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TOPIC HIGHLIGHT

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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.

Key words: Vitamin B6; Plasma pyridoxal 5′-phosphate; Colorectal cancer; Adenoma; Incidence; Case-control study; Cohort study; Randomized controlled trial; Epidemiology

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INTRODUCTION

Colorectal cancer is the third most common cancer worldwide[1]. In the United States, colorectal cancer will account for approximately 143 460 new cases in 2012[2]. 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[3-5], 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 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[3]. 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[6-11] 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[12]. In the United States, the major food sources for vitamin B6 include fortified cereals, starchy vegetables, beef, and poultry[12]. 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[12] although some subgroups of the population including smokers, blacks, seniors, and current and former oral contraceptive users require higher intakes[13]. 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[12]. The 2003-2006 national health and nutrition examination survey found that 11% of vitamin B6 supplement users (approximately 20%-30% of United States adults[14]) and 24% of people in the United States who do not take supplements containing vitamin B6 have suboptimal plasma PLP concentrations (< 20 nmol/L)[13].

VITAMIN B6 AND POTENTIAL MECHANISMS RELATED TO COLORECTAL CARCINOGENESIS

Vitamin B6 may influence colorectal carcinogenesis through its role in DNA synthesis and methylation[15], 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[16,17]. Moreover, vitamin B6 has been shown to inhibit angiogenesis[18], suppress nitric oxide[16], and reduce oxidative stress[19], all of which are associated with preventing carcinogenesis. Further, low vitamin B6 status may link to chronic inflammation[20], a potential risk factor for colorectal cancer[21], based on significantly lower PLP concentrations observed among patients with inflammatory bowel diseases[22] and rheumatoid arthritis[23,24] 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[25,26], C-reactive protein[23,27], and tumor necrosis factor alpha[24].

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[28]. 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 comparing the highest *vs* lowest categories (the associations in three studies were statistically significant) and 5 studies reporting nonsignificant positive associations[29]. 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)[29]. 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[30]. 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[29]. 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 = 0.03)[31]. 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)[32]. Similar 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[35] and the Western Norway B Vitamin Intervention Trial[36]. 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 (≥ 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 = 0.52)[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)[10]. 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)[11].

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[30,40-42]. Because being physically active, not smoking, and having higher intakes of folate, calcium and vitamin D may reduce the risk of colorectal cancer[3,5,43,44], 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[22-24,27,45], a risk factor for colorectal cancer[21]. Studies have shown that patients with inflammatory bowel diseases[22] and rheumatoid arthritis[23,24] have significantly lower plasma PLP concentrations than healthy individuals. Although the data are not in full agreement[46], plasma PLP concentrations also have been found to be inversely correlated with C-reactive protein levels[23,27], and tumor necrosis factor alpha levels[24], both of which are markers of inflammation and possible risk factors for colorectal cancer[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[34]. 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)[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[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[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[50,51], 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[30,52] and one study of plasma PLP levels[31]. In contrast, a stronger inverse association with plasma PLP concentrations[9] or vitamin B6 intake[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[30,31]. With respect to adenomas, studies are limited and results have also been mixed. Results from the Multiethnic Cohort Study showed a non-significant interaction between plasma PLP and alcohol consumption[10] 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)[11].

Timing of intake is important?

Because most cohort studies conducted to date have only a single assessment of vitamin B6 intake[29,30], 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[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[53]. 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[54,55]. The previous observational studies that we identified have focused on vitamin B6 intake in adulthood[30].

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.

REFERENCES

1 **Ferlay J**, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**: 2893-2917 [PMID: 21351269 DOI: 10.1002/ijc.25516]

2 **Siegel R**, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012; **62**: 10-29 [PMID: 22237781 DOI: 10.3322/caac.20138]

3 **World Cancer Research Fund,** American Institute for Cancer Research. Continuous Update Project Report Summary: Food, Nutrition, Physical Activity, and the Prevention of Colorectal Cancer. 2011

4 **World Cancer Research Fund,** American Institute for Cancer Research Expert Panel. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. 2007

5 **Chan AT**, Giovannucci EL. Primary prevention of colorectal cancer. *Gastroenterology* 2010; **138**: 2029-2043.e10 [PMID: 20420944]

6 **Schernhammer ES**, Giovannuccci E, Fuchs CS, Ogino S. A prospective study of dietary folate and vitamin B and colon cancer according to microsatellite instability and KRAS mutational status. *Cancer Epidemiol Biomarkers Prev* 2008; **17**: 2895-2898 [PMID: 18843035 DOI: 10.1158/1055-9965.EPI-08-0638]

7 **Schernhammer ES**, Giovannucci E, Kawasaki T, Rosner B, Fuchs CS, Ogino S. Dietary folate, alcohol and B vitamins in relation to LINE-1 hypomethylation in colon cancer. *Gut* 2010; **59**: 794-799 [PMID: 19828464 DOI: 10.1136/gut.2009.183707]

8 **Schernhammer ES**, Ogino S, Fuchs CS. Folate and vitamin B6 intake and risk of colon cancer in relation to p53 expression. *Gastroenterology* 2008; **135**: 770-780 [PMID: 18619459 DOI: 10.1053/j.gastro.2008.06.033]

9 **Eussen SJ**, Vollset SE, Hustad S, Midttun Ø, Meyer K, Fredriksen A, Ueland PM, Jenab M, Slimani N, Boffetta P, Overvad K, Thorlacius-Ussing O, Tjønneland A, Olsen A, Clavel-Chapelon F, Boutron-Ruault MC, Morois S, Weikert C, Pischon T, Linseisen J, Kaaks R, Trichopoulou A, Zilis D, Katsoulis M, Palli D, Pala V, Vineis P, Tumino R, Panico S, Peeters PH, Bueno-de-Mesquita HB, van Duijnhoven FJ, Skeie G, Muñoz X, Martínez C, Dorronsoro M, Ardanaz E, Navarro C, Rodríguez L, VanGuelpen B, Palmqvist R, Manjer J, Ericson U, Bingham S, Khaw KT, Norat T, Riboli E. Plasma vitamins B2, B6, and B12, and related genetic variants as predictors of colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 2549-2561 [PMID: 20813848 DOI: 10.1158/1055-9965.epi-10-0407]

10 **Le Marchand L**, Wang H, Selhub J, Vogt TM, Yokochi L, Decker R. Association of plasma vitamin B6 with risk of colorectal adenoma in a multiethnic case-control study. *Cancer Causes Control* 2011; **22**: 929-936 [PMID: 21437631 DOI: 10.1007/s10552-011-9759-y]

11 **Figueiredo JC**, Levine AJ, Grau MV, Midttun O, Ueland PM, Ahnen DJ, Barry EL, Tsang S, Munroe D, Ali I, Haile RW, Sandler RS, Baron JA. Vitamins B2, B6, and B12 and risk of new colorectal adenomas in a randomized trial of aspirin use and folic acid supplementation. *Cancer Epidemiol Biomarkers Prev* 2008; **17**: 2136-2145 [PMID: 18708408 DOI: 10.1158/1055-9965.epi-07-2895]

12 **Institute of Medicine.** Dietary Reference Intakes: Thiamin R, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Washington, DC: National Academy Press, 1998

13 **Morris MS**, Picciano MF, Jacques PF, Selhub J. Plasma pyridoxal 5'-phosphate in the US population: the National Health and Nutrition Examination Survey, 2003-2004. *Am J Clin Nutr* 2008; **87**: 1446-1454 [PMID: 18469270]

14 **Bailey RL**, Gahche JJ, Lentino CV, Dwyer JT, Engel JS, Thomas PR, Betz JM, Sempos CT, Picciano MF. Dietary supplement use in the United States, 2003-2006. *J Nutr* 2011; **141**: 261-266 [PMID: 21178089 DOI: 10.3945/jn.110.133025]

15 **Selhub J**. Folate, vitamin B12 and vitamin B6 and one carbon metabolism. *J Nutr Health Aging* 2002; **6**: 39-42 [PMID: 11813080]

16 **Komatsu S**, Watanabe H, Oka T, Tsuge H, Kat N. Dietary vitamin B6 suppresses colon tumorigenesis, 8-hydroxyguanosine, 4-hydroxynonenal, and inducible nitric oxide synthase protein in azoxymethane-treated mice. *J Nutr Sci Vitaminol* (Tokyo) 2002; **48**: 65-68 [PMID: 12026192]

17 **Matsubara K**, Komatsu S, Oka T, Kato N. Vitamin B6-mediated suppression of colon tumorigenesis, cell proliferation, and angiogenesis (review). *J Nutr Biochem* 2003; **14**: 246-250 [PMID: 12832027]

18 **Matsubara K**, Mori M, Matsuura Y, Kato N. Pyridoxal 5'-phosphate and pyridoxal inhibit angiogenesis in serum-free rat aortic ring assay. *Int J Mol Med* 2001; **8**: 505-508 [PMID: 11605018]

19 **Jain SK**, Lim G. Pyridoxine and pyridoxamine inhibits superoxide radicals and prevents lipid peroxidation, protein glycosylation, and (Na+ + K+)-ATPase activity reduction in high glucose-treated human erythrocytes. *Free Radic Biol Med* 2001; **30**: 232-237 [PMID: 11165869]

20 **Shen J**, Lai CQ, Mattei J, Ordovas JM, Tucker KL. Association of vitamin B-6 status with inflammation, oxidative stress, and chronic inflammatory conditions: the Boston Puerto Rican Health Study. *Am J Clin Nutr* 2010; **91**: 337-342 [PMID: 19955400 DOI: 10.3945/ajcn.2009.28571]

21 **Boland CR**, Luciani MG, Gasche C, Goel A. Infection, inflammation, and gastrointestinal cancer. *Gut* 2005; **54**: 1321-1331 [PMID: 16099799 DOI: 10.1136/gut.2004.060079]

22 **Saibeni S**, Cattaneo M, Vecchi M, Zighetti ML, Lecchi A, Lombardi R, Meucci G, Spina L, de Franchis R. Low vitamin B(6) plasma levels, a risk factor for thrombosis, in inflammatory bowel disease: role of inflammation and correlation with acute phase reactants. *Am J Gastroenterol* 2003; **98**: 112-117 [PMID: 12526945 DOI: 10.1111/j.1572-0241.2003.07160.x]

23 **Chiang EP**, Bagley PJ, Selhub J, Nadeau M, Roubenoff R. Abnormal vitamin B(6) status is associated with severity of symptoms in patients with rheumatoid arthritis. *Am J Med* 2003; **114**: 283-287 [PMID: 12681455]

24 **Roubenoff R**, Roubenoff RA, Selhub J, Nadeau MR, Cannon JG, Freeman LM, Dinarello CA, Rosenberg IH. Abnormal vitamin B6 status in rheumatoid cachexia. Association with spontaneous tumor necrosis factor alpha production and markers of inflammation. *Arthritis Rheum* 1995; **38**: 105-109 [PMID: 7818558]

25 **Folsom AR**, Nieto FJ, McGovern PG, Tsai MY, Malinow MR, Eckfeldt JH, Hess DL, Davis CE. Prospective study of coronary heart disease incidence in relation to fasting total ho-

mocysteine, related genetic polymorphisms, and B vitamins: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 1998; **98**: 204-210 [PMID: 9697819]
26 **Robinson K**, Arheart K, Refsum H, Brattström L, Boers G, Ueland P, Rubba P, Palma-Reis R, Meleady R, Daly L, Witteman J, Graham I. Low circulating folate and vitamin B6 concentrations: risk factors for stroke, peripheral vascular disease, and coronary artery disease. European COMAC Group. *Circulation* 1998; **97**: 437-443 [PMID: 9490237]
27 **Friso S**, Jacques PF, Wilson PW, Rosenberg IH, Selhub J. Low circulating vitamin B(6) is associated with elevation of the inflammation marker C-reactive protein independently of plasma homocysteine levels. *Circulation* 2001; **103**: 2788-2791 [PMID: 11401933]
28 **Theodoratou E**, Farrington SM, Tenesa A, McNeill G, Cetnarskyj R, Barnetson RA, Porteous ME, Dunlop MG, Campbell H. Dietary vitamin B6 intake and the risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev* 2008; **17**: 171-182 [PMID: 18199722]
29 **Larsson SC**, Orsini N, Wolk A. Vitamin B6 and risk of colorectal cancer: a meta-analysis of prospective studies. *JAMA* 2010; **303**: 1077-1083 [PMID: 20233826]
30 **Zhang X**, Lee JE, Ma J, Je Y, Wu K, Willett WC, Fuchs CS, Giovannucci EL. Prospective cohort studies of vitamin B-6 intake and colorectal cancer incidence: modification by time? *Am J Clin Nutr* 2012; **96**: 874-881 [PMID: 22875713 DOI: 10.3945/ajcn.112.037267]
31 **Wei EK**, Giovannucci E, Selhub J, Fuchs CS, Hankinson SE, Ma J. Plasma vitamin B6 and the risk of colorectal cancer and adenoma in women. *J Natl Cancer Inst* 2005; **97**: 684-692 [PMID: 15870439 DOI: 10.1093/jnci/dji116]
32 **Weinstein SJ**, Albanes D, Selhub J, Graubard B, Lim U, Taylor PR, Virtamo J, Stolzenberg-Solomon R. One-carbon metabolism biomarkers and risk of colon and rectal cancers. *Cancer Epidemiol Biomarkers Prev* 2008; **17**: 3233-3240 [PMID: 18990766 DOI: 10.1158/1055-9965.EPI-08-0459]
33 **Le Marchand L**, White KK, Nomura AM, Wilkens LR, Selhub JS, Tiirikainen M, Goodman MT, Murphy SP, Henderson BE, Kolonel LN. Plasma levels of B vitamins and colorectal cancer risk: the multiethnic cohort study. *Cancer Epidemiol Biomarkers Prev* 2009; **18**: 2195-2201 [PMID: 19661077 DOI: 10.1158/1055-9965.EPI-09-0141]
34 **Lee JE**, Li H, Giovannucci E, Lee IM, Selhub J, Stampfer M, Ma J. Prospective study of plasma vitamin B6 and risk of colorectal cancer in men. *Cancer Epidemiol Biomarkers Prev* 2009; **18**: 1197-1202 [PMID: 19336555 DOI: 10.1158/1055-9965.EPI-08-1001]
35 **Bønaa KH**, Njølstad I, Ueland PM, Schirmer H, Tverdal A, Steigen T, Wang H, Nordrehaug JE, Arnesen E, Rasmussen K. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med* 2006; **354**: 1578-1588 [PMID: 16531614 DOI: 10.1056/NEJMoa055227]
36 **Ebbing M**, Bleie Ø, Ueland PM, Nordrehaug JE, Nilsen DW, Vollset SE, Refsum H, Pedersen EK, Nygård O. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography: a randomized controlled trial. *JAMA* 2008; **300**: 795-804 [PMID: 18714059 DOI: 10.1001/jama.300.7.795]
37 **Ebbing M**, Bønaa KH, Nygård O, Arnesen E, Ueland PM, Nordrehaug JE, Rasmussen K, Njølstad I, Refsum H, Nilsen DW, Tverdal A, Meyer K, Vollset SE. Cancer incidence and mortality after treatment with folic acid and vitamin B12. *JAMA* 2009; **302**: 2119-2126 [PMID: 19920236 DOI: 10.1001/jama.2009.1622]
38 **Martínez ME**, Henning SM, Alberts DS. Folate and colorectal neoplasia: relation between plasma and dietary markers of folate and adenoma recurrence. *Am J Clin Nutr* 2004; **79**: 691-697 [PMID: 15051616]
39 **Brussaard JH**, Löwik MR, van den Berg H, Brants HA, Bemelmans W. Dietary and other determinants of vitamin B6 parameters. *Eur J Clin Nutr* 1997; **51** Suppl 3: S39-S45 [PMID: 9598767]
40 **Zhang SM**, Moore SC, Lin J, Cook NR, Manson JE, Lee IM, Buring JE. Folate, vitamin B6, multivitamin supplements, and colorectal cancer risk in women. *Am J Epidemiol* 2006; **163**: 108-115 [PMID: 16339055 DOI: 10.1093/aje/kwj016]
41 **Larsson SC**, Giovannucci E, Wolk A. Vitamin B6 intake, alcohol consumption, and colorectal cancer: a longitudinal population-based cohort of women. *Gastroenterology* 2005; **128**: 1830-1837 [PMID: 15940618]
42 **Ishihara J**, Otani T, Inoue M, Iwasaki M, Sasazuki S, Tsugane S. Low intake of vitamin B-6 is associated with increased risk of colorectal cancer in Japanese men. *J Nutr* 2007; **137**: 1808-1814 [PMID: 17585035]
43 **Zhang X**, Giovannucci E. Calcium, vitamin D and colorectal cancer chemoprevention. *Best Pract Res Clin Gastroenterol* 2011; **25**: 485-494 [PMID: 22122765 DOI: 10.1016/j.bpg.2011.10.001]
44 **Martínez ME**. Primary prevention of colorectal cancer: lifestyle, nutrition, exercise. *Recent Results Cancer Res* 2005; **166**: 177-211 [PMID: 15648191]
45 **Chiang EP**, Smith DE, Selhub J, Dallal G, Wang YC, Roubenoff R. Inflammation causes tissue-specific depletion of vitamin B6. *Arthritis Res Ther* 2005; **7**: R1254-R1262 [PMID: 16277678 DOI: 10.1186/ar1821]
46 **Folsom AR**, Desvarieux M, Nieto FJ, Boland LL, Ballantyne CM, Chambless LE. B vitamin status and inflammatory markers. *Atherosclerosis* 2003; **169**: 169-174 [PMID: 12860264]
47 **Chan AT**, Ogino S, Giovannucci EL, Fuchs CS. Inflammatory markers are associated with risk of colorectal cancer and chemopreventive response to anti-inflammatory drugs. *Gastroenterology* 2011; **140**: 799-808 [PMID: 21115010]
48 **Shu XO**, Yang G, Jin F, Liu D, Kushi L, Wen W, Gao YT, Zheng W. Validity and reproducibility of the food frequency questionnaire used in the Shanghai Women's Health Study. *Eur J Clin Nutr* 2004; **58**: 17-23 [PMID: 14679362 DOI: 10.1038/sj.ejcn.1601738]
49 **Harnack L**, Jacobs DR, Nicodemus K, Lazovich D, Anderson K, Folsom AR. Relationship of folate, vitamin B-6, vitamin B-12, and methionine intake to incidence of colorectal cancers. *Nutr Cancer* 2002; **43**: 152-158 [PMID: 12588695]
50 **Lumeng L**, Li TK. Vitamin B6 metabolism in chronic alcohol abuse. Pyridoxal phosphate levels in plasma and the effects of acetaldehyde on pyridoxal phosphate synthesis and degradation in human erythrocytes. *J Clin Invest* 1974; **53**: 693-704 [PMID: 4359937 DOI: 10.1172/JCI107607]
51 **Giovannucci E**. Alcohol, one-carbon metabolism, and colorectal cancer: recent insights from molecular studies. *J Nutr* 2004; **134**: 2475S-2481S [PMID: 15333745]
52 **Slattery ML**, Schaffer D, Edwards SL, Ma KN, Potter JD. Are dietary factors involved in DNA methylation associated with colon cancer? *Nutr Cancer* 1997; **28**: 52-62 [PMID: 9200151]
53 **Lee JE**, Willett WC, Fuchs CS, Smith-Warner SA, Wu K, Ma J, Giovannucci E. Folate intake and risk of colorectal cancer and adenoma: modification by time. *Am J Clin Nutr* 2011; **93**: 817-825 [PMID: 21270374]
54 **Barker DJ**. The fetal and infant origins of adult disease. *BMJ* 1990; **301**: 1111 [PMID: 2252919]
55 **Trichopoulos D**. Hypothesis: does breast cancer originate in utero? *Lancet* 1990; **335**: 939-940 [PMID: 1970028]

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