Folate, Methyl-Related Nutrients, Alcohol, and the MTHFR 677C→T Polymorphism Affect Cancer Risk: Intake Recommendations1,2

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ABSTRACT Colorectal cancer and adenoma risk are inversely associated with higher total folate intake. Significant modifiers of cancer risk also include other methyl-related nutrients and alcohol. Adequate folate intake is particularly important for women at higher risk for breast cancer because of moderate alcohol consumption. The methylenetetrahydrofolate reductase (MTHFR) 677C→T polymorphism is associated with a reduced risk of some forms of cancer. The protective effect of this folate-related polymorphism is dependent on adequate folate status. Cancer risk may be increased in individuals with the homozygous genotype for the MTHFR 677C→T polymorphism who have low status of methyl-related nutrients including folate. Intake recommendations to potentially reduce cancer risk include substitution of low folate foods with folate-dense fruits and vegetables and in countries where there is no mandatory folic acid fortification, increased consumption of folic acid from available fortified foods or supplements. Adequate dietary intake of vitamin B-6 and methionine can be achieved by consumption of low fat, concentrated food sources of these nutrients. The recommended intake for vitamin B-12 for individuals >51 y should be provided predominately in crystalline form (e.g., fortified ready-to-eat cereal, supplements). If alcohol is consumed, consumption should be restricted to <15 g/d or <1 drink/d. The negative effects of low intakes of the methyl-related nutrients with high intakes of alcohol are additive, therefore changes in overall dietary patterns to ensure the consumption of a protective high methyl diet are recommended. J. Nutr. 133: 3748S–3753S, 2003.

KEY WORDS: • folate • methionine • alcohol • vitamin B-6 • vitamin B-12 • MTHFR 677C→T polymorphism • cancer

Folate’s role in DNA synthesis and methylation provides a mechanistic basis for the observed increased cancer risk associated with inadequate folate intake (1–3). Other nutrients, including methionine, vitamin B-6, and vitamin B-12, interact metabolically with folate in these processes and also may influence cancer risk. A common folate-related polymorphism, methylenetetrahydrofolate reductase (MTHFR) 677C→T, results in impaired in vitro stability and reduced activity under low folate conditions (4–6). In population-based studies, the presence of the MTHFR 677C→T polymorphism has been associated with reduced cancer risk when folate status is normal (7,8). Intake of folate and other methyl-related nutrients (i.e., methionine, vitamin B-6, vitamin B-12) and alcohol may influence the effect of the MTHFR 677C→T polymorphism on cancer risk (8,9).

The positive association between alcohol consumption and cancer risk may relate to alcohol’s role as a folate antagonist and its suppressive effects on methyl group metabolism (10). This paper provides a brief review of the reported associations among cancer risk and intake of folate and other methyl-related nutrients, alcohol, and the MTHFR 677C→T polymorphism. Dietary and nutrient-specific intake recommendations relative to cancer risk reduction will be discussed.

Folate intake or status and risk for colorectal adenoma or cancer

Colorectal adenoma risk. The risk of colorectal adenoma, the precancerous stage of colorectal cancer, may be significantly modified by folate status (9,11). The association between folate intake and colorectal adenoma risk was evaluated in the Nurses’ Health Study (NHS) and the Health Professionals’ Follow-Up Study (HPFS) (11). Colorectal adenoma risk was 30–40% lower in individuals whose median folate intakes were 711 μg/d (women) and 847 μg/d (men) related to the risk associated with the lowest folate intakes (166 μg/d for women and 241 μg/d for men). Most individuals in the highest folate intake quintile took multivitamins containing folic acid. Similar

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4 Abbreviations used: HPFS, Health Professionals’ Follow-Up Study; MTHFR, methylenetetrahydrofolate reductase; NHS, Nurses’ Health Study; PHS, Physicians’ Health Study.
inverse associations between folate intake or status and colorectal adenoma risk were found in other studies (12–15).

Colorectal cancer risk. The protective effect of higher folate intake on colorectal cancer was observed in a large number of case-control and cohort studies (14,16–21). To illustrate, women who participated in the NHS whose total folate intake (i.e., diet plus supplements) was ≥400 μg/d had a 31% decreased risk of colon cancer compared with women in the lowest folate intake group (<200 μg/d) (20). Eighty-six percent of the high folate intake (>400 μg/d) group consumed daily multivitamins containing folic acid.

The effect of long-term use of multivitamins containing folic acid on colon cancer risk was examined by Giovannucci and co-workers (20). A 75% reduction in risk for colon cancer was observed in the women who had used supplements for ≥15 y. In contrast, no significant benefit was observed for supplement use for ≤14 y. The risk of colon cancer in individuals who took supplements ≥15 y relative to individuals who either did not take supplements or took them <15 y within different dietary folate intake groups was evaluated. Long-term (>15 y) multivitamin use was associated with a significant risk reduction for colon cancer across all levels of dietary folate intake. Women who consumed the lowest quantity of dietary folate (≤200 μg/d) appeared to benefit the most from the supplements. The protective effect of long-term multivitamin use was also evident in other studies including those in which an inverse association between blood folate concentrations and colorectal cancer risk was observed (8,22). Higher folate intakes (>400 μg/d) compared with ≤200 μg/d significantly reduced the excess risk of colon cancer among women with a family history (23). In agreement with this finding, a marked reduction in the effect of family history was observed among users of multivitamins. The results of this study suggested that individuals with a family history who used multivitamins >5 y may significantly decrease their risk of colon cancer (23).

Effect of the interrelationship of folate, alcohol, and methyl-related nutrients on cancer risk

Alcohol. Folate status in individuals who chronically consume moderate amounts of alcohol may be impaired because the negative effects of alcohol on folate, which include malabsorption, increased excretion, or abnormal folate metabolism (11b). Numerous epidemiologic studies have provided convincing evidence that alcohol consumption is independently associated with the risk of colorectal adenoma or cancer (11,19,24,25). The estimated amount of alcohol consumption that was associated with an increased risk for cancer was for most studies ≥15 g/d, or one drink of any kind daily [approximately equivalent to either 150–180 mL (5–6 oz) of wine, 385–415 mL (13–14 oz) of beer, or 47 mL (1.6 oz) of liquor]. The potential for higher folate intake to reduce the elevated risk for breast cancer associated with alcohol consumption is illustrated by data from a number of studies (26–30). In the NHS, breast cancer risk was significantly elevated in women who consumed ≥15 g/d of alcohol compared with <15 g/d of alcohol for all quintiles of folate intake except the highest folate intake group (Fig. 1) (26). Among women who consumed ≥15 g/d of alcohol with a total folate intake of ≥600 μg/d, the risk reduction was 45% (compared with an intake of 150–299 μg/d). Total folate intake was not associated with breast cancer risk in women who consumed <15 g/d of alcohol. Zhang et al. (27) recently reported the association between breast cancer risk and plasma folate in a subset of the NHS cohort. The inverse association between plasma folate and breast cancer risk was highly significant among women consuming ≥15 g/d of alcohol in contrast with that of women consuming <15 g/d. In women who consumed ≥15 g/d of alcohol and whose plasma folate was in the highest quintile, breast cancer risk was significantly reduced relative to women with the lowest plasma folate concentrations. When data for the women who consumed very high amounts of alcohol >45 g/d of alcohol (3 drinks/d; ~0.6% of women) were excluded, the relative risks did not change significantly. This finding indicates that moderate quantities of alcohol (1–2 drinks/d) accounted for the risk associated with alcohol consumption (27). These data indicate that adequate folate status is particularly important for women at higher risk for breast cancer because of moderate alcohol consumption.

Methionine. The inverse association between methionine intake and adenoma and cancer risk was evaluated in a number of studies (9,11,19,21). A dietary pattern that is low in methionine and folate and high in alcohol has been positively associated with risk for colorectal adenoma and cancer (11,20). Giovannucci et al. (19) reported that the risk of colon cancer was increased more than sevenfold in the Physicians’ Health Study (PHS) participants who consumed a low methyl diet (i.e., low methionine and folate and high alcohol) compared with a high methyl diet (i.e., high methionine and folate and low alcohol) (Fig. 2). These data illustrate the importance of considering methionine intake in the context of the total diet including alcohol consumption.

Vitamins B-6 and B-12. Breast cancer risk was inversely associated with plasma vitamin B-6 concentrations in the NHS (27). When plasma vitamin B-6 concentrations were evaluated jointly with folate concentrations, risk reduction was much greater than when vitamin B-6 was evaluated alone (27). Lower vitamin B-6 concentrations have been associated with increased breast cancer risk in premenopausal women and postmenopausal women (27,31). A combined high intake of vitamin B-6 and folate was inversely associated with risk for proximal colon cancer in the Iowa Women’s Health Study (32). Colon cancer risk was reduced in individuals with higher combined intakes of vitamin B-12 and folate (32).

The MTHFR 677C→T polymorphism

The influence of the MTHFR 677C→T polymorphism on cancer risk has been the focus of a number of investigations as previously reviewed (33,34). MTHFR reduces 5,10-
methyleneTHF to 5-methylTHF, required for the production of methionine and S-adenosylmethionine, the methyl donor for DNA. A decrease in MTHFR activity associated with the 677C→T polymorphism may lead to an elevation in 5,10-methylenetetrahydrofolate, required for DNA synthesis. When folate status is low, the presence of the MTHFR 677C→T polymorphism (TT genotype) is associated with an increase in homocysteine concentration and DNA hypomethylation (35–38). The role of the MTHFR enzyme in DNA synthesis and methylation provides a metabolic explanation for the observed interactions between the MTHFR 677C→T polymorphism and cancer risk (7–9,39).

The presence of the MTHFR 677C→T polymorphism has been associated with a significant reduction in cancer risk (8,33,34). For example, in the PHS, colorectal cancer risk was 50% lower in individuals homozygous for the MTHFR 677C→T polymorphism (TT genotype) compared with individuals with the CC or CT genotypes (8). Among men with normal folate status, the TT genotype was associated with a threefold decrease in risk compared with the risk in the group with CC and CT genotypes combined. The protection associated with the TT genotype was lost in men with deficient folate status. Ulrich et al. (9) investigated the possible influence of folate, vitamin B-12, vitamin B-6, or methionine intake on risk for colorectal adenomas in individuals with the MTHFR TT genotype. These investigators reported that low nutrient intake was associated with an increased risk for adenomas in individuals with the TT genotype compared with the CC genotype. The increased colorectal adenoma risk associated with lower nutrient intake was not observed in individuals with the CC or CT genotypes. The increased risks were particularly striking in the >60 y age group in which low intakes of either vitamins B-6 or B-12 were associated with an approximately threefold increase in colorectal adenoma risk in individuals with the TT genotype (Fig. 4). Proposed interactions between the methylenetetrahydrofolate reductase (MTHFR) TT genotype and folate status on colorectal cancer risk in the Physician’s Health Study (7). Among men with normal folate status, there was a threefold decrease in risk among individuals with the TT genotype compared with the homozygous (CC) normal and heterozygous genotypes combined (CC/CT). The protection associated with the MTHFR TT genotype was lost in men with deficient folate status. Reprinted from Ma et al. (8) with permission.

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mechanisms by which the MTHFR 677C→T polymorphism may modulate cancer risk depending on nutrient status have been described (8,9,39).

**Nutrient intake recommendations relative to cancer risk**

**Folate.** To compare current estimates of folate intake with those that have been previously associated with cancer risk, total folate intake estimates in this review are expressed as μg/d not as μg Dietary Folate Equivalents/d (42,43). The total folate intake associated with colorectal adenoma or cancer risk reduction was estimated to be ~600 μg/d (11,19,20) relative to the lowest folate intake category (~200 μg/d). In individuals who were moderate alcohol consumers, folate intakes of ≥600 μg/d were associated with a reduction in breast cancer risk (26). The studies associating folate intake with cancer risk were conducted before folic acid fortification, when the average dietary folate intake was ~200–220 μg/d for nonusers of supplements (42). Most individuals consuming ≥600 μg/d were taking daily multivitamins that contained 400 μg folic acid (11,19,26). In the United States and Canada, the average postfortification total folate intake is estimated to be ~400 μg/d in supplement nonusers with ~200 μg/d consumed as naturally occurring food folate (42) and ~200 μg/d as folic acid provided in enriched products (44,45). For the 30–40% of the population that takes multivitamins containing folic acid, the estimated total folate intake is ~800 μg/d. In the majority of countries outside the United States and Canada, folic acid fortification is not mandatory and the current total folate intake is similar to that observed prefortification in the United States (~290 μg/d for nonusers and ~690 μg/d for supplement users) (46–48). Estimates of folate intake based on food composition data bases should be considered underestimates because of limitations of analytical methodology previously used to analyze food folate (42).

Dietary approaches to increase folate intake to reduce cancer risk include increased consumption of citrus fruit and juice, strawberries, dark green leafy vegetables, asparagus, dried beans and peas, and peanuts, which are naturally high in folate and other essential nutrients (43). In countries in which the food supply is not fortified on a mandatory basis, total folate intake can be increased by consuming those folic acid–fortified foods that are available (e.g., ready-to-eat breakfast cereal). In situations in which dietary intake is limited, as is the case for some aged individuals, supplements containing folic acid may be warranted. The most effective population-based approach to increase total folate intake in countries outside the United States and Canada is fortification of the food supply (49). To benefit from the protective effects of folate intake in relation to cancer risk that may or may not be associated with genetic predisposition or other environmental factors such as alcohol intake, it is essential that adequate folate be consumed chronically (20). Modifications of folate intake that ensure lifelong consumption of folate-dense foods in addition to folic acid from fortified foods or supplements where appropriate would be consistent with the observational data associating total folate intake with cancer risk.

**Methionine.** The protective effect of higher methionine intake on colorectal cancer risk was detected in individuals at increased risk due to higher alcohol consumption or in the context of a high methyl diet (19). A high methyl diet was characterized by approximately twice the frequency of consumption of methionine-rich foods (e.g., poultry, fish, and low fat dairy products); higher intake of folate sources (e.g., fruit, vegetables, and multivitamins); and low alcohol consumption. Low methyl diets were lower in poultry, fish, low fat dairy products, fruits, and vegetables and higher in alcohol, sweets and other highly refined and processed foods, and high fat products. The alcohol intake of individuals in the high, intermediate, and low methyl groups was 1.8, 10.3, and 28.5 g/d, respectively. The percentages of the individuals in the groups that took multivitamin supplements were 66%, 22%, and 17% for the high, intermediate, and low methyl groups, respectively. The increased risk of colon cancer associated with methyl-deficient diets was not confounded by intakes of red meat, fat, fiber, or other select vitamins and minerals (19).

The inverse association between methionine intake and colon cancer risk may appear to contradict data linking some component of red meat, a concentrated source of methionine, to increased colon cancer risk (50–52). From the analysis of PHS data, it appears unlikely that methionine was the component of red meat associated with the increase in cancer risk (53), and red meat intake was not correlated with the overall methyl-group status of the diet (19). Red meat, however, is only one of many contributors of methionine. Consumption of many animal foods high in methionine other than red meat (including fish, poultry, and milk products), as well as vegetable protein, was reported to be inversely associated with risk of colon cancer and adenoma (50,52).

Overall, the findings suggest that a diet that includes the replacement of high fat meat with poultry, fish, and low fat dairy products; multiple servings of folate-dense fruits and vegetables; and the avoidance of alcohol may be associated with a lower risk for colon cancer. The data do not support the use of methionine supplements because the quantities of methionine consumed as a part of the high methyl diet can be obtained from dietary sources alone and high supplemental doses of methionine have been associated with toxic side effects (54).

**Vitamin B-6.** A recommendation for vitamin B-6 specifically related to cancer risk reduction cannot be made because of limited observational data associating vitamin B-6 intake with cancer risk (9,27,32). Of concern, however, is the fact that a large percentage of select population subgroups in the United States is consuming less than the Dietary Reference Intakes for vitamin B-6 (55). From population-based survey data, the percentages of select adult groups that consume less than the Estimated Average Requirement are as follows: 15% of women 19–50 y, 25–50% of women 51 + y, and 10–25% of men 51 + y (55).

Intake recommendations that focus on ensuring adequate vitamin B-6 intake in individuals with low vitamin B-6 status would be advisable (e.g., Recommended Dietary Allowance for adult men and women >19 y, 1.3–1.7 mg/d) (55). Examples of specific foods that could be recommended to increase vitamin B-6 intake include light-meat skinless chicken or select types of fish (e.g., salmon), ready-to-eat cereal, fortified instant oatmeal, select fruit (e.g., bananas), legumes (e.g., garbanzo beans), and specific vegetables (e.g., potatoes) (53,55).

**Vitamin B-12.** Although the limited observational data are insufficient to base a specific recommendation for vitamin B-12 intake related to cancer risk, it is important to address the fact that an estimated 20% of elderly population subgroups in the United States currently have poor vitamin B-12 status (56–59). The basis for the high prevalence of low vitamin B-12 status in the elderly is a reduced ability to absorb food-bound dietary vitamin B-12, not inadequate dietary vitamin B-12 intake, which on average is estimated to exceed the RDA of 2.4 μg/d (42). Food-bound vitamin B-12 malabsorption is quite common in individuals over age 50 y, who often fail to produce a sufficient amount of gastric acid, which is essential to
free protein-bound vitamin B-12 from dietary sources (42, 60, 61). Individuals who have an impaired ability to absorb food-bound vitamin B-12 can absorb crystalline vitamin B-12 unless they also suffer from pernicious anemia, which is relatively rare (42, 62). To overcome the problem of impaired food-bound vitamin B-12 absorption, the Institute of Medicine (IOM) recommends that individuals ≥51 y of age consume a large percentage of the RDA as crystalline vitamin B-12 (42). Selection of crystalline forms of vitamin B-12 to meet a large percentage of the RDA, such as that provided in fortified products (e.g., ready-to-eat cereals) or as a vitamin B-12 multivitamin or supplement, is recommended (63). Vitamin B-12 is present only in animal foods, including dairy and eggs, so strict vegetarians also need to consume vitamin B-12 in either fortified products or in supplemental form.

Summary of dietary recommendations. Substitution of low folate foods with folate-dense fruits and vegetables is recommended to increase folate intake and to provide other essential nutrients. In countries in which folic acid fortification is not currently mandated, an increase in folic acid from either available fortified foods or supplements is advised. Adequate dietary vitamin B-6 and methionine in population subgroups consuming low intakes can be achieved by frequent consumption of low fat, concentrated food sources of methionine and vitamin B-6. Vitamin B-12 should be provided to individuals ≥51 y predominately in crystalline form as fortified food or supplements. If alcohol is consumed, intake should be limited to <15 g/d or <1 drink/d of any kind.

LITERATURE CITED


