Vitamin B_6 Intake, Alcohol Consumption, and Colorectal Cancer: A Longitudinal Population-Based Cohort of Women

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Background & Aims: **Vitamin B_6 has a crucial role in 1-carbon metabolism, which involves DNA synthesis and DNA methylation. Aberrations in these processes have been implicated in colorectal carcinogenesis. We examined the association between long-term dietary vitamin B_6 intake and risk of colorectal cancer and whether this association is modified by consumption of alcohol, which may disrupt 1-carbon metabolism.** ***Methods:*** **Our study population comprised 61,433 women in the population-based Swedish Mammography Cohort. The women were aged 40 to 76 years, had no history of cancer, and completed a food-frequency questionnaire at baseline in 1987–1990. Dietary information was updated in 1997. During a mean follow-up of 14.8 years, 805 incident colorectal cancer cases were diagnosed.** ***Results:*** **After controlling for age and other potential confounders, long-term intake of dietary vitamin B_6 was significantly inversely associated with risk of colorectal cancer (*P* value for trend = .002). Compared with women in the lowest quintile of vitamin B_6 intake, those in the highest quintile had a 34% lower risk (multivariate rate ratio, 0.66; 95% confidence interval, 0.50–0.86). The association was most pronounced among women with moderate to high alcohol consumption. The multivariate rate ratio of colorectal cancer comparing extreme quintiles of vitamin B_6 intake was 0.28 (95% confidence interval, 0.13–0.59) among women who consumed ≥30 g/wk of alcohol (approximately equivalent to 2 drinks per week).** ***Conclusions:*** **Findings of this study suggest that vitamin B_6 may play a role in the prevention of colorectal cancer, particularly among women who drink alcohol.**

Vitamin B_6 in its principal active form, pyridoxal 5′-phosphate, is involved in nearly 100 enzymatic reactions.[1] One function of vitamin B_6 that makes it potentially important in carcinogenesis relates to its role in 1-carbon metabolism, which involves the transfer of 1-carbon groups for DNA synthesis and DNA methylation (Figure 1). In these metabolic pathways, vitamin B_6 is a crucial coenzyme of serine hydroxymethyltransferase for the synthesis of 5,10-methylenetetrahydrofolate. This form of folate is needed for the synthesis of nucleotides (purines and thymidylate) for DNA synthesis and repair. Alternatively, 5,10-methylenetetrahydrofolate can be reduced to 5-methyltetrahydrofolate and used for the remethylation of homocysteine to methionine, a reaction facilitated by methionine synthase (MS). Methionine is a precursor of *S*-adenosylmethionine, the universal methyl group donor for methylation reactions, including DNA methylation.[2] Vitamin B_6 deficiency has been associated with substantially impaired 1-carbon metabolism in animals.[3] Thus, an inadequate vitamin B_6 intake might lead to disruption of DNA synthesis, repair, and methylation, any of which may enhance colorectal carcinogenesis.[2,4]

Apart from its role in the synthesis, repair, and methylation of DNA, vitamin B_6 is necessary for the synthesis of glutathione from homocysteine via cystathionine and cysteine. These reactions are facilitated by 2 vitamin B_6-dependent enzymes: cystathionine β-synthase and γ-cystathionase (Figure 1). Glutathione is a cofactor of the glutathione *S*-transferases and glutathione peroxidases, which function in the detoxification of many carcinogenic compounds and in the protection of cells from oxidative DNA damage.[5–7] Vitamin B_6 has been shown to reduce oxidative stress as well as cell proliferation and angiogenesis, and moderate doses of vitamin B_6 have been shown to suppress colorectal carcinogenesis in mice given injections of a carcinogen.[8,9]

Alcohol consumption may interfere with 1-carbon metabolism by influencing the absorption and degradation of vitamin B_6 and folate and by inhibition of MS.[10–19] In addition, high alcohol consumption has been associated with lower glutathione levels[20] (Figure 1). Many epidemiological studies have reported that adequate folate intake may be important in the prevention of

Abbreviations used in this paper: CI, confidence interval; MS, methionine synthase; RR, rate ratio.

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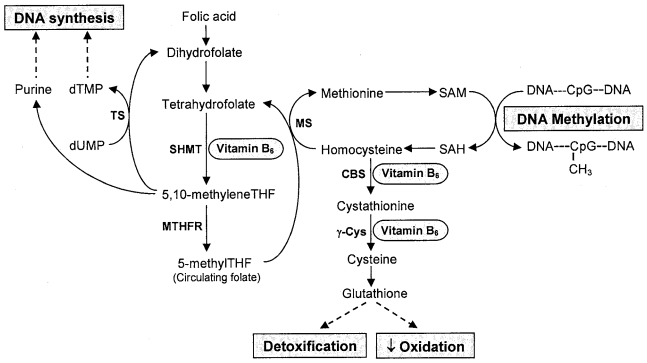

Figure 1. Overview of the role of vitamin B_6 in DNA synthesis, DNA methylation, detoxification of carcinogens, and protection against oxidative DNA damage. CH_3, methyl group; CBS, cystathionine β-synthase; CpG, cytosine-guanine dinucleotide sequence; γ-Cys, γ-cystathionase; dTMP, deoxythymidylate monophosphate; dUMP, deoxyuridylate monophosphate; MS, methionine synthase; MTHFR, 5,10-methylenetetrahydrofolate reductase; SAH, *S*-adenosylhomocysteine; SAM, *S*-adenosylmethionine; SHMT, serine hydroxymethyltransferase; TS, thymidylate synthase; 5,10-methyleneTHF, 5,10-methylenetetrahydrofolate; 5-methylTHF, 5-methyltetrahydrofolate.

colorectal cancer and colorectal adenomas, particularly among individuals who consume alcohol.[21–23] Few studies, however, have examined the relationship between vitamin B_6 intake and colorectal cancer,[24–28] and only 2 studies[25,26] have investigated whether the association is modified by alcohol consumption. Furthermore, only 1 study[26] has evaluated long-term vitamin B_6 intake in relation to colorectal cancer risk.

In this study, we sought to evaluate the association between long-term dietary vitamin B_6 intake (ie, vitamin B_6 from food sources) and colorectal cancer risk and its modification by alcohol consumption in the Swedish Mammography Cohort, a large population-based prospective cohort with repeated measurements of diet.

Materials and Methods

Study Population

The Swedish Mammography Cohort is a population-based cohort study established between 1987 and 1990, when all 90,303 women (then aged 40 to 76 years and living in Västmanland or Uppsala Counties, central Sweden) received a mailed questionnaire that solicited data on diet, educational level, weight, and height; a total of 66,651 women, representing 74% of the source population, returned a completed questionnaire. A follow-up questionnaire sent to all surviving participants in 1997 was expanded to include information on family history of colorectal cancer, smoking, physical activity, and use of dietary supplements and aspirin. The 1997 questionnaire also included a comprehensive survey of diet.

For these analyses, we excluded women with an erroneous National Registration Number and those with cancer (except nonmelanoma skin cancer) diagnosed before baseline. Women who had extreme total energy intake estimates (>3 SDs from the mean value for $\log_e$-transformed energy) were also excluded. After these exclusions, the study cohort comprised 61,433 women at the start of follow-up. This study was approved by the Ethics Committees at the Uppsala University Hospital and the Karolinska Institutet, Stockholm.

Assessment of Diet

A self-administered food-frequency questionnaire with 67 and 96 food items was mailed to participants at baseline (1987–1990) and in 1997, respectively. Participants were asked how often, on average, they had consumed each type of food or beverage during the past 6 months (baseline questionnaire) or the past year (1997 questionnaire), by using 8 predefined response categories. For foods commonly consumed (eg, milk, bread, and butter), there were open-ended questions. Nutrient calculations were based on the mean values of age-specific (<53, 53–65, and ≥66 years) portion sizes of scaled-weighted foods that were recorded for 5922 days by 213 women randomly chosen from the study area. For each woman, we computed nutrient intake by multiplying the frequency response by the nutrient content of the age-specific servings. Values for the nutrient content in foods were obtained from the Swedish National Food Administration Database.[29] All nutrient intakes, except alcohol, were adjusted for total energy intake by using the residual method.[30]

In a study of the validity of the food-frequency questionnaire among 129 women randomly selected from the cohort, Pearson correlation coefficients between estimates from the average of four 1-week diet records and the dietary questionnaire were 0.5 for dietary vitamin B_6 and 0.9 for alcohol (A.W., unpublished data). Among this group of women, the mean estimated dietary vitamin B_6 intake was 1.7 mg/day (SD, 0.4 mg/day).

Case Ascertainment and Follow-up of the Cohort

By using the National Registration Numbers of the participants, incident colorectal cancer cases were identified by computerized record linkages with the National Swedish Cancer Registry and the Regional Cancer Registry covering the study area. Follow-up for cancers through these registries is nearly 100% complete.[31] Ascertainment of deaths in the cohort and the date when a participant moved out of the study area was accomplished by matching with the Swedish Death and Population Registries.

Colon cancers were defined as tumors occurring above the peritoneal delineation of the abdominal cavity, and rectal cancers were tumors occurring below this delineation. Women who had both colon and rectal cancer were excluded from subsite-specific analyses but were included in the overall analyses of colorectal cancer.

Data Analysis

Person-time of follow-up for each woman was computed from the date of her entry into the cohort until the date