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Multivitamin use and colon cancer mortality in the Cancer Prevention Study II cohort (United States)

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Abstract

Objective: Multivitamins contain several nutrients, including folic acid, which are hypothesized to reduce colon cancer risk. Previous epidemiologic studies have suggested that effects of multivitamins containing substantial amounts of folic acid (introduced in 1973) may not be evident until 15 or more years since first use.
Methods: We examined the association between daily multivitamin use and colon cancer mortality among 806,397 US men and women in the Cancer Prevention Study II cohort who completed a questionnaire at enrollment in 1982 and were followed for mortality through 1998.
Results: After multivariate adjustment, multivitamin use at enrollment showed little association with colon cancer mortality. After 15 years since first use of a multivitamin potentially containing folic acid, we observed slightly decreased risk of colon cancer mortality (rate ratio (RR) = 0.89, 95% confidence interval (CI) 0.80–0.99). Consistent with previous reports, this association was stronger among participants consuming two or more alcoholic drinks per day (RR = 0.71, 95% CI 0.56–0.91).
Conclusion: Our results are consistent with a modest reduction in colon cancer mortality associated with use of folic acid-containing multivitamins among moderate to heavy alcohol users.

Introduction

Multivitamins contain several vitamins which are hypothesized to reduce colon cancer risk, most notably folic acid. In 1973 the legal limit on folic acid in multivitamins in the US was increased from a maximum of 100 micrograms to 400 micrograms [1], considerably more than the US median dietary folate intake of 226 micrograms [2]. The relative importance of supplemental folate compared to dietary folate is even greater given that multivitamins contain folate in the form of folic acid, which is much better absorbed than folate obtained from dietary sources [3]. Folate prevents colon carcinogenesis in several rodent models (reviewed in ref. 4). The biological mechanisms for the protective effect of folate on colon carcinogenesis are uncertain, but are hypothesized to involve prevention of DNA hypomethylation (considered to be an early step in colon cancer carcinogenesis) or a reduction in errors in DNA synthesis [5]. Most epidemiologic studies of total or dietary folate intake and colorectal adenomatous polyps [6–11] or incident colon or colorectal cancer [9, 12–18] suggest decreased risk (reviewed in ref. 4). In addition to folic acid, multivitamins typically contain the US Recommended Daily Allowance (USRDA) of vitamins C and E, both important antioxidants, although epidemiologic studies of vitamin C and E and colon cancer have been inconsistent [19].

The association between multivitamin use and colon cancer incidence has been examined in three previous epidemiologic studies. In the Nurses' Health Study (NHS) cohort (follow-up from 1980 to 1994) [20], Giovannucci *et al.* found strongly reduced risk of colon cancer incidence associated with use of folic acid-containing multivitamins (any multivitamin used since 1973), but only after 15 or more years since first use (RR = 0.25, 95% CI 0.13–0.51). A smaller cohort study [18] and a case–control study [21], also found reduced

risk associated with multivitamin use, although to a lesser degree. In contrast, an analysis of the first 7 years of follow-up (1982–1989) in the American Cancer Society's Cancer Prevention Study II (CPS-II) cohort (the same cohort studied in the current analysis) found no association between multivitamin use and colon cancer mortality [22], although follow-up may have ended too early to detect any delayed effect of the addition of higher levels of folic acid to multivitamins.

We reexamined the association between multivitamin use and colon cancer mortality in the CPS-II cohort over 16 years of follow-up (1982–1998). With more years of follow-up we had over 5000 cases of colon cancer, providing excellent statistical power to examine the association between multivitamin use (regardless of folic acid content) and colon cancer mortality. We were also able to investigate whether the introduction of folic acid into multivitamins may have resulted in a delayed reduction in risk, as suggested by results from the NHS cohort [20].

Materials and methods

Study cohort and follow-up

Subjects in this analysis were drawn from the 1,184,622 participants (508,334 men and 676,288 women) in CPS-II. These participants were enrolled in 1982 by American Cancer Society (ACS) volunteers in all 50 US states, the District of Columbia, and Puerto Rico as previously described [23]. Participants completed a four-page baseline self-administered questionnaire in 1982 that included information on demographic characteristics and various behavioral, environmental, occupational, and dietary factors.

The vital status of study participants was determined through 31 December 1998 using two approaches. ACS volunteers made personal inquiries in September 1984, 1986, and 1988 to determine whether the participants they had enrolled were alive or dead and to record the date and place of all deaths. Reported deaths were verified by obtaining death certificates. Automated linkage using the National Death Index [24] extended follow-up of the entire cohort through 31 December 1998, and identified deaths among the 21,704 participants lost to follow-up between 1982 and 1988. At the completion of follow-up in December 1998, 283,636 participants had died (24.0%), 898,090 were alive (75.8%), and 2896 (0.2%) had follow-up truncated on 1 September 1988 because of insufficient data for National Death Index linkage. Death certificates or codes for cause of death were obtained for 98.8% of all known deaths. The underlying cause of death was defined according to the 9th revision of the *International Classification of Disease* (ICD-9) [25]. Colon cancer deaths were defined as ICD-9 codes 153.0–153.9. Selected analyses also examined rectal cancer deaths, defined as ICD-9 codes 154.0–154.9.

We excluded participants who at enrollment reported a history of cancer other than nonmelanoma skin cancer (n = 82,345), who did not provide interpretable information on frequency of multivitamin use (n = 12,315), or who reported less than daily multivitamin use (n = 156,003). Most multivitamin users reporting less than daily use reported using multivitamins less than five times per month. We also excluded participants with uninterpretable or missing information on vitamin C or vitamin E supplement use, dietary factors, education, or body mass index (n = 127,580). Analyses are based on the remaining 806,379 participants, of whom 5093 died of colon cancer during follow-up. For analyses requiring duration of multivitamin use we excluded an additional 29,477 participants with missing or uninterpretable information on duration of multivitamin use, leaving 776,902 participants for analysis, of whom 4517 died of colon cancer during follow-up.

Ascertainment of vitamin supplement use

Vitamin use was ascertained from the 1982 baseline questionnaire, which included a section asking about duration and frequency of current use of four vitamin supplements (multivitamins, vitamin A, vitamin C, and vitamin E). Participants were asked to fill in two boxes for each vitamin, the first box reporting the number of times in the past month they had used this vitamin and the second box reporting the number of years of use. We considered participants reporting use of multivitamins 25 or more times during the past month to be "daily users." As described above, less than daily multivitamin users were excluded from all analyses. No information was collected on the dose or brand of vitamin supplements, use of any other dietary supplements, or any past vitamin supplement use that had stopped before study enrollment.

Statistical analysis

We used Cox proportional hazards modeling to examine the association of multivitamin use with colon cancer mortality while adjusting for other potential risk factors. The referent group for all comparisons consisted of participants reporting no use of multivitamins at enrollment. The time-axis used was follow-up time since enrollment in 1982. Age adjustment was accomplished

by stratifying on exact year of age at enrollment within each Cox model. All Cox models were also adjusted for educational level, body mass index, use of aspirin and estrogen replacement therapy, use of vitamin C and vitamin E supplements, and consumption of two food groups (vegetables and high-fiber grain foods) associated with decreased risk of colon cancer mortality in this cohort [26]. All covariates, other than age, were modeled as dummy variables using the categories shown in Table 1. Participants who left blank the questions on aspirin or estrogen replacement therapy (for women) were categorized as nonusers. Food consumption variables were derived from items on the questionnaire which asked about the frequency of eating 32 common food items. The derivation of food group variables from this questionnaire has been described previously [26]. Of particular relevance to this analysis, the vegetable variable was derived by summing the numbers of days per week that each participant reported eating each of the six vegetable items, other than potatoes, on the questionnaire (carrots, tomatoes, squash/corn, green leafy vegetables, raw vegetables, cabbage/broccoli/Brussels sprouts). Similarly, the high-fiber grain foods variable was derived by summing reported consumption of three food items (bran/corn muffins, brown rice/whole wheat/barley, and oatmeal/shredded wheat/bran cereals). Race, cigarette smoking, alcohol use, exercise level, consumption of citrus fruits/juices, consumption of low-fat meats (fish and chicken), consumption of high-fat meats (red meats), use of vitamin A supplements, family history of colorectal cancer, and personal history of colorectal polyps, heart disease and hypertension were also examined as potential confounders. However, we did not adjust for these factors in the final models because such adjustment had virtually no effect on our results.

In order to more specifically examine the association between use of folic acid-containing multivitamins and colon cancer mortality, we calculated a time-dependent variable for time elapsed since first use of a multivitamin potentially containing folic acid. In calculating this variable we assumed any multivitamin use occurring in 1973 or later to be use of a multivitamin potentially containing folic acid. Time since first use of a multivitamin potentially containing folic acid was defined as the sum of years of use of a multivitamin potentially containing folic acid before enrollment (years of use between 1973 and 1982) and years of follow-up. For example, a multivitamin user reporting 12 years of multivitamin use at enrollment in 1982 would be considered to have 9 years since first use of a multivitamin potentially containing folic acid (1973–1982) at the start of follow-up. After 6 years of follow-up this

Table 1. Colon cancer mortality risk factors by multivitamin supplement use at enrollment[a] (Cancer Prevention Study II, 1982–1998)

	Women (%)		Men (%)	
	No use (n = 323, 971)	Daily use (n = 111, 500)	No use (n = 299, 193)	Daily use (n = 71, 715)
Age (years)				
30–39	5.2	5.9	3.7	3.7
40–49	23.6	22.7	19.3	16.7
50–59	34.7	36.4	38.3	38.1
60–69	25.0	24.9	27.8	30.4
70–79	9.5	8.3	9.5	9.6
≥80	2.0	1.9	1.4	1.5
Race				
White	92.8	96.3	94.3	96.7
Black	5.0	2.1	3.6	1.6
Other	2.2	1.7	2.1	1.7
Education				
Less than high school	14.6	8.3	16.7	9.8
High school graduate	32.7	28.3	21.5	16.0
Some college	28.8	33.7	26.9	28.2
College graduate	14.2	17.0	17.2	21.8
Graduate school	9.6	12.8	17.7	24.1
Body mass index (kg/m^2)				
< 20.0	9.1	12.1	2.2	2.6
20.0–< 22.5	24.6	29.9	9.6	12.6
22.5–< 25.0	25.5	26.4	26.0	30.4
25.0–< 27.5	18.6	16.3	34.1	33.2
27.5–< 30.0	9.3	6.9	16.8	13.5
≥30.0	12.8	8.5	11.3	7.8
Exercise level				
None	2.4	1.8	2.2	1.8
Slight	24.0	24.1	21.8	22.9
Moderate	66.1	67.1	63.2	63.1
Heavy	5.8	5.8	11.8	11.5
Unclassifiable	1.7	1.2	0.9	0.7
Cigarette smoking				
Never	53.8	52.1	44.7	48.5
Current	20.6	18.7	21.5	18.0
Former	19.3	24.6	29.5	30.7
Unclassifiable	6.3	4.7	4.3	2.8
Alcohol use (drinks/day)				
No regular use	84.0	79.9	68.0	65.6
1–< 2	5.9	7.5	9.0	10.0
2–< 3	5.0	6.5	8.6	9.4
≥3	5.0	6.2	14.4	15.0
Vegetable consumption[b] (servings/day)				
< 1	18.5	10.7	23.2	15.0
1–< 2	30.2	26.4	36.0	33.6
2–< 3	29.2	32.0	25.9	29.8
≥3	22.2	30.9	14.8	21.6
High-fiber grain foods[c] (servings/week)				
< 1	44.1	31.2	42.7	30.7
1–< 3	15.1	13.7	16.7	15.2

Table 1. (Continued)

	Women (%)		Men (%)	
	No use (n = 323, 971)	Daily use (n = 111, 500)	No use (n = 299, 193)	Daily use (n = 71, 715)
3–<6	18.2	20.1	18.1	19.8
≥6	22.6	34.9	22.5	34.3
Vitamin C use				
None	84.0	62.2	86.7	65.1
Occasional	7.9	5.8	6.7	4.2
Daily, <10 years	4.5	16.1	3.6	15.0
Daily, ≥10 years	2.1	11.5	2.0	12.0
Daily, unknown	1.5	4.4	1.0	3.7
Vitamin E use				
None	89.1	72.2	91.7	75.5
Occasional	4.7	4.2	3.7	2.9
Daily, <10 years	3.9	14.7	2.7	12.2
Daily, >10 years	1.1	5.9	1.2	6.8
Daily, unknown	1.1	3.0	0.7	2.7
Aspirin use (times/month)				
None	40.5	35.4	44.9	38.8
Occasional	37.4	37.1	32.7	32.1
1–9	14.0	13.7	14.3	14.4
≥10	8.1	13.8	8.0	14.7
Estrogen replacement therapy				
Never	69.8	59.7	–	–
Current use				
<5 years	2.5	3.5	–	–
≥5 years	4.8	8.2	–	–
Former use				
<5 years	9.6	11.3	–	–
≥5 years	5.4	8.0	–	–
Ever use unspecified	7.9	9.3	–	–

[a] Percentages adjusted to the age distribution of the entire study population.

[b] Based on consumption of six food items (carrots, tomatoes, squash/corn, green leafy vegetables, raw vegetables, cabbage/broccoli/Brussels sprouts).

[c] Based on consumption of three food items (bran/corn muffins, brown rice/whole wheat/barley, oatmeal/shredded wheat).

multivitamin user would be considered to have 15 years since first use of a multivitamin potentially containing folic acid.

We also examined if the association of colon cancer mortality with use of a multivitamin potentially containing folic acid was modified by demographic factors or factors that may affect nutrient status. Specifically, we modeled an interaction term between a variable for 15 or more years since first use of a multivitamin potentially containing folic acid (yes/no), and a dichotomous variable for each potential effect modifier, including attained age (<65 years/≥65 years), sex, educational level (≤high school graduate/>high school graduate), daily use of vitamin C or E supplements (yes/no, less than daily users excluded), current cigarette smoking (yes/no, former smokers excluded) and alcohol consumption (<2 drinks per day/≥2 drinks per day). The CPS-II dietary data were not sufficiently detailed to estimate dietary intake of two potential dietary effect modifiers, folate and methionine.

Results

Table 1 compares participants who were daily multivitamin users at enrollment with participants who reported no use of multivitamins at enrollment. Most participants were white and middle-aged or elderly, regardless of multivitamin use status. However, daily multivitamin users were slightly more likely than nonusers to be white. Compared to nonusers, multivitamin users were much more likely to use vitamin C or E supplements. In general, multivitamin users were slightly more likely than nonusers to have characteristics associated with lower risk of colon cancer mortality in this cohort. Specifically, multivitamin users were more likely to be well educated, to have lower body mass index, to report frequent consumption of vegetables and high-fiber grain foods, to use aspirin regularly, and to be nonsmokers. Female multivitamin users were also more likely than nonusers to be current or former users of estrogen replacement therapy.

After multivariate adjustment, multivitamin use at study enrollment was weakly associated with reduced risk of colon cancer mortality (Table 2). There was no suggestion of decreasing risk with increasing duration of multivitamin use before enrollment. However, the association between multivitamin use and colon cancer mortality differed by follow-up year ($p = 0.02$ for interaction between multivitamin use and follow-up year). Decreased risk was observed only during the intervals 1991–1994 and 1995–1998, the second half of the 16-year follow-up. Years since first use of a multivitamin potentially containing folic acid was associated with slightly decreased risk of colon cancer only after 15 years since first use (RR = 0.89, 95% CI 0.80–0.99). Daily multivitamin use was not associated with rectal cancer mortality regardless of follow-up time (RR = 1.0, 95% CI 0.74–1.3 for 1982–1990, RR = 1.1, 95% CI 0.84–1.4 for 1991–1998) or years since first use of a multivitamin potentially containing folic acid (RR = 1.1 for ≥15 years since first use of a multivitamin potentially containing folic acid).

Table 3 shows rate ratios for colon cancer mortality associated with time since first use of multivitamin

Table 2. Rate ratios and 95% confidence intervals for colon cancer mortality associated with daily multivitamin use[a] (Cancer Prevention Study II, 1982–1998)

	Men	Women	Men and Women
Use at enrollment			
Nonuser			
RR	1.0 (ref)	1.0 (ref)	1.0 (ref)
Deaths	2271	1840	4111
User			
RR	0.91	0.93	0.92
(95% CI)	(0.82–1.0)	(0.84–1.0)	(0.86–1.0)
Deaths	469	513	982
Duration of use before enrollment (years)			
< 10			
RR	0.89	0.85	0.87
(95% CI)	(0.76–1.0)	(0.73–1.0)	(0.78–0.98)
Deaths	186	182	368
≥10			
RR	0.96	1.0	0.99
(95% CI)	(0.83–1.1)	(0.88–1.2)	(0.89–1.1)
Deaths	211	227	438
Duration unknown			
RR	0.85	0.93	0.89
(95% CI)	(0.67–1.1)	(0.75–1.1)	(0.76–1.1)
Deaths	72	104	176
Use at enrollment by follow-up year			
1982–1986			
RR	1.1	1.2	1.1
(95% CI)	(0.86–1.4)	(0.91–1.5)	(0.95–1.4)
Deaths	90	88	178
1987–1990			
RR	1.0	0.95	0.99
(95% CI)	(0.83–1.3)	(0.77–1.2)	(0.85–1.1)
Deaths	117	132	249
1991–1994			
RR	0.79	0.92	0.85
(95% CI)	(0.65–0.96)	(0.76–1.1)	(0.74–0.98)
Deaths	132	144	276
1995–1998			
RR	0.85	0.83	0.84
(95% CI)	(0.69–1.0)	(0.68–1.0)	(0.73–0.96)
Deaths	130	149	279
Years since first use of a multivitamin potentially containing folic acid[b]			
> 0– < 5			
RR	0.97	1.3	1.1
(95% CI)	(0.52–1.8)	(0.74–2.2)	(0.75–1.7)
Deaths	10	14	24
5– < 10			
RR	0.99	0.97	0.98
(95% CI)	(0.74–1.3)	(0.73–1.3)	(0.80–1.2)
Deaths	51	52	103
10– < 15			
RR	1.03	0.89	0.96
(95% CI)	(0.86–1.2)	(0.73–1.1)	(0.84–1.1)
Deaths	131	114	245
≥15			
RR	0.85	0.93	0.89
(95% CI)	(0.73–0.99)	(0.80–1.1)	(0.80–0.99)
Deaths	205	229	434

[a] Adjusted for age, sex (for combined sex results), education, body mass index, vegetable consumption, consumption of high-fiber grain foods, and use of vitamin C supplements, vitamin E supplements, aspirin and estrogen replacement therapy. Nonusers of multivitamins at enrollment are the referent group for all comparisons.

[b] Calculated by adding (1) years of multivitamin use between 1973 and 1982 (enrollment) and (2) years of follow-up since 1982, if a multivitamin user (a time-dependent variable).

Table 3. Rate ratios and 95% confidence intervals for colon cancer mortality associated with years since first use of a multivitamin potentially containing folic acid, by alcohol use[a] (Cancer Prevention Study II, 1982–1998)

Alcohol use	Years since first use[b]			*p*-Value for interaction
	Nonuser	> 0– < 15	≥15	
< 2 drinks/day				
RR	1.0	0.98	0.94	
(95% CI)	(ref)	(0.87–1.11)	(0.84–1.06)	
Deaths	3333	305	353	
≥2 drinks/day				$p = 0.13$
RR	1.0	0.94	0.71	
(95% CI)	(ref)	(0.72–1.2)	(0.56–0.91)	
Deaths	778	67	81	

[a] Adjusted for age, sex (for combined sex results), education, body mass index, vegetable consumption, consumption of high-fiber grain foods, and use of vitamin C supplements, vitamin E supplements, aspirin and estrogen replacement therapy. Nonusers of multivitamins at enrollment are the referent group for all comparisons.

[b] Calculated by adding (1) years of multivitamin use between 1973 and 1982 (enrollment) and (2) years of follow-up since 1982, if a multivitamin user (a time-dependent variable).

potentially containing folic acid, stratified by alcohol use. Among participants with low alcohol use (<2 drinks/day), there was no clear reduction in risk associated with multivitamin use. In contrast, among participants with moderate to heavy alcohol use at enrollment (≥2 drinks/day), those with 15 or more years since first use of a multivitamin potentially containing folic acid were at decreased risk of colon cancer mortality compared to those who did not use multivitamins (RR = 0.71, 95% CI 0.56–0.91). In this analysis, moderate to heavy alcohol use (≥2 drinks/day) was associated with increased risk of colorectal cancer only among participants who did not use multivitamins (multivariate adjusted RR = 1.3, 95% CI 1.2–1.4 compared to < 2 drinks/day).

We found little evidence that the association between time since first use of a multivitamin potentially containing folic acid and colon cancer mortality was modified by attained age, sex, educational level, smoking status, vitamin C use, or vitamin E use (results not shown). The p-value for statistical interaction was >0.2 for these potential effect modifiers.

To estimate the continuity of multivitamin use during the follow-up period, we compared use reported on the 1982 baseline CPS-II questionnaire with use reported on a 1992–1993 follow-up questionnaire completed by a subgroup of CPS-II participants from 21 selected states. A total of 135,400 participants included in this analysis completed both questionnaires. Among the daily multivitamin users in this analysis who also completed the 1992–1993 questionnaire, most were still using multivitamins approximately 10 years later (60% daily, an additional 9% at least weekly). Among the participants in this analysis who reported no multivitamin use in 1982, a small proportion were using multivitamins in 1992–1993 (18% daily, an additional 5% at least weekly).

Discussion

In the CPS-II cohort, multivitamin use was associated with a small reduction in risk of colon cancer mortality after 15 years since first use of a multivitamin potentially containing folic acid (RR = 0.89, 95% CI 0.80–0.99). A clearer reduction in risk was seen among moderate to heavy alcohol users with at least 15 years since first use of a multivitamin potentially containing folic acid (RR = 0.71, 95% CI 0.56–0.91).

The reduction in risk of colon cancer mortality associated with multivitamin use in this study is smaller than that observed in three previous studies of colon cancer incidence: the NHS cohort [20], the Health Professionals' cohort [18], and a Seattle-area case–control study [21]. In the NHS cohort (442 cases during follow-up from 1980 to 1994), participants with 15 years since first use of a folic acid-containing multivitamin were at greatly reduced risk of incident colon cancer (RR = 0.25, 95% CI 0.13–0.51), although no clear reduction in risk was observed among those with less than 15 years since first use. In the Health Professionals' cohort (205 cases during follow-up from 1986 to 1992), current multivitamin use of 10 or more years duration at enrollment was associated with a RR of 0.74 (95% CI 0.47–1.2). In the Seattle case–control study (444 cases diagnosed from 1985 to 1989), substantially reduced risk (RR = 0.51, 95% CI 0.34–0.77) was observed among participants with an average daily intake of one or more multivitamins over a 10-year period ending 2 years before diagnosis date. This 10-year period occurred entirely after the introduction of higher levels of folic acid to multivitamins in 1973.

One possible reason for the weaker associations observed in this study, as compared to previous studies, is that we examined colon cancer mortality rather than incidence. Colon cancer mortality reflects survival following diagnosis as well as incidence. Poorer survival among multivitamin users could conceivably obscure a protective effect of multivitamins on colon cancer incidence. However, we know of no evidence that multivitamin use adversely affects colon cancer survival. Misclassification of the cause of death reported on death certificates could also have biased our results since it is likely that some deaths classified on the death certificate as colon cancer were due to rectal cancer or other causes. However, the degree of death certificate misclassification is likely to be modest [27], and is unlikely to fully account for the differing results between studies. Finally, the weaker association observed in our mortality study compared to the incidence studies could be due to chance.

In both our CPS-II cohort and the NHS cohort, reduced risk of colon cancer was observed only after 15 or more years since first use of a multivitamin potentially containing folic acid. At least two interpretations are possible. First, folate may inhibit the early events in colon carcinogenesis and therefore a long period of time may be required before any effect of folate on colon cancer incidence or mortality can be observed. An effect of folate on early stages of colon carcinogenesis is suggested by a mouse model of colon carcinogenesis in which folate was effective in preventing colonic tumors only if administered before the development of macroscopically visible adenomas [28]. A second possibility is that long duration use of folic acid-containing multivitamins may be required to reduce risk of colon cancer. We could not distinguish between these possibilities because time since first use and duration of use are identical until use is stopped, and we had no information on when during follow-up participants may have stopped using multivitamins.

We found a clear reduction in risk associated with use of a multivitamin potentially containing folic acid among moderate to heavy alcohol users (two or more drinks per day), but little evidence of reduced risk among those with lower alcohol use. This difference by alcohol use could be due to chance. However, effect modification by alcohol is biologically plausible. Alcohol reduces folate absorption [29] and consumption of two or more drinks per day has been associated with low erythrocyte folate levels [10], a marker of folate status.

Low folate status may result in DNA hypomethylation or errors in DNA synthesis [4]. Therefore, supplementation with folic acid may be particularly beneficial among alcohol users by preventing low folate status due to alcohol use. This hypothesis is supported by epidemiologic studies of folate intake and colorectal adenomas [9, 11], colon cancer [16, 18], and breast cancer [30–32] that found high folate intake to be associated with stronger reductions in risk among alcohol users. Additional evidence of interaction between folate and alcohol use is provided by two prospective studies in which alcohol use was associated with increased risk of colorectal cancer only among individuals with a polymorphism in the methylene tetrahydrofolate reductase gene (MTHFR) that reduces plasma folate levels [33, 34].

This analysis examined use of multivitamins, which by definition contain many different vitamins. Therefore, we cannot definitively attribute any of the associations we observed specifically to folic acid, or to any other single multivitamin component. Nevertheless, the pattern of results we observed is consistent with an effect of folic acid. We found that multivitamin use was associated with reduced risk of colon cancer mortality only in the last 8 years of our 16-year follow-up. This delayed reduction in risk is consistent with the increase in folic acid supplementation in multivitamins only a few years before the start of our follow-up given that evidence suggests that folate may act early in colon carcinogenesis [28, 35]. A specific effect of folic acid is also consistent with the suggestion of effect modification by alcohol use that we observed, given the evidence (discussed above) that the effect of folate on colon cancer and other diseases may be greater among those with lower folate status due to alcohol use. Finally, the most plausible chemopreventive vitamins in multivitamins, other than folic acid, are vitamins C and E. However, an effect of vitamin C and E in multivitamins seems unlikely in our cohort, given that we found no suggestion of decreased risk associated with use of individual vitamin C and E supplements, which contain doses much higher than those in multivitamins [36].

Limitations of our measure of multivitamin use could have biased our results towards underestimating any effect of multivitamin use. One limitation was that we had no information about past multivitamin use for participants who were former multivitamin users at enrollment. Our referent group therefore included some former multivitamin users. A second limitation of our measure of multivitamin use was that we had no information on changes in multivitamin use after enrollment. Due to the absence of updated information on multivitamin use, we could only examine duration of multivitamin use before enrollment. However, our results are unlikely to have been substantially altered by initiation of multivitamin use after enrollment. We observed reduced risk only after 15 years since first use of a multivitamin potentially containing folic acid, and few nonusers at enrollment would have achieved this time since first use during our follow-up period. Finally, our measure of time since first use of a multivitamin containing folic acid is based on the assumption that any multivitamin used in 1973 or after contained folic acid, when in fact some multivitamins may not have contained substantial amounts of folic acid until some years later. It should be noted, however, that the two previous prospective analyses of multivitamin use detected reduced risk of colon cancer [18, 20] despite similar limitations in measurement of multivitamin use.

The small reduction in risk associated with multivitamin use we observed could be due to health-conscious behavior among multivitamin users, particularly colorectal cancer screening. However, participants who used vitamin C and E supplements were very similar to participants who used multivitamins with respect to a variety of health-related behaviors and characteristics but did not show any decreased risk of colon cancer mortality [36]. No information on colorectal cancer screening was available for the cohort as a whole. However, approximately 118,000 participants in this analysis from 21 selected states completed a 1997 questionnaire that included information on colorectal cancer screening. In this subset of the cohort, colorectal cancer screening (ever having had a sigmoidoscopy or colonoscopy) was only slightly more common among daily multivitamin users in 1982 (53%) than among nonusers in 1982 (48%).

Strengths of this analysis are its prospective design and exceptionally large size, which allowed us to obtain fairly precise estimates for multivitamin use even when adjusting for multiple potential confounders. In addition, the large study size enabled us to examine the effect of multivitamin use stratified by factors such as alcohol use and follow-up time.

Our results indicate that any reduction in risk of colon cancer mortality due to use of folic acid-containing multivitamins may be smaller than the 50–75% decreased risk observed in the two largest studies of colon cancer incidence [20, 21]. However, given the high rate of colon cancer mortality, even a small reduction would be of public health importance. Our results, consistent with those from the NHS, also suggest that there may be a lengthy induction period between first use of folic acid-containing multivitamins and any reduction in colon cancer risk. Finally, our results suggest that any reduction in risk associated with multivitamin use may

be more apparent among moderate or heavy alcohol users than among those with low alcohol consumption.

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