Prospective cohort studies of vitamin B-6 intake and colorectal cancer incidence: modification by time?[1–4]

Xuehong Zhang, Jung Eun Lee, Jing Ma, Youjin Je, Kana Wu, Walter C Willett, Charles S Fuchs, and Edward L Giovannucci

ABSTRACT

Background: The relation between vitamin B-6 intake and colorectal cancer risk remains uncertain.

Objective: We prospectively evaluated whether a higher vitamin B-6 intake in the remote past is more strongly associated with a lower risk of colorectal cancer than is an intake in the recent past in the Nurses' Health Study and the Health Professionals Follow-Up Study.

Design: We assessed vitamin B-6 intake every 4 y by using validated food-frequency questionnaires and followed 86,440 women and 44,410 men for ≤28 y. Cox proportional hazards regression was used to estimate multivariable RRs and 95% CIs.

Results: The total vitamin B-6 intake was significantly associated with an ∼20–30% lower risk of colorectal cancer in age-adjusted results, but this association became attenuated and nonsignificant after additional adjustment for nondietary and dietary factors. When the highest to lowest quintiles of cumulative total vitamin B-6 intake were compared, RRs (95% CIs) for colorectal cancer were 0.99 (0.80, 1.24; *P*-trend = 0.55) for women and 0.95 (0.73, 1.23; *P*-trend = 0.75) for men. For the same comparison, RRs were 0.92 (0.73, 1.16) for total vitamin B-6 intake 0–4 y before diagnosis, 0.99 (0.78, 1.26) for intake 4–8 y before diagnosis, 0.92 (0.71, 1.21) for intake 8–12 y before diagnosis, and 0.93 (0.69, 1.26) for intake 12–16 y before diagnosis in women. Corresponding RRs for men were 0.86 (0.63, 1.17), 0.96 (0.70, 1.32), 0.90 (0.63, 1.29), and 1.16 (0.75, 1.79). Results did not differ by cancer subsite, source of vitamin B-6 (food or supplement), alcohol consumption, or folate intake.

Conclusion: Our data do not support a strong role of adulthood vitamin B-6 intake in colorectal carcinogenesis in these US health professionals. *Am J Clin Nutr* 2012;96:874–81.

INTRODUCTION

Vitamin B-6 plays an important role in one-carbon metabolism, which is essential for DNA synthesis and methylation (1). Aberrations in these processes may play a role in colorectal carcinogenesis. In addition, vitamin B-6 is involved in >100 coenzyme reactions and has also been shown in experimental studies to reduce oxidative stress, cell proliferation, and inflammation (2), all of which are associated with carcinogenesis. However, human epidemiologic evidence that examined vitamin B-6 intake and colorectal cancer risk has been inconclusive. In contrast to a significant inverse association reported from a meta-analysis of case-control studies (3), overall null associations were observed for 9 cohort studies conducted on this topic to date (4).

Although not totally understood, the misclassification of vitamin B-6 intake and lack of consideration of timing of vitamin B-6 intake may partly explain the inconsistent results. Of note, a one-time assessment of vitamin B-6 intake was conducted in 7 (of 9) of these cohort studies (4). In addition, the timing of vitamin B-6 intake might be important because a recent study (5) showed that total folate (another nutrient related to one-carbon metabolism) intake 12–16 y before diagnosis of colorectal cancer was associated with 35% lower risk of colorectal cancer, which indicated that the benefit of folate may be limited to the initiation or early development of colorectal cancer (5). However, it is uncertain when in the natural history vitamin B-6 intake may prevent colorectal cancer. Because a substantial proportion of US populations had suboptimal vitamin B-6 status according to the US NHANES (6), the identification of the optimal timing of vitamin B-6 intake for colorectal cancer prevention is of practical significance. To the best of our knowledge, no studies have investigated how the timing of vitamin B-6 intake influences risk of developing colorectal cancer.

The aim of this study was to evaluate whether vitamin B-6 intake, especially in the remote past, is associated with a lower risk of colorectal cancer. We used an updated and repeated assessment of vitamin B-6 intake every 4 y in the Nurses' Health Study (NHS)[5] and the Health Professionals Follow-Up Study (HPFS) to address our hypothesis.

[1] From the Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA (XZ, JM, WCW, CSF, and ELG); the Department of Food and Nutrition, Sookmyung Women's University, Seoul, Korea (JEL); the Departments of Nutrition (YJ, KW, WCW, and ELG) and Epidemiology (WCW and ELG), Harvard School of Public Health, Boston, MA; and the Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA (CSF).

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[4] Address reprint requests and correspondence to X Zhang, Brigham and Women's Hospital and Harvard Medical School, Channing Laboratory at Landmark Center (West Wing), 401 Park Drive, Suite 301 West, Boston, MA 02115. E-mail: xuehong.zhang@channing.harvard.edu.

[5] Abbreviations used: FFQ, food-frequency questionnaire; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; PLP, plasma pyridoxal 5′-phosphate; RDA, Recommended Daily Allowance.

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SUBJECTS AND METHODS

Study population

The NHS and the HPFS have been described in detail elsewhere (7). In brief, the NHS is a prospective cohort study of 121,700 registered female nurses who were aged 30–55 y at baseline in 1976 in the United States. The HPFS is a prospective cohort study of 51,529 US male professionals who were aged 40–75 y at baseline in 1986. The participants in these 2 cohorts have been sent a questionnaire every 2 y since 1976 and 1986, respectively, to collect information on demographic and lifestyle factors, medical history, and disease outcomes. The follow-up rate has been >90% for both cohorts. These studies have been approved by the institutional review board at the Harvard School of Public Health and Brigham and Women's Hospital, Boston, Massachusetts. We excluded participants with a history of cancer (except for nonmelanoma skin cancer), ulcerative colitis, or missing or extreme vitamin B-6 intake (ie, >3 SDs for log-transformed B-6 intake), which left 86,440 women and 44,410 men for the analysis.

Identification of incident colorectal cancer cases

In both cohorts, participants reported cancer and other disease endpoints in biennial questionnaires. Researchers obtained permission from study participants to obtain their medical records and pathologic reports and, while blinded to exposure information, abstracted the information on the anatomic location, stage, and histologic type of cancer. Colorectal cancer was defined according to the International Classification of Diseases, Ninth Revision (8). A total of 1614 incident adenocarcinoma colorectal cancer cases were documented in the NHS from 1980 to 2008, and 1013 cases were documented in the HPFS from 1986 to 2008.

Assessment of vitamin B-6 intake

Information on usual dietary intakes over the past year was obtained by using validated semi-quantitative food-frequency questionnaires (FFQs) for NHS participants in 1980 and was repeated in 1984, 1986, and every 4 y thereafter (7). Similar FFQs were administered for men in 1986 and were repeated every 4 y thereafter. Nine possible frequency choices were available that range from almost never to ≥6 times/d. Nutrient intake was calculated by multiplying the frequency of each food consumed and the nutrient content of specified portion sizes. Food-composition values for vitamin B-6 were mainly derived from the USDA. Supplemental vitamin B-6 intake was derived by using information collected on the dose and duration of multivitamin use and use of vitamin B-6 supplements. The total intake of vitamin B-6 was calculated by summing amounts from food and supplemental sources. The nutrients including total and dietary intakes of vitamin B-6 were adjusted for the total energy intake by using the residual method (7). The validity of the FFQs has been evaluated in 173 women from the NHS (9) and in 127 men from the HPFS (10). Pearson's correlation coefficients for total vitamin B-6 between mean intakes from multiple 1-wk diet records (4 for women and 2 for men) and Pearson's correlation coefficients from FFQs completed after these dietary records were 0.58 for women (9) and 0.85 for men (10). In addition, we evaluated whether vitamin B-6 intake was associated with plasma pyridoxal 5′-phosphate (PLP; which is the active form of vitamin B-6) concentrations in 381 women and 345 men who were representative random samples of the full cohorts and provided blood samples and served as control subjects in a nested case-control study of colorectal cancer (Y Ye, unpublished data, March 2012). As shown in **Table 1**, when top and bottom quintile categories of total vitamin B-6 intake were compared, mean plasma PLP concentrations were 98.3 and 38.9 pmol/mL in women and 183.2 and 66.0 pmol/mL in men.

Assessment of other variables

We also collected information on other dietary factors such as the consumption of red meat, processed meat, alcohol, folate, calcium, vitamin D, fruit, and vegetables from baseline and subsequent FFQs. In addition, we inquired about potential colorectal cancer risk factors such as height, body weight, physical activity, cigarette smoking, aspirin use, family history of colorectal cancer, menopausal status (women only), and postmenopausal hormone use (women only) in the biennial questionnaires.

Statistical analyses

We calculated the person-time for each participant from the date of the return of the baseline questionnaire to the date of death, colorectal cancer diagnosis, loss to follow-up, or end of follow-up (31 May 2008 for the NHS, 1 January 2008 for the HPFS), whichever came first. We used a Cox proportional hazards regression model (11) to calculate HRs, RRs, and 95% CIs and adjusted simultaneously for age (mo) and the year of questionnaire return. We observed no violation of the proportional hazard assumption.

We categorized energy-adjusted vitamin B-6 intake into quintiles on the basis of the distribution in the study population. We assigned median values of these categories and entered these values as continuous variables into the model to conduct trend tests. In addition to adjustment for age, in the multivariate models, we further adjusted for established nondietary risk factors (models 2 and 3) and additional dietary factors (model 3 only; these variables and categorizations are shown in **Table 2**). We further conducted additional analyses in which we adjusted for multivitamin use and intakes of fiber, red meat, riboflavin, vitamin B-12, and methionine. Additional adjustment of these factors, one at a time or simultaneously, did not materially alter the results and, thus, were not included in the final model. To compare the extreme vitamin B-6 intake, we modeled vitamin B-6 intake as deciles in secondary analyses.

We first modeled vitamin B-6 by using the baseline intake because most early cohort studies did. Second, to take advantage of repeated assessment in these cohorts, better represent long-term dietary intake, and minimize the influence of random measurement errors by using dietary assessments, we calculated the cumulative average intake of vitamin B-6. To evaluate the latency between vitamin B-6 intake and colorectal cancer, we performed analyses by using a varying lag time, as described previously (5). For example, in the NHS, for a latency of 0–4 y, we used vitamin B-6 intake in 1980 for cases diagnosed from 1980 to 1984, vitamin B-6 intake in 1984 for cases diagnosed

TABLE 1
Age-standardized characteristics (in 1990) by quintiles of total vitamin B-6 in the NHS and HPFS[1]

	NHS			HPFS		
Characteristic	Quintile 1	Quintile 3	Quintile 5	Quintile 1	Quintile 3	Quintile 5
Intake of total vitamin B-6 (mg/d)[2]	<1.6 (1.4)	2.1–3.4 (2.5)	>4.9 (7.8)	<2.1 (1.8)	2.6–4.0 (3.1)	>6.0 (11.4)
Age (y)	55.3 ± 7.1[3]	57.4 ± 7.0	57.6 ± 7.1	56.2 ± 9.3	58.5 ± 9.7	59.6 ± 9.7
BMI (kg/m^2)	25.8 ± 5.1	25.9 ± 4.8	25.4 ± 4.7	25.8 ± 3.3	25.6 ± 3.3	25.2 ± 3.2
Physical activity (MET-h/wk)[4]	12.4 ± 18.8	16.5 ± 22.6	17.5 ± 23.4	25.1 ± 28.6	30.6 ± 32.9	30.8 ± 36.1
History of colorectal cancer in a parent or sibling (%)	12	11	11	11	11	12
Current smoker (%)	24	13	14	10	5	7
Regular aspirin use (%)[5]	36	38	44	28	32	39
Multivitamin use (%)	2	18	84	3	17	91
Ever had a colonoscopy or sigmoidoscopy before 1990 (%)	10	12	14	40	44	47
Dietary intake						
Total energy (kcal/d)	1617 ± 503	1850 ± 505	1708 ± 509	1748 ± 542	2054 ± 601	1867 ± 572
Total carbohydrate (g/d)	193 ± 34	203 ± 30	204 ± 33	236 ± 42	253 ± 40	254 ± 46
Total fat (g/d)	60.5 ± 10.8	53.5 ± 9.5	53.4 ± 10.7	75.3 ± 13.5	66.3 ± 12.7	65.7 ± 14.5
Total protein (g/d)	68.9 ± 11.5	79.4 ± 12.9	78.4 ± 14.7	83.3 ± 13.6	94.6 ± 15.2	93.0 ± 17.0
Fruit and vegetables (servings/d)	4.0 ± 1.6	5.7 ± 2.1	5.4 ± 2.1	4.2 ± 1.7	6.4 ± 2.5	6.1 ± 2.7
Dietary fiber (g/d)[6]	14.8 ± 4.0	19.7 ± 5.2	19.6 ± 6.2	18.1 ± 5.2	24.2 ± 6.6	24.5 ± 8.5
Alcohol consumption (g/d)	6.0 ± 10.9	4.4 ± 8.1	4.8 ± 9.2	11.0 ± 15.6	9.5 ± 13.4	10.1 ± 14.3
Total calcium intake (mg/d)[6]	792 ± 414	928 ± 409	1222 ± 579	799 ± 342	876 ± 323	1064 ± 491
Total vitamin D intake (IU/d)[6]	177 ± 115	259 ± 127	565 ± 299	242 ± 132	343 ± 158	727 ± 366
Total folate intake (μg /d)[6]	245 ± 67	364 ± 81	662 ± 269	291 ± 75	420 ± 93	805 ± 320
Total vitamin B-12 intake (μg/d)[6]	5.9 ± 4.3	7.6 ± 5.0	16.8 ± 18.0	7.3 ± 5.0	9.3 ± 5.7	23.0 ± 30.2
Methionine intake (mg/d)[6]	1.6 ± 0.3	1.9 ± 0.4	1.8 ± 0.4	1.9 ± 0.4	2.2 ± 0.4	2.2 ± 0.5
Total riboflavin intake (mg/d)[6]	1.5 ± 0.6	2.0 ± 0.7	10.3 ± 12.6	1.7 ± 0.4	2.3 ± 0.7	13.0 ± 16.2
Beef, pork, or lamb as a main dish (servings/wk)	2.1 ± 1.2	2.1 ± 1.2	1.9 ± 1.2	1.8 ± 1.3	1.9 ± 1.5	1.5 ± 1.3
Processed meat intake (servings/wk)	1.1 ± 1.3	0.9 ± 1.1	0.8 ± 1.0	1.3 ± 1.6	1.1 ± 1.5	0.9 ± 1.5
PLP (pmol/mL)[7]	38.9 (33.9, 44.7)	49.9 (42.8, 58.2)	98.3 (83.9, 115.3)	66.0 (58.4, 74.6)	91.5 (80.3, 104.2)	183.2 (160.6, 209.0)

[1] HPFS, Health Professionals Follow-Up Study; MET-h, metabolic equivalent task hours; NHS, Nurses' Health Study; PLP, plasma pyridoxal 5′-phosphate.
[2] All values are ranges; medians in parentheses.
[3] Mean ± SD (all such values).
[4] MET-h = sum of the average time spent in each activity × the MET value of each activity.
[5] Defined as consumption of at least two 325-mg tablets per week. Nonregular user was defined otherwise.
[6] Nutrient values were energy-adjusted intake.
[7] All values are means; 95% CIs in parentheses. PLP is the active form of vitamin B-6 and was measured in a random sample of 381 women in the NHS and 345 men in the HPFS.

from 1984 to 1986, vitamin B-6 intake in 1986 for cases diagnosed from 1986 to 1990, vitamin B-6 intake in 1990 for cases diagnosed from 1990 to 1994, and so forth. For a latency of 4–8 y, we used vitamin B-6 intake in 1980 for cases diagnosed from 1984 to 1988, vitamin B-6 intake in 1984 for cases diagnosed from 1988 to 1990, vitamin B-6 intake in 1986 for cases diagnosed from 1990 to 1994, and so forth. Because the HPFS started in 1986, we examined colorectal cancer cases diagnosed from 1986 onward for the latency of 0–4 y, from 1990 onward for latency of 4–8 y, and so forth. We calculated RRs as the incidence in participants in a given category of exposure divided by the incidence in a specific reference category.

We conducted stratified analysis by alcohol consumption (nondrinkers and >0 to 15, >15 to <30, and ≥30 g/d) and folate intake (less than the median and at least the median). We constructed cross-product terms between total vitamin B-6 (medians of intake category) and alcohol or folate (medians of each intake category) and tested whether β coefficients of the cross-product terms were significant by using Wald's test. In addition, we conducted interaction analyses to assess whether associations with vitamin B-6 intake were modified by endoscopy screening (no or yes), family history of colorectal cancer (no or yes), aspirin use (no or yes), smoking status (never or ever), BMI (in kg/m^2; <25 or ≥25), physical activity (<9 or ≥9

TABLE 2
RRs of colorectal cancer by total vitamin B-6 intake in the Nurses' Health Study (1980–2008)[1]

	Quintiles of intake					
	1	2	3	4	5	*P*-trend
Baseline						
No. of cases (n = 1614)	324	329	400	260	301	
Model 1	1.0 (reference)[2]	0.85 (0.73, 0.99)	0.91 (0.78, 1.05)	0.73 (0.62, 0.86)	0.73 (0.63, 0.86)	<0.001
Model 2	1.0 (reference)	0.87 (0.74, 1.01)	0.94 (0.81, 1.09)	0.78 (0.66, 0.91)	0.79 (0.67, 0.93)	0.01
Model 3	1.0 (reference)	0.86 (0.73, 1.02)	0.95 (0.80, 1.14)	0.83 (0.65, 1.04)	0.84 (0.66, 1.07)	0.45
Cumulative average						
No. of cases (n = 1614)	320	360	328	303	303	
Model 1	1.0 (reference)	0.96 (0.83, 1.12)	0.84 (0.72, 0.98)	0.77 (0.66, 0.91)	0.78 (0.66, 0.91)	0.003
Model 2	1.0 (reference)	1.03 (0.89, 1.20)	0.96 (0.82, 1.12)	0.90 (0.77, 1.06)	0.92 (0.79, 1.08)	0.22
Model 3	1.0 (reference)	0.98 (0.82, 1.17)	0.91 (0.74, 1.12)	0.95 (0.76, 1.19)	1.00 (0.80, 1.24)	0.55
Simple update (0–4-y lag)						
No. of cases (n = 1375)	319	283	281	247	245	
Model 1	1.0 (reference)	0.87 (0.74, 1.02)	0.81 (0.69, 0.95)	0.71 (0.60, 0.84)	0.70 (0.59, 0.83)	<0.001
Model 2	1.0 (reference)	0.92 (0.78, 1.08)	0.89 (0.76, 1.05)	0.81 (0.68, 0.96)	0.80 (0.67, 0.95)	0.02
Model 3	1.0 (reference)	0.95 (0.80, 1.13)	1.00 (0.81, 1.23)	0.94 (0.74, 1.19)	0.92 (0.73, 1.16)	0.52
4–8-y lag						
No. of cases (n = 1249)	270	262	256	226	235	
Model 1	1.0 (reference)	0.95 (0.80, 1.13)	0.85 (0.72, 1.01)	0.77 (0.64, 0.91)	0.79 (0.67, 0.95)	0.02
Model 2	1.0 (reference)	0.99 (0.83, 1.17)	0.92 (0.77, 1.09)	0.85 (0.71, 1.01)	0.88 (0.74, 1.05)	0.17
Model 3	1.0 (reference)	0.96 (0.80, 1.16)	0.92 (0.75, 1.14)	0.97 (0.75, 1.25)	0.99 (0.78, 1.26)	0.73
8–12-y lag						
No. of cases (n = 1065)	234	238	217	203	173	
Model 1	1.0 (reference)	0.99 (0.83, 1.19)	0.84 (0.69, 1.01)	0.80 (0.66, 0.97)	0.68 (0.55, 0.83)	<0.001
Model 2	1.0 (reference)	1.03 (0.86, 1.24)	0.89 (0.74, 1.08)	0.89 (0.73, 1.08)	0.75 (0.62, 0.92)	0.002
Model 3	1.0 (reference)	1.10 (0.90, 1.34)	1.03 (0.82, 1.29)	1.09 (0.83, 1.44)	0.92 (0.71, 1.21)	0.17
12–16-y lag						
No. of cases (n = 770)	203	176	177	168	146	
Model 1	1.0 (reference)	0.82 (0.66, 1.02)	0.75 (0.61, 0.93)	0.77 (0.62, 0.96)	0.66 (0.53, 0.83)	0.004
Model 2	1.0 (reference)	0.85 (0.68, 1.06)	0.79 (0.64, 0.98)	0.85 (0.68, 1.06)	0.74 (0.59, 0.92)	0.045
Model 3	1.0 (reference)	0.91 (0.72, 1.15)	0.89 (0.68, 1.15)	1.04 (0.76, 1.42)	0.93 (0.69, 1.26)	0.71

[1] Model 1 was adjusted for age (mo). Model 2 was adjusted as for model 1 and for smoking before age 30 y (0, 1–4, 5–10, or >10 pack-years), history of colorectal cancer in a parent or sibling (yes or no), history of endoscopy (yes or no), regular aspirin use (yes or no), BMI (in kg/m^2; <25, 25 to <30, or ≥30), physical activity (<3, 3 to <27, or ≥27 metabolic equivalent task hours per week), and postmenopausal hormone use (premenopausal, never, past, or current user). Model 3 was adjusted as for model 2 and for consumption of processed meat (quintiles), alcohol consumption (0 to <5, 5 to <10, 10 to <15, or ≥15 g/d), energy-adjusted total calcium intake (quintiles), total folate (quintiles), total vitamin D intake (quintiles), and total energy intake (quintiles). *P*-trend values were calculated by using Wald's test.

[2] RR; 95% CI in parentheses (all such values).

metabolic equivalent task hours per week), and intakes of riboflavin, methionine, and vitamin D (less than the median or at least the median in each cohort).

We conducted all analyses with SAS software (version 9; SAS Institute Inc). All statistical analyses were 2-sided, and $P < 0.05$ indicated significance.

RESULTS

A total of 2627 incident adenocarcinoma colorectal cancer cases (1614 in women and 1013 in men) were documented in these 2 cohorts for ≤28 y of follow-up. In people who were taking supplements or multivitamins, the vitamin B-6 supplements and multivitamin use constituted ∼80–90% of the total vitamin B-6 intake. In people who were not taking multivitamins or vitamin B-6 supplements, the top 5 food contributors (approximate percentage of contribution) included cold cereal (12%), bananas (10%), mashed potatoes (7%), chicken (5%), and beef (4%). Mean intakes were 2.2 mg/d for women and 2.3 mg/d for men, which were above the Recommended Daily Allowance (RDA) intakes of vitamin B-6 (1.7 mg/d for men and 1.5 mg/d for women aged ≥51 y) (12). Averaged over the entire follow-up, ∼5% of men and 5–10% of women were below RDA intakes of vitamin B-6.

Selected demographic and lifestyle characteristics and potential confounding factors were compared across total vitamin B-6 intakes (Table 1). Individuals with a higher intake of total vitamin B-6 were slightly older, more likely to be physically active and use aspirin and multivitamins, and more likely to have had endoscopy screening. These individuals tended to consume more fruit and vegetables, dietary fiber, total calcium, total vitamin D, total folate, riboflavin, and vitamin B-12 but consumed less alcohol, red meat, and processed meat and smoked less. In addition, Spearman's correlation coefficients between total vitamin B-6 intake and plasma PLP concentrations were 0.52 in women and 0.54 in men.

The total vitamin B-6 intake (baseline or cumulative average) was generally significantly associated with ∼20–30% lower risk

of colorectal cancer in age-adjusted results in both women (Table 2) and men (**Table 3**). However, the significant inverse associations were attenuated after adjustment for nondietary factors and became largely nonsignificant after additional adjustment for other dietary factors, especially for total folate intake. The only exception is that we observed suggestive inverse associations on baseline vitamin B-6 intake when we pooled results. In comparison with the lowest quintile, pooled RRs (95% CIs) for quintiles 2–5 were 0.91 (0.80, 1.03), 0.90 (0.76, 1.06), 0.81 (0.68, 0.96), and 0.83 (0.69, 0.99), respectively (*P*-trend = 0.14).

We further conducted latency analyses to evaluate whether the timing of vitamin B-6 is important. When extreme quintiles were compared, RRs (95% CIs) were 0.92 (0.73, 1.16) for total vitamin B-6 intake 0–4 y before colorectal cancer diagnosis, 0.99 (0.78, 1.26) for intake 4–8 y before diagnosis, 0.92 (0.71, 1.21) for intake 8–12 y before diagnosis, and 0.93 (0.69, 1.26) for intake 12–16 y before diagnosis (Table 2). Corresponding RRs for men were 0.86 (0.63, 1.17), 0.96 (0.70, 1.32), 0.90 (0.63, 1.29), and 1.16 (0.75, 1.79), respectively (Table 3). Of note, in the multivariable analyses, we observed that folate intake in the remote past (ie, 12–16 y) was significantly inversely associated with colorectal cancer risk as previously reported (5). In addition, no discernible pattern of findings was evident when we analyzed dietary vitamin B-6 and vitamin B-6 from supplemental sources or by cancer subsites or deciles of vitamin B-6 intake (data not shown).

The potential effect of vitamin B-6 on colorectal cancer could be stronger in heavy alcohol drinkers because alcohol consumption may reduce the bioavailability or amounts of vitamin B-6 (13). However, we showed no apparent pattern with alcohol (**Table 4**). In addition, if vitamin B-6 influences colorectal cancer through the one-carbon metabolism pathway, the potential benefit of vitamin B-6 might be stronger in individuals with low intakes of other nutrients related to one-carbon metabolism such as folate, riboflavin, methionine, and vitamin B-12. However, no evident pattern was seen when stratified by other one-carbon nutrients. In addition, results did not differ by follow-up period (before or after folate-fortification year 1998), endoscopy screening (no or yes), BMI (<25 or ≥25), physical activity (less

TABLE 3
RRs of colorectal cancer by total vitamin B-6 intake in the Health Professionals Follow-Up Study (1986–2008)[1]

	Quintiles of intake					
	1	2	3	4	5	*P*-trend
Baseline						
No. of cases (*n* = 1013)	250	204	181	194	184	
Model 1	1.0 (reference)[2]	0.91 (0.75, 1.09)	0.71 (0.59, 0.87)	0.69 (0.57, 0.83)	0.69 (0.57, 0.84)	0.002
Model 2	1.0 (reference)	0.92 (0.77, 1.12)	0.76 (0.62, 0.92)	0.75 (0.62, 0.91)	0.75 (0.62, 0.91)	0.02
Model 3	1.0 (reference)	0.97 (0.80, 1.19)	0.81 (0.64, 1.02)	0.78 (0.60, 1.01)	0.80 (0.62, 1.04)	0.30
Cumulative average						
No. of cases (*n* = 1013)	206	206	192	202	207	
Model 1	1.0 (reference)	0.87 (0.72, 1.06)	0.75 (0.62, 0.92)	0.78 (0.64, 0.95)	0.78 (0.64, 0.94)	0.10
Model 2	1.0 (reference)	0.93 (0.76, 1.13)	0.84 (0.68, 1.02)	0.88 (0.72, 1.07)	0.87 (0.71, 1.06)	0.42
Model 3	1.0 (reference)	0.94 (0.75, 1.16)	0.84 (0.65, 1.07)	0.95 (0.73, 1.23)	0.95 (0.73, 1.23)	0.75
Simple update (0–4-y lag)						
No. of cases (*n* = 825)	178	171	154	161	161	
Model 1	1.0 (reference)	0.93 (0.75, 1.15)	0.78 (0.63, 0.97)	0.77 (0.62, 0.96)	0.80 (0.64, 0.99)	0.11
Model 2	1.0 (reference)	0.97 (0.78, 1.20)	0.83 (0.67, 1.04)	0.84 (0.67, 1.04)	0.86 (0.69, 1.08)	0.32
Model 3	1.0 (reference)	0.97 (0.77, 1.22)	0.75 (0.57, 1.00)	0.81 (0.59, 1.11)	0.86 (0.63, 1.17)	0.99
4–8-y lag						
No. of cases (*n* = 717)	164	145	134	130	144	
Model 1	1.0 (reference)	0.90 (0.72, 1.13)	0.74 (0.58, 0.93)	0.69 (0.55, 0.88)	0.80 (0.63, 1.00)	0.20
Model 2	1.0 (reference)	0.94 (0.75, 1.18)	0.79 (0.62, 1.00)	0.76 (0.60, 0.96)	0.87 (0.69, 1.09)	0.51
Model 3	1.0 (reference)	0.98 (0.77, 1.25)	0.84 (0.63, 1.12)	0.83 (0.60, 1.16)	0.96 (0.70, 1.32)	0.56
8–12-y lag						
No. of cases (*n* = 576)	135	112	107	106	116	
Model 1	1.0 (reference)	0.87 (0.68, 1.13)	0.76 (0.58, 0.98)	0.75 (0.58, 0.97)	0.82 (0.63, 1.05)	0.40
Model 2	1.0 (reference)	0.89 (0.69, 1.15)	0.79 (0.61, 1.02)	0.80 (0.62, 1.04)	0.87 (0.68, 1.13)	0.71
Model 3	1.0 (reference)	0.94 (0.71, 1.23)	0.80 (0.58, 1.10)	0.78 (0.54, 1.14)	0.90 (0.63, 1.29)	0.75
12–16-y lag						
No. of cases (*n* = 374)	97	66	82	67	62	
Model 1	1.0 (reference)	0.73 (0.53, 1.01)	0.86 (0.64, 1.16)	0.65 (0.48, 0.89)	0.63 (0.45, 0.87)	0.02
Model 2	1.0 (reference)	0.76 (0.55, 1.04)	0.91 (0.67, 1.22)	0.72 (0.52, 0.99)	0.70 (0.50, 0.97)	0.08
Model 3	1.0 (reference)	0.90 (0.64, 1.27)	1.27 (0.89, 1.82)	1.26 (0.82, 1.94)	1.16 (0.75, 1.79)	0.73

[1] Model 1 was adjusted for age (mo). Model 2 was adjusted as for model 1 and for smoking before age 30 y (0, 1–4, 5–10, or >10 pack-years), history of colorectal cancer in a parent or sibling (yes or no), history of endoscopy (yes or no), regular aspirin use (yes or no), BMI (in kg/m^2; <25, 25 to <30, or ≥30), and physical activity (<3, 3 to <27, or ≥27 metabolic equivalent task hours per week). Model 3 was adjusted as for model 2 and for consumption of processed meat (quintiles), alcohol consumption (0 to <5, 5 to <10, 10 to <15, or ≥15 g/d), energy-adjusted total calcium intake (quintiles), total folate (quintiles), total vitamin D intake (quintiles), and total energy intake (quintiles). *P*-trend values were calculated by using Wald's test.

[2] RR; 95% CI in parentheses (all such values).

TABLE 4
Multivariable RRs of colorectal cancer according to tertiles of total vitamin B-6 intake and alcohol consumption and total folate intake in the Nurses' Health Study and the Health Professionals Follow-Up Study[1]

	Nurses' Health Study (Women)				Health Professionals Follow-Up Study (Men)			
	Tertiles of total vitamin B-6 intake				Tertiles of total vitamin B-6 intake			
	1	2	3	*P*-interaction	1	2	3	*P*-interaction
Alcohol consumption								
Nondrinkers	1.0 (reference)	0.97 (0.78, 1.22)	0.86 (0.67, 1.11)	0.81	1.0 (reference)	0.90 (0.61, 1.32)	1.04 (0.69, 1.56)	0.57
>0–15 g/d	1.06 (0.88, 1.29)	1.00 (0.80, 1.25)	0.89 (0.69, 1.15)		1.17 (0.86, 1.59)	0.96 (0.68, 1.35)	0.98 (0.67, 1.42)	
>15 to <30 g/d	0.78 (0.51, 1.19)	1.34 (0.93, 1.92)	1.15 (0.76, 1.74)		1.48 (1.01, 2.16)	0.93 (0.59, 1.44)	0.99 (0.62, 1.57)	
≥30 g/d	1.28 (0.89, 1.84)	1.16 (0.74, 1.82)	0.94 (0.55, 1.60)		1.18 (0.78, 1.78)	1.48 (0.97, 2.25)	1.31 (0.83, 2.06)	
Folate intake[2]								
Less than or equal to the median	1.0 (reference)	0.84 (0.69, 1.02)	0.93 (0.69, 1.26)	>0.99	1.0 (reference)	0.89 (0.69, 1.15)	0.81 (0.55, 1.18)	0.85
Greater than the median	1.14 (0.92, 1.42)	1.15 (0.95, 1.38)	0.96 (0.79, 1.16)		0.96 (0.64, 1.44)	0.79 (0.56, 1.10)	0.88 (0.62, 1.26)	

[1] All values are RRs; 95% CIs in parentheses. Values were adjusted for age (mo), smoking before age 30 (0, 1–4, 5–10, or >10 pack-years), history of colorectal cancer in a parent or sibling (yes or no), history of endoscopy (yes or no), regular aspirin use (yes or no), BMI (in kg/m^2; <25, 25 to <30, ≥30), physical activity (<3, 3 to <27, or ≥27 metabolic equivalent task hours per week), postmenopausal hormone use (premenopausal, never, past, or current user; women only), consumption of processed meat (quintiles), energy-adjusted total calcium intake (quintiles), total vitamin D intake (quintiles), and total energy intake (quintiles). Total folate (quintiles) was adjusted for in the analysis of alcohol consumption, and alcohol consumption (0 to <5, 5 to <10, 10 to <15, or ≥15 g/d) was adjusted for in the analysis of folate intake. Results were based on a simple update. Similar null results were observed by using the cumulative average. *P*-interaction values were calculated by using Wald's test.

[2] Median values for total folate intake were 390 mg/d for women and 508 mg/d for men.

than the median or at least the median), family history of colorectal cancer (no or yes), smoking status (never or ever), regular aspirin use (no or yes), multivitamin use (no or yes), or total vitamin D intake (less than the median or at least the median) (all *P*-interaction > 0.15; data not shown).

DISCUSSION

Vitamin B-6 intake in adulthood was not independently associated with risk of colorectal cancer in our analyses of 2 large cohorts of middle-aged to elderly US health professionals. In addition, the nonsignificant associations were not modified by the timing of intake, cancer subsite, alcohol consumption, or several other colorectal cancer risk factors.

Epidemiologic studies that examined the influence of vitamin B-6 intake on colorectal cancer have been inconclusive. Our overall nonsignificant inverse associations were generally in line with the pooled results of 9 cohort studies (pooled RR: 0.90; 95% CI: 0.75, 1.07; high compared with low intake categories, *P*-heterogeneity = 0.01) (4). In contrast, several nested case-control studies consistently reported that higher prediagnostic plasma PLP concentrations were associated with 30–50% lower risk of colorectal cancer (pooled RR of 4 studies: 0.52; 95% CI: 0.38, 0.71; *P*-heterogeneity = 0.95) (4).

The discrepancy between plasma- and dietary-based studies remains poorly understood. The lack of an inverse association with vitamin B-6 intake might have arisen from measurement errors by using FFQs to assess vitamin B-6 intake. However, relatively high correlations (range: 0.4 to 0.7) between FFQs and reference methods in early studies (14–19) reduced the possibility of missing a strong association. In addition, the majority of case-control studies of vitamin B-6 intake measured by using FFQs have shown significant inverse associations with a higher vitamin B-6 intake (pooled OR of 6 studies: 0.67; 95% CI: 0.60, 0.75; *P*-heterogeneity = 0.09), (3) although recall or selection bias might have influenced the results. Also, the estimated vitamin B-6 intake may poorly predict metabolically active PLP in those study populations. Although, to the best of our knowledge, no previous studies reported the association between vitamin B-6 intake and plasma PLP concentrations, we observed a relatively high correlation ($r \approx 0.5$) in the current study. In addition, the difference in medians between highest and lowest intake categories of total or dietary vitamin B-6 intake ranged from 0.6 to 5.4 mg/d in previous studies. Our current study had a similar, albeit slightly wider, range of total vitamin B-6 intake (ie, 6.4 mg/d for women and 9.6 mg/d for men). Moreover, the ability of our FFQ to predict an almost 3-fold difference in plasma PLP argued against excessive measurement error entirely masking an association.

In contrast, as shown in current and early studies (16–18), individuals with a high vitamin B-6 intake tend to have healthy behaviors such as higher physical activity, less smoking, and higher intakes of calcium, vitamin D, and folate. Although previous studies controlled for these factors (4), residual confounding may still have existed, and more studies are necessary to determine whether plasma PLP per se or the reflected healthy behaviors conferred the benefit. In addition, a variation in plasma PLP could possibly reflect metabolic states (ie, inflammation) (20), which may influence colorectal cancer risk, but the alteration of concentrations of PLP by intake may not necessarily directly reduce risk. Moreover, because one-carbon metabolism is critical for methylation reactions, the influence of vitamin B-6 on colorectal cancer may differ by molecular subtypes or single nucleotide polymorphisms related to one-carbon metabolism. Epidemiologic studies are sparse (21–23). In addition, results from observational studies (24, 25) and randomized trials (26, 27) on the association between vitamin B-6 intake or plasma PLP concentrations and adenoma risk have also been inconsistent.

To the best of our knowledge, no previous studies have investigated whether the timing of vitamin B-6 intake influences colorectal cancer risk because most previous studies assessed vitamin B-6 only at baseline. With the repeated assessment of vitamin B-6 intake every 4 y for 22–28 y of follow-up, we specifically examined the latency between vitamin B-6 intake and colorectal cancer risk. Although total folate intake 12–16 y before diagnosis of colorectal cancer was more strongly associated with lower risk of colorectal cancer than was intake in the recent past (ie, 0–4 and 4–8 y) (5), we did not observe any clear pattern of timing with vitamin B-6 in this study. Of note, in the multivariable model in which we conducted a 12–16-y lag analysis, we saw a significant inverse association with total folate intake. This result suggested that vitamin B-6 has a weaker relation with risk of colorectal cancer than does folate. In addition, although nonsignificant, inverse associations observed in analysis in which baseline intake was modeled suggested that vitamin B-6 intake in childhood or adolescence might be important to the extent that the baseline intake reflected intakes in the distant past. Additional studies that evaluate early-life vitamin B-6 intake may provide more insights.

Because alcohol consumption may influence vitamin B-6 concentrations (13), one would expect that any effect of vitamin B-6 on colorectal cancer or adenomas would be stronger in heavy drinkers. Results have been conflicting on the basis of 6 studies we identified. The nonsignificant interaction between vitamin B-6 intake and alcohol consumption observed in the current study was in agreement with data from 2 case-control studies on plasma PLP (25) or vitamin B-6 intakes (28). In contrast, a stronger inverse association with plasma PLP concentrations (22) or vitamin B-6 intake (18) has been reported in alcohol drinkers. With regard to adenomas, one study reported a nonsignificant interaction with alcohol consumption (24), and the Aspirin/Folate Polyp Prevention Study showed that the inverse association with plasma PLP was evident only in nondrinkers (27).

Some limitations of this study need consideration. Although the timing of vitamin B-6 intake was examined in several time-lagged analyses in adulthood, we lacked data on early-life exposure, which may be important for colorectal carcinogenesis. Overall, our study was large, but we had limited power for certain interaction analyses. In addition, although the decile analysis did not suggest any significant associations, a relatively low prevalence of individuals below the RDA intake (ie, with deficiency) limited our ability to test the potential effect of low vitamin B-6 intake on colorectal cancer risk in these subgroups.

Strengths of the study included its prospective design with a long follow-up time and high follow-up rate, large size, and measurement of established risk factors for colon cancer. The detailed and repeated measurement of vitamin B-6 intake allowed us to conduct different latency analyses, which were not available in previous studies.

In conclusion, our prospective data do not support a strong role of vitamin B-6 intake in adulthood in colorectal carcinogenesis in middle-aged to elderly US health professionals. Studies on early-life intake (ie, childhood or adolescence) and molecular subtypes of colorectal cancer may be informative.

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