron WF, Lumeng L, Li TK. Genetic polymorphism of enzymes of alcohol metabolism and susceptibility to alcoholic liver disease. Mol Aspects Med 1988;10:147–58.
35. Whitfield JB. ADH and ALDH genotypes in relation to alcohol metabolic rate and sensitivity. Alcohol Alcohol Suppl 1994;2:59–65.
36. Seitz HK, Maurer B, Stickel F. Alcohol consumption and cancer of the gastrointestinal tract. Dig Dis 2005;23:297–303.
37. Giovannucci E, Chen J, Smith-Warner SA, et al. Methylenetetrahydrofolate reductase, alcohol dehydrogenase, diet, and risk of colorectal adenomas. Cancer Epidemiol Biomarkers Prev 2003;12:970–9.
38. Wang D, Ritchie JM, Smith EM, Zhang Z, Turek LP, Haugen TH. Alcohol dehydrogenase 3 and risk of squamous cell carcinomas of the head and neck. Cancer Epidemiol Biomarkers Prev 2005;14:626–32.
39. Chen J, Ma J, Stampfer MJ, Hines LM, Selhub J, Hunter DJ. Alcohol dehydrogenase 3 genotype is not predictive for risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev 2001;10:1303–4.
40. van der Logt EM, Bergevoet SM, Roelofs HM, et al. Role of epoxide hydrolase, NAD(P)H:quinone oxidoreductase, cytochrome P450 2E1 or alcohol dehydrogenase genotypes in susceptibility to colorectal cancer. Mutat Res 2006;593:39–49.
41. Visvanathan K, Crum RM, Strickland PT, et al. Alcohol dehydrogenase genetic polymorphisms, low-to-moderate alcohol consumption, and risk of breast cancer. Alcohol Clin Exp Res 2007;31:467–76.
42. Yokoyama A, Omori T. Genetic polymorphisms of alcohol and aldehyde dehydrogenases and risk for esophageal and head and neck cancers. Jpn J Clin Oncol 2003;33:111–21.
43. Ulrich CM, Bigler J, Bostick R, Fosdick L, Potter JD. Thymidylate synthase promoter polymorphism, interaction with folate intake, and risk of colorectal adenomas. Cancer Res 2002;62:3361–4.
44. Giovannucci E. Epidemiologic studies of folate and colorectal neoplasia: a review. J Nutr 2002;132:2350–5S.
45. Chen J, Hunter DJ, Stampfer MJ, et al. Polymorphism in the thymidylate synthase promoter enhancer region modifies the risk and survival of colorectal cancer. Cancer Epidemiol Biomarkers Prev 2003;12:958–62.
46. Ulrich CM. Nutrigenetics in cancer research—folate metabolism and colorectal cancer. J Nutr 2005;135:2698–702.
47. Potter JD, Bostick RM, Grandits GA, et al. Hormone replacement therapy is associated with lower risk of adenomatous polyps of the large bowel: the Minnesota Cancer Prevention Research Unit Case-Control Study. Cancer Epidemiol Biomarkers Prev 1996;5:779–84.
48. O'Brien MJ, Winawer SJ, Zauber AG, et al. The National Polyp Study. Patient and polyp characteristics associated with high-grade dysplasia in colorectal adenomas. Gastroenterology 1990;98:371–9.
49. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51–65.
50. Munger RG, Folsom AR, Kushi LH, Kaye SA, Sellers TA. Dietary assessment of older Iowa women with a food frequency questionnaire: nutrient intake, reproducibility, and comparison with 24-hour dietary recall interviews. Am J Epidemiol 1992;136:192–200.
51. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135:1114–26; discussion 1127–36.
52. Giovannucci E, Stampfer MJ, Colditz GA, et al. Folate, methionine, and alcohol intake and risk of colorectal adenoma. J Natl Cancer Inst 1993;85:875–84.
53. Liang K-Y, Zeger S. Longitudinal data analysis using generalized linear models. Biometrika 1986;73:13–22.
54. Morimoto LM, Newcomb PA, Ulrich CM, Bostick RM, Lais CJ, Potter JD. Risk factors for hyperplastic and adenomatous polyps: evidence for malignant potential? Cancer Epidemiol Biomarkers Prev 2002;11:1012–8.
55. Ulrich CM, Kampman E, Bigler J, et al. Colorectal adenomas and the C677T MTHFR polymorphism: evidence for gene-environment interaction? Cancer Epidemiol Biomarkers Prev 1999;8:659–68.
56. Bigler J, Whitton J, Lampe JW, Fosdick L, Bostick RM, Potter JD. CYP2C9 and UGT1A6 genotypes modulate the protective effect of aspirin on colon adenoma risk. Cancer Res 2001;61:3566–9.
57. Woodson K, Mason J, Choi SW, et al. Hypomethylation of p53 in peripheral blood DNA is associated with the development of lung cancer. Cancer Epidemiol Biomarkers Prev 2001;10:69–74.
58. Stern LL, Mason JB, Selhub J, Choi SW. Genomic DNA hypomethylation, a characteristic of most cancers, is present in peripheral leukocytes of individuals who are homozygous for the C677T polymorphism in the methylenetetrahydrofolate reductase gene. Cancer Epidemiol Biomarkers Prev 2000;9:849–53.
59. Feinberg AP, Gehrke CW, Kuo KC, Ehrlich M. Reduced genomic 5-methylcytosine content in human colonic neoplasia. Cancer Res 1988;48:1159–61.
60. Feinberg AP, Vogelstein B. Hypomethylation distinguishes genes of some human cancers from their normal counterparts. Nature 1983;301:89–92.
61. Baylin SB, Herman JG, Graff JR, Vertino PM, Issa JP. Alterations in DNA methylation: a fundamental aspect of neoplasia. Adv Cancer Res 1998;72:141–96.

Downloaded from cebp.aacrjournals.org on November 30, 2021. © 2008 American Association for Cancer Research.

62. Eden A, Gaudet F, Waghmare A, Jaenisch R. Chromosomal instability and tumors promoted by DNA hypomethylation. Science 2003;300:455.
63. Bariol C, Suter C, Cheong K, et al. The relationship between hypomethylation and CpG island methylation in colorectal neoplasia. Am J Pathol 2003;162:1361 – 71.
64. Ehrlich M. DNA methylation in cancer: too much, but also too little. Oncogene 2002;21:5400 – 13.
65. Esteller M, Fraga MF, Guo M, et al. DNA methylation patterns in hereditary human cancers mimic sporadic tumorigenesis. Hum Mol Genet 2001;10:3001 – 7.
66. Robertson KD, Uzvolgyi E, Liang G, et al. The human DNA methyltransferases (DNMTs) 1, 3a and 3b: coordinate mRNA expression in normal tissues and overexpression in tumors. Nucleic Acids Res 1999;27:2291 – 8.
67. Kanai Y, Ushijima S, Nakanishi Y, Sakamoto M, Hirohashi S. Mutation of the DNA methyltransferase (DNMT) 1 gene in human colorectal cancers. Cancer Lett 2003;192:75 – 82.
68. Woodson K, Weisenberger DJ, Campan M, et al. Gene-specific methylation and subsequent risk of colorectal adenomas among participants of the polyp prevention trial. Cancer Epidemiol Biomarkers Prev 2005;14:1219 – 23.
69. Toyota M, Sasaki Y, Satoh A, et al. Epigenetic inactivation of CHFR in human tumors. Proc Natl Acad Sci U S A 2003;100:7818 – 23.
70. Eads CA, Danenberg KD, Kawakami K, Saltz LB, Danenberg PV, Laird PW. CpG island hypermethylation in human colorectal tumors is not associated with DNA methyltransferase overexpression. Cancer Res 1999;59:2302 – 6.
71. Rhee I, Bachman KE, Park BH, et al. Vogelstein B, DNMT1 and DNMT3b cooperate to silence genes in human cancer cells. Nature 2002;416:552 – 6.
72. Waterland RA, Jirtle RL. Early nutrition, epigenetic changes at transposons and imprinted genes, and enhanced susceptibility to adult chronic diseases. Nutr 2004;20:63 – 8.
73. Kim YI, Baik HW, Fawaz K, et al. Effects of folate supplementation on two provisional molecular markers of colon cancer: a prospective, randomized trial. Am J Gastroenterol 2001;96:184 – 95.
74. Cravo ML, Pinto AG, Chaves P, et al. Effect of folate supplementation on DNA methylation of rectal mucosa in patients with colonic adenomas: correlation with nutrient intake. Clin Nutr 1998;17:45 – 9.
75. Kim YI. Folate and DNA methylation: a mechanistic link between folate deficiency and colorectal cancer? Cancer Epidemiol Biomarkers Prev 2004;13:511 – 9.
76. Rampersaud GC, Kauwell GP, Hutson AD, Cerda JJ, Bailey LB. Genomic DNA methylation decreases in response to moderate folate depletion in elderly women. Am J Clin Nutr 2000;72:998 – 1003.
77. Gregory JF III, Swendseid ME, Jacob RA. Urinary excretion of folate catabolites responds to changes in folate intake more slowly than plasma folate and homocysteine concentrations and lymphocyte DNA methylation in postmenopausal women. J Nutr 2000;130:2949 – 52.
78. Cebrian A, Pharoah PD, Ahmed S, et al. Genetic variants in epigenetic genes and breast cancer risk. Carcinogenesis 2006;27: 1661 – 9.
79. van den Brandt PA, Goldbohm RA. Nutrition in the prevention of gastrointestinal cancer. Best Pract Res Clin Gastroenterol 2006;20: 589 – 603.

Downloaded from cebp.aacrjournals.org on November 30, 2021. © 2008 American Association for Cancer Research.

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

DNA Methyltransferase and Alcohol Dehydrogenase: Gene-Nutrient Interactions in Relation to Risk of Colorectal Polyps

Audrey Y. Jung, Elizabeth M. Poole, Jeanette Bigler, et al.

Cancer Epidemiol Biomarkers Prev 2008;17:330-338.

Updated version	Access the most recent version of this article at: http://cebp.aacrjournals.org/content/17/2/330

Cited articles	This article cites 78 articles, 29 of which you can access for free at: http://cebp.aacrjournals.org/content/17/2/330.full#ref-list-1
Citing articles	This article has been cited by 4 HighWire-hosted articles. Access the articles at: http://cebp.aacrjournals.org/content/17/2/330.full#related-urls

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, use this link http://cebp.aacrjournals.org/content/17/2/330. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.

Downloaded from cebp.aacrjournals.org on November 30, 2021. © 2008 American Association for Cancer Research.