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Vitamin B6 and colorectal cancer: Current evidence and future directions

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Abstract
Colorectal cancer remains the third most common cancer in both women and men worldwide. Identifying modifiable dietary factors is crucial in developing primary prevention strategies. Vitamin B6 is involved in more than 100 coenzyme reactions, and may influence colorectal cancer risk in multiple ways including through its role in one-carbon metabolism related DNA synthesis and methylation and by reducing inflammation, cell proliferation, and oxidative stress. Observational studies of dietary or dietary plus supplementary intake of vitamin B6 and colorectal cancer risk have been inconsistent with most studies reporting non-significant positive or inverse associations. However, published studies of plasma pyridoxal 5’-phosphate (the active form of vitamin B6) levels consistently support an approximately 30%-50% reduction in risk of colorectal cancer comparing high with low concentrations. The reasons for the discrepancy in the results between dietary-based and plasma-based studies remain unresolved. Other unresolved questions include the effects of vitamin B6 intake in early life (i.e., childhood or adolescence) and of suboptimal vitamin B6 status on colorectal cancer risk, whether the associations with vitamin B6 differ across molecular subtypes of colorectal cancer, and whether the vitamin B6-colorectal cancer association is modified by genetic variants of one-carbon metabolism.

INTRODUCTION
Colorectal cancer is the third most common cancer worldwide. In the United States, colorectal cancer will account for approximately 143,460 new cases in 2012. The wide variation in age-adjusted incidence rates for colorectal cancer between countries suggests a role of environmental factors such as diet in colorectal carcinogenesis. However, as summarized in several recent reviews, the effect of dietary factors on colorectal cancer remains largely inconclusive. For example, based on a comprehensive review of published studies, the 2011 World Cancer Research Foundation and American Institute for Cancer Research report on diet and colorectal cancer.
cancer identified that there was convincing evidence only for red meat, processed meat, and alcoholic drinks (in men) as risk factors and for dietary fiber as a protective factor for colorectal cancer. The effect of other dietary factors such as vitamin B6 on colorectal cancer remains to be elucidated. Vitamin B6, a one-carbon metabolism related nutrient, may have a potential role in colorectal carcinogenesis. The current epidemiologic studies examining vitamin B6 and risk of sporadic colorectal cancer and adenomas are briefly summarized here. Although the possible effect of vitamin B6 may differ by molecular subtype of colorectal cancer or be mediated by genetic variants in one-carbon metabolism, few data are available to date and thus are not reviewed here.

Vitamin B6 is a water-soluble vitamin that participates in more than 100 coenzyme reactions involved in the metabolism of protein, carbohydrates, and lipids. In the United States, the major food sources for vitamin B6 include fortified cereals, starchy vegetables, beef, and poultry. The recommended daily allowance (RDA) for vitamin B6 intake is 1.7 mg/d for men and 1.5 mg/d for women aged 51 years or older, although some subgroups of the population including smokers, blacks, seniors, and current and former oral contraceptive users require higher intakes. Plasma pyridoxal 5'-phosphate (PLP) is the active form of vitamin B6 and is most commonly used to measure vitamin B6 status. A PLP level of more than 20 nmol/L is an indicator of adequate vitamin B6 status in adults. The 2003-2006 national health and nutrition examination survey found that 11% of vitamin B6 supplement users (approximately 20%-30% of United States adults) and 24% of people in the United States who do not take supplements containing vitamin B6 have suboptimal plasma PLP concentrations (< 20 nmol/L).

**VITAMIN B6 AND POTENTIAL MECHANISMS RELATED TO COLORECTAL CARCINOGENESIS**

Vitamin B6 may influence colorectal carcinogenesis through its role in DNA synthesis and methylation, both of which are potentially involved in colorectal carcinogenesis. In addition, animal models have demonstrated that supplemental vitamin B6 suppressed cell proliferation and reduced the number of tumors in the colon. Moreover, vitamin B6 has been shown to inhibit angiogenesis, suppress nitric oxide, and reduce oxidative stress, all of which are associated with preventing carcinogenesis. Further, low vitamin B6 status may link to chronic inflammation, a potential risk factor for colorectal cancer, based on significantly lower PLP concentrations observed among patients with inflammatory bowel diseases and rheumatoid arthritis compared to generally healthy populations. Other evidence of the link between vitamin B6 and inflammation includes the inverse relation of plasma PLP with cardiovascular disease, C-reactive protein, and tumor necrosis factor alpha.

**OBSERVATIONAL STUDIES OF VITAMIN B6 INTAKE AND COLORECTAL CANCER RISK**

Despite potential mechanisms supporting the hypothesis that vitamin B6 may reduce colorectal cancer risk, epidemiologic evidence examining vitamin B6 intake and colorectal cancer risk has been inconclusive. At least 9 case-control studies have examined the relation between vitamin B6 intake and colorectal cancer risk. The majority of the case-control studies reported a modest significant inverse association for comparisons of the highest with the lowest vitamin B6 intake categories. For example, a quantitative review of six case-control studies published in 2008 reported a summary multivariable relative risk (RR) of 0.67 (95% CI: 0.60-0.75) comparing high with low vitamin B6 intake. However, there was borderline significant heterogeneity among these case-control studies (P value for heterogeneity = 0.09) with risk estimates ranging from 0.51 to 1.00. In addition, a meta-analysis of nine cohort studies that included eleven risk estimates (3 studies analyzed men and women separately) found no substantial effect of vitamin B6 intake on colorectal cancer risk (high vs low intake categories, summary RR = 0.90, 95% CI: 0.75-1.07). However, there was statistically significant heterogeneity in the results from the cohort studies (P value for heterogeneity = 0.01) with 6 cohort studies reporting 18%-39% lower risks of colorectal cancer compared to the highest vs lowest categories (the associations in three studies were statistically significant) and 5 studies reporting nonsignificant positive associations.

In the meta-analysis, only two cohort studies had evaluated associations with total vitamin B6 intake and a nonsignificant association was observed (summary RR = 0.90, 95% CI: 0.73-1.11). The only subsequently published study of two cohorts examined potential latency effects of vitamin B6 intake on colorectal cancer risk and found no difference for intakes measured 0-4 years before diagnosis compared to intakes measured 12-16 years before diagnosis. Of note, the study populations in these studies were relatively well nourished, with a low prevalence (i.e., 5%-10%) of individuals below the RDA levels of vitamin B6 intake, limiting the ability to test the potential effect of suboptimal vitamin B6 status on colorectal cancer risk.

**NESTED CASE-CONTROL STUDIES OF PLASMA PLP CONCENTRATIONS AND COLORECTAL CANCER RISK**

Four out of five nested case-control studies conducted to date have shown that higher pre-diagnostic plasma PLP concentrations were statistically significantly associated with a 30%-50% lower risk of colorectal cancer. The first study was from the United States (n = 188 cases, highest vs lowest quartile, RR = 0.48, 95% CI: 0.25-0.92, P value for trend = 0.05). The second study conducted...
in Finland found that men in the highest quartile of PLP concentrations had non-significant lower risk of colorectal cancer ($n = 275$ cases, $RR = 0.61$, $95\% CI: 0.32-1.14$, $P$ value for trend = 0.08$[33]$). Similarly, magnitudes of inverse associations were also observed in subsequent analyses using data from the Multiethnic Cohort study ($n = 223$ cases, $RR = 0.52$, $95\% CI: 0.29-0.92$, $P$ value for trend = 0.03$[33]$) and the Physicians’ Heath Study ($n = 197$ cases, $RR = 0.49$, $95\% CI: 0.26-0.92$, $P$ value for trend = 0.01$[34]$).

Likewise, in the largest and most recent analysis to date ($n = 1365$ cases), the $RR$ comparing the highest to lowest quintile was 0.68 ($95\% CI: 0.53-0.87$, $P$ value for trend < 0.001) in the European Prospective Investigation into Cancer and Nutrition cohort$[9]$. As shown in the meta-analysis of these studies$[29]$, the pooled $RR$ of colorectal cancer for the highest vs lowest categories of PLP levels was 0.52 ($95\% CI: 0.38-0.71$).

**CLINICAL TRIALS OF VITAMIN B6 SUPPLEMENT AND COLORECTAL CANCER**

The effect of treatment with vitamin B6 supplements (40 mg/d) on colorectal cancer incidence and mortality has been evaluated, to the best of our knowledge, in only two randomized double-blind, placebo-controlled trials, the Norwegian Vitamin Trial$[36]$ and the Western Norway B Vitamin Intervention Trial$[37]$. These studies were not primarily designed to examine cancer outcomes and included 6837 participants with ischemic heart disease after a median of 39 mo of treatment and an additional 38 mo of post-trial observational follow-up$[37]$. In both trials, participants were randomized into one of four groups: (1) folic acid (0.8 mg/d), vitamin B12 (0.4 mg/d), and vitamin B6 (40 mg/d); (2) folic acid (0.8 mg/d) and vitamin B12 (0.4 mg/d); (3) vitamin B6 alone (40 mg/d); or (4) placebo. The pooled analysis of data from these two trials showed no benefit of vitamin B6 supplementation on incident colorectal cancer or fatal colorectal cancer. Of note, only a limited number of colorectal cancer cases and deaths were included in the analysis. A total of 26 participants (1.5%) who received vitamin B6 and 22 (1.3%) participants in the placebo group were diagnosed with incident colorectal cancer during the trial (vitamin B6 vs non-vitamin B6 group, $RR = 1.18$, $95\% CI: 0.69-2.00$)$[37]$. Furthermore, there were only 5 deaths due to colorectal cancer in the vitamin B6 group and 7 in the placebo group (vitamin B6 vs non-vitamin B6 group, $RR = 0.51$, $95\% CI: 0.17-1.55$)$[37]$.

**VITAMIN B6 INTAKE, PLASMA PLP CONCENTRATIONS AND COLORECTAL ADENOMAS**

The evidence for the association between vitamin B6 intake or plasma PLP concentrations and risk of colorectal adenoma, precursors of colorectal cancer, is less consistent than observed for colorectal cancer, with only a small number of studies published$[10,11,31,38]$. Specifically, the first study found a suggestive inverse association between plasma PLP concentration and advanced ($\geq 1$ cm in size, or villous or tubulovillous) distal colorectal adenoma ($n = 408$ cases, $RR = 0.65$, $95\% CI: 0.37-1.11$, $P$ value for trend = 0.08), but a weaker association with low risk of (small and tubulous) adenoma ($n = 210$ cases, $RR = 0.85$, $95\% CI: 0.52-1.38$, $P$ value for trend = 0.05$[31]$). The other cohort study showed that high plasma levels of PLP were inversely associated with risk of colorectal adenoma ($n = 210$ cases, highest vs lowest tertile, $RR = 0.44$, $95\% CI: 0.26-0.74$, $P$ value for trend = 0.002)$[38]$. Among 2 studies that evaluated the effect of vitamin B6 and adenoma recurrence, the first study from the Wheat Bran Fiber intervention trial showed a lower odds of adenoma recurrence for higher vitamin B6 intake ($n = 495$ recurrences, highest vs lowest quartile, OR = 0.65, $95\% CI: 0.45-0.94$, $P$ value for trend = 0.03$[38]$). The Aspirin/Folate Polyp Prevention Study, a trial of folic acid supplementation, found a borderline significant inverse association with plasma PLP concentrations and risk of adenoma recurrence ($n = 430$ recurrences, highest vs lowest quartile, $RR = 0.78$, $95\% CI: 0.61-1.00$, $P$ value for trend = 0.08$[39]$).

**DISCUSSION**

Overall, based on a meta-analysis of nine cohort studies a substantial effect of vitamin B6 intake in adulthood and colorectal cancer risk was not evident although the study-specific results were inconsistent. In contrast, all five studies of circulating PLP levels found that participants with higher plasma PLP levels had a 30%-50% lower risk of colorectal cancer with the associations being statistically significant in four of the studies. Of note, only two nested case-control studies$[31,33]$ have examined associations with both vitamin B6 intake and PLP levels and colorectal cancer risk and in these two studies inverse associations of similar magnitude were observed for vitamin B6 intake and plasma PLP concentrations and colorectal cancer risk. Several issues related to examining associations between vitamin B6 and colorectal cancer risk are discussed below.

**Confounding by other factors?**

Vitamin B6 intake is an important determinant of PLP levels$[39]$. However, individuals with high vitamin B6 intake tend to have healthy behaviors such as higher physical activity, less smoking, and higher intakes of folate, calcium, and vitamin D compared to individuals with lower vitamin B6 intake$[30,40,41]$. Because being physically active, not smoking, and having higher intakes of folate, calcium and vitamin D may reduce the risk of colorectal cancer$[35,34]$, the inverse associations observed with higher PLP concentrations might be simply due to the correlations between vitamin B6 intake and these healthy behaviors. Although previous studies have adjusted for these potential confounding factors$[29,30]$, residual confounding may still exist. Further, it is challenging to tease
out the independent effect of vitamin B6 from certain other nutrients such as folate, calcium, and vitamin D given that their intakes are positively correlated, particularly for intakes from food and supplemental sources combined. In addition, variation in plasma PLP could possibly reflect metabolic states such as chronic inflammation\cite{22,24,27,49}, a risk factor for colorectal cancer\cite{21}. Studies have shown that patients with inflammatory bowel diseases\cite{22} and rheumatoid arthritis\cite{23,24} have significantly lower plasma PLP concentrations than healthy individuals. Although the data are not in full agreement\cite{44}, plasma PLP concentrations also have been found to be inversely correlated with C-reactive protein levels\cite{23,27}, and tumor necrosis factor alpha levels\cite{54}, both of which are markers of inflammation and possible risk factors for colorectal cancer\cite{47}. Possibly, lower PLP levels could reflect a patho-physiologic state such as inflammation, which may be associated with higher risk of colorectal cancer, but increasing plasma PLP concentrations through increased intake may not necessarily lead to lower colorectal cancer risk. However, one study found that the inverse association with higher plasma PLP concentrations did not change even after adjustment for plasma concentrations of homocysteine, C-reactive protein, tumor necrosis factor alpha, and interleukin-6\cite{46}. Nonetheless, it is unclear whether plasma PLP levels per se or the healthy behaviors or physiologic states associated with plasma PLP levels conferred the benefits observed in the studies of PLP concentrations and colorectal cancer risk.

Measurement error in assessment of vitamin B6?

Measurement error may have occurred in estimated vitamin B6 intake assessed using food frequency questionnaires (FFQs). However, the relatively high correlations (ranged from 0.4 to 0.8) observed between vitamin B6 intake assessed by FFQs and intake assessed using a reference methods (i.e., dietary records\cite{6,30,40-42,48,49}) reduce the possibility of missing a strong association between vitamin B6 intake and colorectal cancer risk in cohort studies. Moreover, total vitamin B6 intake (from food and supplemental sources combined) appears to be a good predictor of plasma PLP concentrations. For example, among representative random samples from the Nurses’ Health Study (n = 381 women) and the Health Professionals Follow-up Study (n = 345 men) who had provided blood samples and served as controls in a nested case-control study of colorectal cancer\cite{30}, an approximately 3-fold difference was observed in mean plasma PLP concentrations comparing the top vs bottom quintiles of total vitamin B6 intake. Specifically, for the top and bottom quintile categories of total vitamin B6 intake, the mean plasma PLP concentrations were 98.3 nmol/L and 38.9 nmol/L in women and 183.2 nmol/L and 66.0 nmol/L in men. In addition, the Spearman correlation coefficients between total vitamin B6 intake and plasma PLP concentrations were 0.52 in women and 0.54 in men\cite{30}. Thus, the ability of FFQs to predict an almost 3-fold difference in plasma PLP levels argues against measurement error in vitamin B6 intake masking detection of a strong association between vitamin B6 intake and colorectal cancer risk. Misclassification of vitamin B6 status also may occur in studies of PLP levels and colorectal cancer risk given that the studies published to date have only used one blood sample to measure PLP levels which may not reflect long-term vitamin B6 status.

Interaction with other factors?

Inconsistent results might also result from differences in distributions of potential effect modifiers of the association between vitamin B6 and colorectal cancer risk. Given that alcohol consumption may decrease vitamin B6 levels\cite{30,31}, any effect of vitamin B6 on colorectal cancer risk might therefore be stronger among heavy drinkers. To date, results have been conflicting among the six studies we identified. A non-significant interaction between vitamin B6 and total alcohol consumption including wine, beer, spirits was observed in three studies of vitamin B6 intakes\cite{30,31} and one study of plasma PLP levels\cite{30}. In contrast, a stronger inverse association with plasma PLP concentrations\cite{50} or vitamin B6 intake\cite{41} has been reported among alcohol drinkers compared to nondrinkers. In addition, if vitamin B6 influences the development of colorectal cancer through the one-carbon metabolism pathway, the potential benefit of vitamin B6 might be stronger among individuals with low intake of other one-carbon metabolism related nutrients such as folate, riboflavin, methionine, and vitamin B12. However, current studies are limited and found no evident pattern\cite{30,31}. With respect to adenomas, studies are limited and results have also been mixed. Results from the Multi-ethnic Cohort Study showed a non-significant interaction between plasma PLP and alcohol consumption\cite{31} and the Aspirin/Folate Polyp Prevention Study found that the inverse association with plasma PLP was evident only among nondrinkers (P value for interaction = 0.03)\cite{51}.

Timing of intake is important?

Because most cohort studies conducted to date have only a single assessment of vitamin B6 intake\cite{26,30}, it is uncertain when in the natural history vitamin B6 intake may influence colorectal cancer risk. However, a recent study that specifically evaluated the timing using time lagged analyses found no clear pattern\cite{30}. In contrast, when potential latency effects of total folate intake (another one-carbon metabolism related nutrient) were examined, only total folate intake measured 12-16 years prior to diagnosis of colorectal cancer was significantly associated with a lower risk of colorectal cancer, consistent with the only prior study examining the timing of folate intake on colorectal cancer risk\cite{31}. When total folate and total vitamin B6 intakes measured 12-16 years prior to diagnosis were simultaneously included in the multivariate model, a statistically significant inverse association continued to be observed for total folate intake while a weak, nonsignificant association was observed for total vitamin B6 intake. However, it is unknown whether vitamin B6 intake in childhood, adolescence, or early adulthood might be important in colorectal carcinogenesis because dietary
habits experienced early in development may play an important role in adult disease. The previous observational studies that we identified have focused on vitamin B6 intake in adulthood.

CONCLUSION

In contrast to the inverse associations observed in most studies of plasma PLP concentrations, the results from cohort studies of vitamin B6 intake in adulthood and colorectal cancer risk in relatively nourished populations have been inconsistent. The reason for this discrepancy between dietary-based and plasma-based studies remains unresolved and a better understanding is needed of the determinants of plasma PLP concentrations. Future studies should focus on early life intake (i.e., childhood or adolescence), the effects of suboptimal vitamin B6 status, molecular subtypes of colorectal cancer, and effect modification by genetic variants of one-carbon metabolism.

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