Alcohol, One-Carbon Metabolism, and Colorectal Cancer: Recent Insights from Molecular Studies¹

Edward Giovannucci²

Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, 181 Longwood Avenue, Boston MA 02115 and Departments of Nutrition and of Epidemiology, Harvard School of Public Health, Boston MA 02115

ABSTRACT A growing body of evidence implicates alcohol intake as a risk factor for colorectal cancer. Until recently, most of the data were based on epidemiologic data that examined alcohol intake in relation to risk of colorectal neoplasia, but the evidence has now been broadened by recent molecular studies on mechanisms. In particular, a number of observations strongly support a role for alcohol acting through disruptions in one-carbon metabolism. Excessive alcohol intake is a fairly consistent risk factor for colorectal neoplasia in most studies, and studies show much higher risks of colorectal neoplasia in those with high alcohol and low folate than with high alcohol or low folate individually. Interactions between high alcohol-low folate and the MTHFR677TT genotype with risk of colorectal neoplasia suggest that alcohol is acting through its effects on one-carbon metabolism because the combination of high alcohol-low folate and the MTHFR677TT genotype are related to markedly elevated serum levels of homocysteine and to DNA hypomethylation. In addition, in Japanese studies, consumers of alcohol possessing the ALDH2*2 allele, who have very elevated levels of acetaldehyde, are at high risk for colorectal cancer. The relatively high prevalence of the ALDH2*2 allele may thus account for the stronger association between alcohol and colorectal neoplasia that is frequently observed in studies in Japanese populations. Further research integrating studies with more detailed data on alcohol intake levels and patterns, folate and other related nutrient status, and relevant genotypes may help clarify unresolved questions regarding the health consequences of moderate to high alcohol drinking. J. Nutr. 134: 2475S–2481S, 2004.

KEY WORDS: ● alcohol ● cancer ● large bowel ● acetaldehyde ● folate ● MTHFR

An association between higher alcohol intake and increased risk for several cancer sites is well-established. These include cancer sites that are in direct contact with ingested alcohol and cancers of the liver, where most alcohol is catabolized. However, whether alcohol consumption causally increases risk of colorectal cancer has been controversial because, while most studies support an association, the magnitude of the association appears relatively modest and alcohol intake could be related to potentially confounding factors. Nonetheless, the conclusion from a report from the World Cancer Research Fund and American Institute for Cancer Research, which extensively summarized the evidence, was that alcohol “probably” increases risk of colorectal cancer (1).

Resolving whether alcohol increases risk of colorectal cancer is important because a substantial number of individuals drink alcohol and colorectal cancer is quite common, so even a relatively modest effect may involve a substantial number of cases. Ideally, long-term randomized trials of alcohol could resolve the question of causality, but such studies are not feasible for alcohol, so other types of evidence are required. Fortunately, several lines of studies have helped address this relationship in recent years. Our better understanding of the role of alcohol in interfering with one-carbon metabolism, the role of one-carbon metabolism in colorectal carcinogenesis, and the identification of polymorphisms in genes that influence alcohol and one-carbon metabolism have increased our ability to study how alcohol influences colorectal carcinogenesis. In this review, an integrated model of how alcohol influences risk of colorectal cancer is presented.

Alcohol and risk of colorectal neoplasia in epidemiologic studies

In many though not all studies (2–4), men or women who consume relatively high intakes of alcohol have been found to be at increased risk of colorectal cancer as well as its adenomatous precursor (5–20). An extensive review of the scientific
Evidence up to 1991 concluded that alcohol is likely to be an etiologic factor for colorectal cancer (21). The World Cancer Research Fund/AICR reviewed the evidence up to 1997 and concluded that the evidence that alcohol increases risk of colorectal cancer is “probable” (1). More recently, investigators have addressed this hypothesis using data from the Pooling Project of Prospective Studies, which combined data from eight large prospective studies (22). In the pooled analysis, compared to nondrinkers of alcohol, individuals who consumed 30 to <45 g/d of alcohol had a multivariate relative risk of 1.16 (95% CI: 0.99–1.37) and those who consumed ≥45 g/d of alcohol had a multivariate relative risk of 1.42 (95% CI: 1.16–1.73). There was no significant heterogeneity by study or sex. Alcohol was not related to risk among those who took multivitamins, most of which contain folic acid. In general, risk of both proximal and distal colon cancers and rectal cancer appear to be increased by high alcohol intake.

Based on alcohol’s antagonist effect on folate (23), and on increasing evidence of a role of folate status on colorectal cancer risk (24), some investigators have hypothesized that the risk associated with alcohol was related to its anti-folate effect (8) or more specifically to its effects on DNA methylation (11). Based on this hypothesis, some studies examined risk of colorectal cancer or adenoma in individuals with high alcohol and low folate intakes. Most studies, but not all (2,4), have found an ~2- to 5-fold elevation in colorectal cancer or adenoma risk observed among individuals with high intakes of alcohol and low intakes of folate compared to those with low alcohol and high folate (see Fig. 1) (5,6,8,11,14,15,17,18,25). The definitions of high and low alcohol and folate varied across studies. In general, these relative risks are higher than would be expected from the additive effects of alcohol and folate. In eleven populations studied, 8 had statistically significant associations in at least 1 of the gender subgroups. All 7 studies that included men or examined subgroups of men reported a statistically significant increase in risk, but the data have been inconsistent for women (see Fig. 1). This may reflect a true gender difference or the fact that males tend to drink more alcohol. Although a causal association cannot be assumed, these data strongly support the hypothesis that high intake of alcohol is primarily a risk factor when folate status is poor, especially in men, suggesting that alcohol may influence colorectal carcinogenesis through an influence on one-carbon metabolism. Why the relationship between alcohol and folate and colorectal cancer risk in women appears weaker needs to be resolved.

**One-carbon metabolism and methylenetetrahydrofolate reductase (MTHFR)**

To understand how alcohol may influence colorectal carcinogenesis, it is important to appreciate the role of folate and one-carbon metabolism in carcinogenesis. Because the role of folate in one-carbon metabolism is quite complex, for purposes of this review on colorectal carcinogenesis, 2 competing forms of folate will be emphasized. This simplified model is shown in Figure 2. Firstly, folate is required in the form of 5-methyltetrahydrofolate (THF) in order that homocysteine is methylated to form methionine. Methionine, in the activated form of S-adenosylmethionine, is the methyl donor required for the numerous methylation reactions in the cell, including DNA methylation. Secondly, folate is required in another form, 5,10-methyleneTHF, to convert deoxyuridylate (dUMP) into deoxythymidylate (dTMP), a limiting nucleotide for DNA synthesis.

In theory, deficiency of folate in either of these forms could influence carcinogenesis (26). It has been proposed that an imbalance between biologic methylation and nucleotide synthesis is responsible for folate-related carcinogenesis (27). When 5,10-methyleneTHF is deficient, inadequate methylation of dUMP to dTMP can lead to misincorporation of uracil into DNA by DNA polymerase (28). In one study of folate-deficient individuals, about 4,000,000 uracil molecules per cell were observed in white blood cell DNA; after supplementation with folic acid, this amount was reduced to <200,000 uracil molecules per cell (29). Supplementation also decreased the frequency of chromosomal breaks (29). During repair of uracil in DNA, transient nicks are formed, and 2 opposing nicks could lead to chromosomal breaks. Misincorporation of uracil into DNA has been shown to result in various potential genomic abnormalities, including an increase in spontaneous mutation rates (30), greater sensitivity to DNA-damaging agents (31), higher frequency of chromosomal aberrations (32,33) and errors in DNA replication (33–35). A folate- or methyl-deficient diet in rats was shown to induce breaks in genomic DNA and within the p53 gene (36), and to induce mutations in the p53 tumor suppression gene (37) in intestinal cells. On the other hand, when 5-methylTHF is low, abnormalities in methylation may occur, including DNA methylation. DNA methylation abnormalities are commonly seen as an early event in colorectal neoplasms. Methylation of specific CpG sites in DNA may be one mechanism that reduces gene expression, probably by modulating the interaction between the promoter sites of genes and tran-

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**FIGURE 1** Summary of relative risks from studies comparing high alcohol and low folate categories to low alcohol and high folate. Some studies (Giovannucci, 1993; Giovannucci, 1995; Glynn, 1996; La Vecchia, 2002) also included methionine in addition to folate.
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### FIGURE 2

In this model, under conditions of low folate/high alcohol status, the MTHFR 677C→T polymorphism may increase risk through abnormalities in DNA methylation. When folate is high and alcohol is low, this polymorphism may be beneficial by increasing the pool of 5,10-methylene THF for DNA synthesis (see text for details).

### Schematic

<table>
<thead>
<tr>
<th>Low Folate / High Alcohol:</th>
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<tbody>
<tr>
<td>5,10-methylene THF</td>
</tr>
<tr>
<td>MTHFR 677C→T</td>
</tr>
<tr>
<td>5-methyl THF</td>
</tr>
<tr>
<td>DNA synthesis</td>
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<tr>
<td>DNA methylation</td>
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<td>(dysregulates gene expression)</td>
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<td>DNA synthesis</td>
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<td>(uracil misincorporation into DNA)</td>
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### Discussion

DNA methylation is also an important determinant of the conformational configuration and structural stability of DNA (26).

The enzyme methylenetetrahydrofolate reductase (MTHFR) is at a critical metabolic branch point that directs the folate pool towards remethylation of homocysteine to methionine, at the expense of thymidylate synthesis (see Fig. 2). A single nucleotide polymorphism of the MTHFR gene (677C→T) is associated with an alanine-to-valine substitution and with reduced enzyme activity (39). This polymorphism is critical in directing folate pools into different pathways, and thus could influence many physiologic and pathologic conditions that are potentially related to one-carbon metabolism. Folate-replete individuals with the MTHFR 677 TT genotype tend to accumulate intracellularly appreciable levels of 5,10-methyleneTHF, whereas CC and CT individuals have 5-methylTHF predominantly (40). When levels of 5,10-methyleneTHF are low, as discussed above, misincorporation of uracil for thymidine may occur during DNA synthesis (28), leading to increased frequency of chromosomal breaks (29). Thus, when folate is sufficient, the TT genotype may be beneficial by enhancing the pool of 5,10-methyleneTHF. However, when folate is relatively deficient, this TT genotype may become deleterious. Both TT genotype and poor folate status appear to be required to disrupt DNA methylation because individuals with other genotypes (CT or CC) do not experience DNA hypomethylation even if they have low folate levels (41).

Thus, the specific MTHFR genotype may have phenotypic advantages or disadvantages that depend on folate status. Evolutionarily, selective advantages were likely to be independent of colorectal cancer incidence and mortality, which tend to occur past the reproductive period. For example, under conditions of high folate, the TT genotype may improve fetal health (42) and enhance hematopoiesis (43), presumably by allowing the accumulation of folate in the forms required for DNA and RNA synthesis (40). Thus, when folate is plentiful, the TT genotype could provide a selective advantage. However, because both chronic alterations in DNA synthesis and DNA methylation may be important for carcinogenesis, the MTHFR 677C→T genotype, in combination with folate status, could potentially influence carcinogenesis.

### The influence of alcohol on one-carbon metabolism

The antagonist influence of alcohol on folate status in rapidly proliferating tissues has been well established for decades [reviewed by Hillman (23) and by Halsted et al. (44)]. Many of the initial observations in this area involved cellular activity in the bone marrow, where the effects can be observed most acutely. Alcohol, in combination with poor folate status, impairs hematopoiesis causing megaloblastic anemia; in addition, neutropenia and thrombocytopenia may occur. Alcohol accelerates the induction of megaloblastic anemia in subjects on a low folate diet (23). Alcohol also prevents the hematologic response to folic acid in subjects with folate-deficient anemia, but this suppression can be overcome with larger doses of folic acid (23). A number of potential mechanisms may contribute to alcohol’s impairment of erythropoiesis: blockage of release of folate from the hepatocyte; intestinal malabsorption of folate; inhibition of critical enzymes including DNA methyltransferase or methionine synthetase, which may trap folate as 5-methylTHF which effectively depletes 5,10-methyleneTHF; cellular depletion of overall folate because 5-methylTHF is a poor substrate for polyglutamation, which is required to retain folate in cells (23,44).

Although these mechanisms may contribute to folate deficiency in the colon and rectum, evidence from studies in rats suggests an additional mechanism relevant for the large bowel mucosa, the cleavage of folate at the C9-N10 bond by alcohol catabolite acetaldehyde (45). This mechanism was believed to be irrelevant in humans because concentrations of acetaldehyde that far exceed typical concentrations in the blood and most tissues appear to be required for this effect. However, studies in rats have clearly shown that intestinal bacteria, because of their high alcohol dehydrogenase (ADH) activity, can oxidize ethanol in colorectal tissue to produce levels of acetaldehyde up to 1000-fold higher than that in blood (46,47). In one study, ethanol consumption in rats profoundly decreased the colonic mucosal folate level by approximately half (47). This folate depleting property of alcohol was prevented by the antibiotic ciprofloxacin, which reduces the microbial production of acetaldehyde from ethanol. In rats, alcohol enhances chemically-induced carcinogenesis primarily in the distal regions of the bowel (48), which have higher concentrations of bacteria and higher pH, both of which accentuate acetaldehyde production. In rats, chronic alcohol consumption induces genomic DNA hypomethylation in the intestinal mucosa (49).

Intestinal bacterial catabolism of ethanol has been studied mostly in rats, but evidence suggests that similar mechanisms are likely to occur in humans. Intestinal conversion of ethanol to high concentrations of acetaldehyde is not unique to rats and is known to occur in other species (50). Incubation of human colonic contents in vitro at 37°C with ethanol at concentrations that occur in tissues of alcohol drinkers leads to significant production of acetaldehyde (51), suggesting that the human intestinal microflora has similar capabilities in this regard as for other species. Ethanol concentrations in the terminal ileum (52) and colon in humans (53) are equal to blood concentrations of ethanol, so ethanol clearly reaches the large bowel mucosa when alcohol is ingested. Although reports of acetaldehyde measurements in colorectal mucosa in humans were not identified in the literature, one study showed...
that rectal mucosal proliferation is increased in men who drink heavily, consistent with mucosal hyperregeneration following acetaldehyde toxicity (54).

Thus, alcohol is likely to adversely influence folate and one-carbon metabolism in the large intestine mucosa, where the proliferation rate is high. Because intestinal bacteria have high ADH activity, a profound increase of the concentration of acetaldehyde, which has a strong anti-folate effect, may occur. Whereas the relative importance of the various mechanisms described is unsettled, their combined influence may contribute to a profound deleterious effect of alcohol on folate and one-carbon metabolism in humans, and perhaps particularly in the large bowel.

**Insights from molecular studies**

As described above, epidemiologic evidence suggests that alcohol intake is associated with an increased risk of colorectal adenoma and cancer, particularly when folate status is poor. Data also confirm a strong anti-folate effect of alcohol, at relevant intakes for humans. In general, alcohol may influence folate through a variety of mechanisms, but in the large bowel, direct destruction of folate may occur through high levels of acetaldehyde produced by bacterial ADH activity. These pathways are shown in Figure 3. This figure also shows 3 potentially relevant enzymes, 2 related to alcohol catabolism (ADH and ALDH), and 1, MTHFR, related to folate metabolism. In recent years, genetic polymorphisms related to the enzymes have been identified and have begun to be examined in studies of alcohol and folate and colorectal cancer and adenoma risk. These studies are summarized next.

**Methylenetetrahydrofolate reductase (MTHFR)**

The MTHFR 677C→T polymorphism has been examined in relation to colorectal cancer and adenoma risk in several studies. In all 4 studies that have examined the MTHFR 677C→T polymorphism in relation to colorectal cancer (55–58) and for 5 (59–62) of 6 (59–64) studies of adenomas, the lowest risk has been associated with the TT genotype and “low-risk” diet (high folate and/or low alcohol). In contrast, among individuals with low folate or high alcohol intakes, this benefit becomes attenuated and the risk in the TT homozygotes may even exceed that of all others. Thus, MTHFR TT homozygotes appear to be hyper-responders to folate status; these individuals are relatively resistant to develop colorectal neoplasia when folate is high and alcohol is low, but are at high risk when folate intake is low, or when excess alcohol is consumed. These results fit the model presented in Figure 2. When folate status is adequate, MTHFR TT homozygotes may benefit from a reduction of chromosomal damage; however, when folate status is poor, their risk of cancer may become enhanced as a result of DNA methylation abnormalities.

Of note, in the reported studies, the interaction between the MTHFR 677C→T polymorphism and colorectal neoplasia has been most striking for alcohol (55,56,60,64), but less evident for folate. This finding may indicate that, in populations with relatively good folate status, alcohol may be of particular importance in causing a functional folate deficiency. This hypothesis is supported by one study of alcoholics in Spain. In that study, the prevalence of hyperhomocysteinemia in heavy alcohol drinkers was 84.2% in TT homozygotes, 54.3% in CT heterozygotes, and 31.6% in CC homozygotes (65). Extremely high concentrations of serum homocysteine, up to a remarkable 10-fold increase, were observed in the alcoholics who had low serum folate and the TT genotype in that study. (For comparison, studies have found plasma homocysteine associated with significantly increased risk of myocardial infarction at less than double the normal values (66).)

However, alcoholics with the TT genotype with high plasma folate status, or alcoholics with the CC genotype regardless of plasma folate, had only slightly elevated serum homocysteine level. This study shows that a combination of high alcohol and low folate and MTHFR TT homozygosity has a dramatic adverse influence on methylation (indicated by hyperhomocysteinemia).

**ALDH**

The initial critical steps in the breakdown of ethanol, which occur mostly in the liver, are its catabolism to acetaldehyde by ADH followed by the further breakdown of acetaldehyde to acetate by ALDH (67,68). A well-known variant of ALDH that causes slow breakdown of acetaldehyde and hence high levels of this compound occurs exclusively in Asian populations. Specifically, there are 2 alleles, ALDH2*1, the wild type, and ALDH2*2, the mutant type with reduced activity due to a single point mutation at codon 481 in exon 12 of the ALDH2 gene. Those with the mutant homozygote genotype (ALDH2*2/2) have a high intolerance to alcohol and do not generally drink alcoholic beverages. In contrast, ALDH2*1/2 heterozygotes have an intermediate tolerance and overall drink about half as much as ALDH2*1/1 homozygotes, but attain substantially higher blood concentrations of acetaldehyde if they drink alcohol (69).

Several studies in Japan have examined alcohol drinking and the ALDH2 genotypes in relation to colorectal cancer. Murata et al. (70) found that higher alcohol intake increased risk of colon cancer overall, and that the elevated risk was greater for those with the ALDH2*1/2 genotype (odds ratio = 3.1 for 1.0+ versus 0 drinks daily) than for ALDH2*1/1 homozygotes (odds ratio = 1.9) (despite the likelihood that drinking was even higher in the homozygotes). Matsuo et al. (71) found similar results for rectal though not for colon
cancer in a small study. In another study, Japanese alcoholics with the slow-metabolizing ALDH variant had a much higher risk of alcohol-related cancers, including colon cancer (72). Thus, the ALDH variant, associated with higher levels of acetaldehyde in alcohol drinkers, appears to modify the association between alcohol and colorectal cancer. Interestingly, some investigators have noted that the magnitude of the association between alcohol intake and colorectal cancer risk is generally higher in Japanese studies than in studies of Caucasians (70); this pattern would be predicted by the higher levels of acetaldehyde expected in Japanese populations because all Caucasians essentially have the high activity wild type form of ALDH. Thus, it is possible that population differences in frequencies of metabolic-related genotype could account in part for heterogeneity of risk across populations for some risk factors.

The studies of ALDH tend to support the hypothesis that acetaldehyde is the major deleterious component of alcohol metabolism that increases risk of colorectal cancer. Acetaldehyde is known to have strong adverse effects on folate metabolism. Whether the anti-folate effects are relevant for carcinogenesis, or whether other adverse functions of acetaldehyde are critical, remains to be proven.

ADH

The theoretical relationship between ADH, alcohol, and colorectal carcinogenesis is less clear than that of ALDH, which clearly influences acetaldehyde levels. ADH is important in the rate of conversion of alcohol to acetaldehyde. Variants that influence the conversion rate of ethanol to acetaldehyde have been described for ADH3 and ADH1 (67,68). In Caucasians, a common polymorphism has been described for ADH1, for which a 2.5-fold higher rate of maximal velocity of ethanol oxidation has been observed for the homodimeric y1 enzyme relative to the homodimeric y2 enzyme (73); germline variants in ADH2 are uncommon in Caucasians. Variation in ADH activity, by determining the rate of ethanol breakdown and acetaldehyde production, may possibly influence colorectal carcinogenesis, but an influence of this genotype on short-term blood alcohol levels has not been clearly demonstrated. Nonetheless, studies have associated the ADH1 polymorphism with risk of alcoholism (74) and cirrhosis (75), HDL cholesterol levels and risk of myocardial infarction (76), and the response to some plasma hormones to alcohol (77), suggesting that this polymorphism is functional. However, the relationship between human ADH3 and colorectal neoplasia may be complex because intestinal bacterial ADH activity may be the major generator of acetaldehyde in the large bowel mucosa of alcohol drinkers (51). Thus, slow phenotypes of human ADH may possibly increase acetaldehyde concentrations in the large bowel mucosa through maintaining high circulating levels of ethanol that can be catabolized into acetaldehyde by intestinal bacteria. Opposing this, however, fast phenotypes of human ADH may increase acetaldehyde production rate in the liver, which may have deleterious effects on folate metabolism.

Because the functionality of the ADH3 genotype is not established, and because bacterial ADH activity may complicate the picture for the large bowel, the prediction of ADH3 genotypes and colorectal neoplasia risk is not clear. Thus far, data on ADH1 and colorectal neoplasia risk have been sparse and conflicting. A recent study from the Physicians’ Health Study (78) found alcohol more strongly related to cancer risk among slow-metabolizers. These were confirmed for colorectal adenoma in a recent study from the Health Professionals Follow-Up Study (64). However, a case-control study conducted in the Netherlands found risk highest in alcohol drinkers with the rapid metabolizers, although the test for interaction between alcohol and ADH3 was not statistically significant (P = 0.4) (79). Clearly, further study is needed in this area.

Implications

Colorectal cancer is an important malignancy in developed countries. In the United States, ~105,500 cases of colon cancer and 42,000 rectal cancer cases were expected to occur in 2003 (80). It is the third leading cause of cancer deaths in each sex and second for both sexes combined. At current rates, ~6% of individuals will develop colorectal cancer sometime in their lifetime, and about half of diagnosed individuals will die of this disease. As discussed above, evidence implicates a role for one-carbon metabolism, especially folate, for this cancer. Other B vitamins that influence one-carbon metabolism may be relevant, but these have been less studied. Some other potentially relevant nutritional factors for this cancer (e.g., energy balance, fat, or meat intake) are difficult to alter in the general population. Thus, a potentially beneficial role of micronutrients (such as B vitamins) is critical to establish as the population’s status can be altered with relative ease, through fortification, modest dietary alterations, and supplementation. Although fortification with folic acid has improved folate status in the United States, whether current folate intakes are optimal remains unclear. In particular, the requirements may differ for those with genetic susceptibility (e.g., MTHFR677TT genotype, or family history of colorectal cancer), or those with substantial intakes of alcohol, particularly if associated with the ALDH2*2 allele.

As summarized here, a growing body of evidence implicates alcohol intake as a risk factor for colorectal cancer. Until recently, most of the data were based on epidemiologic data that examined alcohol intake in relation to risk of colorectal neoplasia, but these studies are now complemented by recent molecular evidence on mechanisms. In particular, the following observations strongly support a role for alcohol acting through disruption in one-carbon metabolism: 1) excess alcohol intake is a relatively consistent risk factor for colorectal neoplasia in most studies; 2) epidemiologic studies show markedly high risk of colorectal neoplasia in individuals with high alcohol and low folate, compared with those with high alcohol or low folate, especially in men; 3) interactions between alcohol and the MTHFR677TT genotype and colorectal neoplasia suggest that alcohol is acting through its effects on one-carbon metabolism; 4) the combination of high alcohol-low folate and the MTHFR677TT genotype is related to extremely elevated levels of homocysteine, a marker for DNA hypomethylation; and 5) in Japanese studies, consumers of alcohol who possess the ALDH2*2 allele, who have very elevated acetaldehyde, are at high risk for colorectal cancer. Perhaps the relatively high prevalence of the variant ALDH2*2 genotype in Asian populations also accounts for the stronger association between alcohol and colorectal neoplasia observed in Japanese studies. The model presented here can serve as a focus for future research and consideration of public health implications. This model can be potentially extended to other nutrients that influence one-carbon metabolism (e.g., other B vitamins such as B-6 and B-12, methionine, choline), and other polymorphisms that are identified for one-carbon metabolism and alcohol catabolism. Whether the influence of alcohol on colonic acetaldehyde and folate levels observed in the animal models is relevant to humans needs to be established; this
would help resolve apparently conflicting data related to ADH2 genotype and colorectal neoplasia risk in humans. Another area of fruitful research may be to examine the molecular characteristics of tumors. For example, if aberrant DNA methylation associated with the MTHFR677TT genotype and low folate/high alcohol enhances carcinogenesis, it is reasonable to postulate that the affected cancers have a distinct phenotype. In fact, some investigators (81) have noted that the characteristics of tumors observed in MTHFR677TT homozygotes in some studies (57,81) include the tendency for occurrence at older ages, for proximal location, and for an MSI+ phenotype. Of note, the majority of sporadically occurring MSI+ tumors have methylation of the hMLH1 gene, possibly reflecting an abnormal methylator pattern (82). Thus, it is possible that diverse combinations of folate, alcohol, and MTHFR may relate to colorectal tumors of a distinct phenotype characterized by an abnormal methylation pattern, though this has not been definitively demonstrated to date.

In regard to public health, many individuals consume alcohol, which may have beneficial effects on cardiovascular disease, so it is important to identify adverse effects of moderate drinking and elucidate ways that they can be minimized. Obviously, excessive alcohol drinking has negative health and social consequences, but the health consequences of moderate drinking may vary depending on various modifiable and susceptibility factors. These factors may include pattern of drinking, interactions with other dietary factors, such as folate and methionine, and various genotypes related to alcohol and one-carbon metabolism. For example, some evidence indicates that the overall influence of moderate alcohol intake on major chronic diseases may depend to large extent on folate intake (83). Further research integrating studies of alcohol intake levels and patterns, nutrient status, and relevant genotypes may help clarify resolved questions.

LITERATURE CITED


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