Multivitamin Use and Colorectal Cancer Incidence in a US Cohort: Does Timing Matter?

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Multivitamins contain several nutrients, including folic acid, that are hypothesized to reduce the risk of colorectal cancer. Previous studies suggest that multivitamin use may reduce colorectal cancer risk but only after a long latency period. The authors examined the association between regular multivitamin use (four or more times per week) and colorectal cancer incidence among 145,260 men and women in the Cancer Prevention Study II Nutrition Cohort. Current multivitamin use was reported on a questionnaire at enrollment in 1992–1993. All participants had also reported multivitamin use on a questionnaire completed for a different study approximately 10 years earlier (in 1982). The authors observed 797 incident cases of colorectal cancer during follow-up from 1992 to 1997. After multivariate adjustment, regular multivitamin use at enrollment was not associated with risk of colorectal cancer (rate ratio = 1.04, 95% confidence interval: 0.87, 1.23), whereas regular multivitamin use 10 years before enrollment was associated with reduced risk (rate ratio = 0.71, 95% confidence interval: 0.57, 0.89). Regular multivitamin users 10 years before enrollment were at similarly reduced risk whether they were still regular multivitamin users at enrollment or had stopped. These results are consistent with the hypothesis that past, but not recent, multivitamin use may be associated with modestly reduced risk of colorectal cancer.

Abbreviations: CI, confidence interval; CPS-II, Cancer Prevention Study II; RR, rate ratio.

Multivitamins contain several vitamins that are hypothesized to reduce colorectal cancer risk, most notably folic acid. In 1973, the legal limit on folic acid in multivitamins in the United States was increased from 100 µg to 400 µg (1). The folic acid content of different multivitamin brands increased over time (based on a review of successive editions of the Physicians’ Desk Reference starting in 1973), but 1985 was the first year that the majority of US multivitamin brands listed in the Physicians’ Desk Reference included 400 µg of folic acid (2, 3). Analyses of blood samples collected in 1982 from Physicians’ Health Study participants showed that multivitamin users had over twice the level of serum folate as nonusers (4). Daily use of a multivitamin containing 400 µg of folic acid would have more than doubled the folate intake of most US residents (mean dietary intake, 283 µg) (5), at least until folic acid fortification of grain started in 1996–1998 (6).

Evidence from both laboratory (7) and epidemiologic (8–10) studies suggests that folic acid may inhibit colorectal carcinogenesis, although epidemiologic results have not been entirely consistent. Folic acid prevents colon carcinogenesis in several rodent models (7). In a mouse model, folic acid supplementation was effective in preventing colonic adenomas if started before the establishment of neoplastic foci, whereas supplementation after the establishment of neoplastic foci had no effect, indicating that folic acid inhibits only early stages of colorectal carcinogenesis (11). If folic acid also selectively inhibits early stages of colorectal carcinogenesis in humans, we might expect a long latency period between folic acid supplementation and any reduction in risk of incident colorectal cancer.

In addition to folic acid, multivitamins typically contain the US Recommended Daily Allowance of several other vitamins, including vitamin D, which has been associated with decreased risk of colorectal cancer in some epidemio-
logic studies (12). It should be noted that associations between multivitamin use and disease outcomes cannot be definitively attributed to any single nutrient.

The association between multivitamin use and colon cancer incidence or mortality has been examined in three cohort studies (13–15) and one case-control study (16). All four studies found reduced risk of colon cancer with either a long interval since first use or a long duration of use. In the Nurses’ Health Study cohort, use of a multivitamin potentially containing 400 µg of folic acid (excluding multivitamin use before 1973) was associated with strongly reduced risk of colon cancer incidence, but only after 15 or more years since first use (rate ratio (RR) = 0.25, 95 percent confidence interval (CI): 0.13, 0.51) (14). A similar analysis of colon cancer mortality in the Cancer Prevention Study II (CPS-II) cohort found weakly reduced risk after 15 or more years since first use of a multivitamin potentially containing 400 µg of folic acid (RR = 0.89, 95 percent CI: 0.80, 0.99) (15). The reductions in risk associated with a long interval since first use observed in both the Nurses’ Health Study and the CPS-II mortality study are consistent with a long latency period between multivitamin use and risk of colorectal cancer diagnosis. However, because time since first use is likely to be strongly correlated with duration of use, the reduced risk observed in these studies could be due solely to longer duration of use. In the Health Professionals’ Follow-up Study, multivitamin use of 10 or more years’ duration at enrollment in 1986 was associated with a rate ratio of 0.74 (95 percent CI: 0.47, 1.17) for colon cancer incidence (13). A case-control study of colon cancer incidence in the Seattle, Washington, area examined average daily multivitamin intake over a 10-year period ending 2 years before the diagnosis date (16). Use of one or more multivitamin tablets per day during this period was associated with substantially reduced risk of colon cancer incidence (RR = 0.51, 95 percent CI: 0.34, 0.77).

We examined the association between multivitamin use and colorectal cancer incidence in the CPS-II Nutrition Cohort, a large cohort of predominantly elderly US adults. Participants in this cohort had reported multivitamin use at two time points, at study enrollment in 1992–1993 and approximately 10 years earlier (in 1982), which enabled us to examine the role of timing of multivitamin use.

**MATERIALS AND METHODS**

**Study cohort and follow-up**

Men and women in this analysis were participants in the CPS-II Nutrition Cohort (hereafter referred to simply as the Nutrition Cohort), a prospective study of cancer incidence in approximately 184,000 US adults (17). The Nutrition Cohort, established in 1992, is a subgroup of the approximately 1.2 million participants in the CPS-II cohort, a prospective study of cancer mortality established in 1982 (18). The CPS-II cohort was recruited by American Cancer Society volunteers in all 50 US states, the District of Columbia, and Puerto Rico and included men and women aged 30 or more years at enrollment in 1982. Nutrition Cohort participants were recruited from CPS-II cohort participants who resided in 21 states with population-based state cancer registries. The recruitment and characteristics of Nutrition Cohort participants are described in detail elsewhere (17). All aspects of the CPS-II Nutrition Cohort study are approved by the Emory University Institutional Review Board.

At enrollment in 1992 or 1993, Nutrition Cohort participants completed a self-administered questionnaire that included information on demographic characteristics, medical history, and various behavioral, occupational, and dietary factors. Usual dietary intake was assessed using a semiquantitative 68-item food frequency questionnaire, which is a modification of the brief Health Habits and History Questionnaire developed by Block et al. (19). Nutrient intakes were estimated using Diet Analysis System version 3.8a (20), which did not account for the subsequent fortification of the grain supply with folic acid (6). Exercise level (measured in metabolic equivalent hours per week) was calculated by multiplying the number of hours spent at each of seven leisure-time physical activities by an estimated intensity level for each activity (21) and summing across activities. Additional risk factor information from approximately 10 years earlier, including information on multivitamin use, was available from the four-page self-administered questionnaire participants completed in 1982 at enrollment in the earlier CPS-II cohort.

In 1997, a follow-up questionnaire was sent to all Nutrition Cohort members to update information and to ascertain newly diagnosed cancers. Information on use of sigmoidoscopy and colonoscopy was collected for the first time on this questionnaire. Among living Nutrition Cohort participants, the response rate for the 1997 follow-up questionnaire was approximately 91 percent (17).

From the overall Nutrition Cohort population of 184,190 we excluded from this analysis participants who reported at enrollment a history of cancer, other than nonmelanoma skin cancer (n = 23,630), did not respond to the 1997 follow-up questionnaire (unless known to be deceased) (n = 13,227), did not have complete information on multivitamin use (n = 1,820), or had self-reported colorectal cancers that could not be verified by obtaining medical records or by linkage with state registries (n = 253). Analyses include the remaining 145,260 participants (68,934 men and 76,326 women).

This analysis includes 797 incident cases of colorectal cancer diagnosed between enrollment in 1992 or 1993 and August 31, 1997. Most incident cases of colorectal cancer were identified initially through a self-report of cancer on the 1997 follow-up questionnaire (n = 595). Previous pilot work linking self-reports of cancer from the 1997–1998 questionnaire with information from four state cancer registries indicated that the ability of our participants to self-report an incident cancer is high (sensitivity = 0.93) (22). Self-reports of cancer were verified by obtaining medical records (n = 463), or if medical records could not be obtained, through linkage with state cancer registries (n = 132). An additional 202 cases of colorectal cancer were identified through automated linkage of all cohort members with the National Death Index (23), which was current through December 31, 1998, at the time of linkage. Participants who died between enrollment and August 31, 1997, and whose death certificates
listed colon or rectal cancer as a primary or contributory cause of death were categorized as cases of colorectal cancer. Colorectal tumors known to be not adenocarcinomas (e.g., carcinoid tumors) were not considered cases in this analysis because these tumors comprise only a very small proportion of colorectal cancers and may have a different etiology than adenocarcinomas.

**Ascertainment of use of multivitamins and other dietary supplements**

The 1992–1993 Nutrition Cohort questionnaire asked about the use of six supplements (multivitamins, vitamin A, beta-carotene, vitamin C, vitamin E, and calcium) during the past year. For each supplement they had used at least once a week, participants were asked to report the number of tablets taken. Response categories were 1–3 per week, 4–6 per week, one per week, two per week, three per week, four per week, or five per week. No information was collected on duration of supplement use.

Because all Nutrition Cohort participants were also participants in the original CPS-II cohort, information on past multivitamin use was available from the 1982 CPS-II questionnaire. The 1982 CPS-II questionnaire asked about current use of four supplements (multivitamins, vitamin A, vitamin C, and vitamin E). For each supplement, participants were asked to report the number of times used in the last month and the number of years of use. Participants who used a vitamin only “occasionally” were instructed to report times per month as “1/2.”

**Statistical analysis**

We used proportional hazards modeling to examine the association between multivitamin use and colorectal cancer incidence while adjusting for other potential risk factors (24). We used follow-up time since enrollment in 1992–1993 as the time-axis. We created variables for “recent” multivitamin use based on responses to the 1992–1993 Nutrition Cohort questionnaire. Participants who reported taking four or more multivitamin tablets per week were categorized as regular users, while participants who reported taking 1–3 multivitamin tablets per week were categorized as occasional users. We created separate variables for “past” multivitamin use based on responses to the 1982 CPS-II questionnaire. Participants reporting multivitamin use 16 or more times per month (equivalent to four times per week in a 4-week month) were categorized as regular users, while participants reporting unquantified “occasional” use, or use 1–15 times per month, were categorized as occasional users. Although the category of occasional users included participants reporting multivitamin use up to 15 times per month, only 20 percent of these occasional users reported use more than four times per month.

We used two approaches to model the association between multivitamin use and colorectal cancer incidence. The first modeling approach simultaneously included variables for past multivitamin use (defined as multivitamin use in 1982) and recent multivitamin use (defined as use at enrollment in 1992–1993), thereby adjusting risk estimates for past multivitamin use for recent multivitamin use and vice versa. The second modeling approach categorized participants into five mutually exclusive groups on the basis of combinations of past and recent multivitamin use: 1) no multivitamin use in either 1982 or 1992–1993, 2) occasional use only in 1982 and/or 1992–1993, 3) regular multivitamin use in 1982 but no use or occasional use only in 1992–1993, 4) regular multivitamin use in 1992–1993 but no use or occasional use only in 1982, and 5) regular use in both 1982 and 1992–1993.

We could not examine lifetime duration of multivitamin use because the 1992–1993 Nutrition Cohort questionnaire did not ask about duration of use. Lifetime duration of multivitamin use may be of limited relevance because multivitamins were not permitted to contain more than 100 µg of folic acid before 1973 (1).

All proportional hazards models were adjusted for age, sex, educational level, body mass index, exercise level, intake of saturated fat and dietary fiber, and use of vitamin C and calcium supplements. All covariates, except age and vitamin C use, were modeled as dummy variables using the exact categories shown in table 1, including the category “unclassifiable” for some covariates. We adjusted for age using the stratified Cox procedure with 1-year age strata (25). We adjusted for vitamin C use both as reported in 1982 (none, occasional, regular, unknown) and as reported in 1992–1993 (none, occasional, regular, unknown). The variable for educational level was based on information from the 1982 questionnaire. All other covariates were based on information from the 1992–1993 questionnaire.

We also examined potential confounding by race, cigarette smoking, alcohol use, aspirin use, postmenopausal hormone replacement therapy, vitamin E supplement use, dietary intake of calcium, methionine, vitamin D, and folate, and consumption of red meat, fruits, vegetables, whole grains, and total energy. However, we did not adjust for these factors in the final models because such adjustment had negligible effects on results.

We examined whether the association between regular multivitamin use and colorectal cancer incidence varied by intake of dietary folate, dietary methionine, and alcohol, which might be expected to modify the effect of folic acid from multivitamins (8). Specifically, we modeled interaction terms between either past multivitamin use (use in 1982) or recent multivitamin use (use at enrollment in 1992) and a dichotomous term for dietary folate (median split), dietary methionine (median split), or alcohol (<2 drinks/day vs. ≥2 drinks per day). P values for heterogeneity of rate ratios were calculated using the likelihood ratio statistic (26).

Because folic acid may be the multivitamin component that reduces colorectal cancer risk, we also examined the association between colorectal cancer and total folate intake (from diet and multivitamins combined) at enrollment in 1992–1993. Total folate was calculated as the sum of dietary folate (adjusted for total energy using the residuals method (27)) and folate from multivitamins (400 µg per tablet). We could not examine total folate intake 10 years before enrollment, because the 1982 CPS-II questionnaire did not include sufficiently detailed dietary questions to calculate dietary folate intake.
RESULTS

Approximately 50 percent of participants included in this analysis reported no multivitamin use, while 8 percent reported regular multivitamin use only in the past (in 1982), 19 percent reported regular multivitamin use only recently (at enrollment in 1992–1993), and 14 percent reported regular multivitamin use both in the past and recently. An additional 9 percent of participants reported only occasional multivitamin use. Table 1 compares these groups with respect to potential colorectal cancer risk factors, omitting results for participants who reported only occasional multivitamin use. Most participants in this cohort, regardless of multivitamin use, were White and middle-aged or elderly. All categories of regular multivitamin users were much more likely to take vitamin C and calcium supplements than were nonusers. In addition, all categories of regular multivitamin users were more likely than nonusers to be highly educated, to have a lower body mass index, to exercise, and to consume less saturated fat and more fiber.

Table 2 shows the association between incident colon, rectal, and colorectal cancer and past regular multivitamin use (use in 1982) and recent regular multivitamin use (use at enrollment in 1992–1993), adjusted for multiple covariates. This analysis examines the importance of timing of multivitamin use by comparing the separate effects of past and recent multivitamin use. Past regular multivitamin use was associated with decreased risk of colorectal cancer (RR = 0.71, 95 percent CI: 0.57, 0.89), whereas recent regular multivitamin use was not (RR = 1.04, 95 percent CI: 0.87, 1.23). Results were similar when past and recent multivitamin use was modeled separately, without adjusting for

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**Table 1.** Selected demographic and colorectal cancer risk factors by multivitamin use, Cancer Prevention Study II Nutrition Cohort, 1992–1997*

<table>
<thead>
<tr>
<th>Multivitamin use</th>
<th>Men (%)</th>
<th>Women (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No use† (n = 38,924)</td>
<td>Past use but not recent use‡ (n = 4,688)</td>
</tr>
<tr>
<td>Age at enrollment (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>50–59</td>
<td>25.6</td>
<td>24.0</td>
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<tr>
<td>60–69</td>
<td>58.4</td>
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<tr>
<td>70–79</td>
<td>15.3</td>
<td>16.0</td>
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<tr>
<td>≥80</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Race</td>
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<td></td>
</tr>
<tr>
<td>White</td>
<td>97.5</td>
<td>97.9</td>
</tr>
<tr>
<td>Black</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Other</td>
<td>1.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>9.3</td>
<td>7.4</td>
</tr>
<tr>
<td>High school graduate</td>
<td>21.3</td>
<td>16.6</td>
</tr>
<tr>
<td>Some college</td>
<td>25.4</td>
<td>26.8</td>
</tr>
<tr>
<td>College graduate</td>
<td>20.3</td>
<td>22.7</td>
</tr>
<tr>
<td>Graduate school</td>
<td>22.9</td>
<td>25.9</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
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</tr>
<tr>
<td>&lt;22.5</td>
<td>9.9</td>
<td>11.8</td>
</tr>
<tr>
<td>22.5–&lt;25</td>
<td>23.3</td>
<td>26.4</td>
</tr>
<tr>
<td>25.0–&lt;27.5</td>
<td>31.5</td>
<td>31.0</td>
</tr>
<tr>
<td>27.5–&lt;30</td>
<td>18.5</td>
<td>17.3</td>
</tr>
<tr>
<td>≥30.0</td>
<td>15.4</td>
<td>12.3</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>1.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Exercise (metabolic equivalents/week)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.5</td>
<td>13.5</td>
<td>10.4</td>
</tr>
<tr>
<td>3.5–&lt;4.5</td>
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<td>27.1</td>
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<td>4.5–&lt;14.0</td>
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<td>16.3</td>
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<td>21.2</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>1.7</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Table continues
multivitamin use at the other time point (RR = 0.72, 95 percent CI: 0.58, 0.89 for past regular multivitamin use; RR = 0.95, 95 percent CI: 0.80, 1.12 for recent regular multivitamin use).

The association between regular multivitamin use and colorectal cancer incidence was similar in men and women. The adjusted rate ratio for past regular multivitamin use was 0.67 (95 percent CI: 0.50, 0.92) in men and 0.75 (95 percent CI: 0.54, 1.03) in women. The adjusted rate ratio for recent regular multivitamin use was 1.02 (95 percent CI: 0.81, 1.28) in men and 1.06 (95 percent CI: 0.81, 1.39) in women.

The association with past regular multivitamin use appeared to be similar for colon and rectal cancers (table 2). Recent regular multivitamin use was not associated with colon cancer (RR = 0.92, 95 percent CI: 0.74, 1.14) but was associated with marginally increased risk of rectal cancer (RR = 1.36, 95 percent CI: 1.00, 1.85), although confidence intervals were wide because of small numbers of rectal cancers. We also examined results by subsite within the colon, after excluding 67 cases of colon cancer with an unknown or an overlapping subsite. Adjusted rate ratios for past regular multivitamin use were 0.61 (95 percent CI: 0.42, 0.89) for proximal colon cancer (cecum to splenic flexure) and 0.89 (95 percent CI: 0.58, 1.36) for distal colon cancer (descending and sigmoid colon). Adjusted rate ratios for recent regular multivitamin use were 0.96 (95 percent CI: 0.72, 1.28) for proximal colon cancer and 0.90 (95 percent CI: 0.63, 1.29) for distal colon cancer.

We found no evidence that the association between regular multivitamin use (either past or recent) and colorectal cancer incidence varied by alcohol use or intake of dietary folate or dietary methionine.

Analyses in this report exclude the 253 participants whose self-report of colorectal cancer could not be verified (Materials and Methods). Results were similar when we included these 253 participants as cases of colorectal cancer (for past regular multivitamin use, RR = 0.76, 95 percent CI: 0.56, 1.05).
For recent regular multivitamin use, RR = 0.96, 95 percent CI: 0.82, 1.12).

Table 3 shows the association between incident colon, rectal, and colorectal cancer and combinations of past regular multivitamin use (use in 1982) and recent regular multivitamin use (use at enrollment in 1992–1993), adjusted for multiple covariates. The reduction in risk of colorectal cancer appeared similar for participants who reported regular multivitamin use only in the past (RR = 0.74, 95 percent CI: 0.54, 1.02) and for those who reported both past and recent regular multivitamin use (RR = 0.73, 95 percent CI: 0.56, 0.94), a group which likely included many long duration multivitamin users. No reduction in colorectal cancer risk was observed for participants who reported only recent regular multivitamin use (RR = 1.03, 95 percent CI: 0.85, 1.25).

We also examined the association between duration of multivitamin use reported on the 1982 CPS-II questionnaire and colorectal cancer incidence, although it was not until 1985 that the majority of US multivitamin brands listed in the Physicians’ Desk Reference contained 400 µg of folic acid (2, 3). The risk of colorectal cancer appeared similar for participants who reported 10 or more years of multivitamin use in 1982 and for participants who reported less than 10 years of multivitamin use in 1982 (results not shown), as was true in our previous analysis of colon cancer mortality in the larger CPS-II cohort (15).

After adjustment for covariates, total folate intake (from diet and multivitamins) at enrollment in 1992–1993 was not associated with colorectal cancer risk. The adjusted rate ratio for the highest versus the lowest quintile of total folate was 1.17 (95 percent CI: 0.89, 1.55). Total folate intake was strongly influenced by intake of folic acid from multivitamins; 99 percent of participants in the highest quintile of total folate were regular multivitamin users, compared with none of the participants in the lowest quintile. Because many multivitamin users in 1992–1993 were not past multivitamin users, total folate intake in 1992–1993 may correlate only weakly with past folate intake, which may be more important in colorectal cancer etiology.

**DISCUSSION**

In this large prospective study, past multivitamin use was associated with a decreased risk of colorectal cancer, whereas recent multivitamin use was not. These results are consistent with the hypothesis that multivitamin use may reduce the risk of colorectal cancer but only after a long latency period.
Confounding by “health conscious” behaviors among multivitamin users cannot be ruled out as an explanation for the reduced risk associated with multivitamin use. In this cohort, multivitamin users were more likely than nonusers to practice health conscious behaviors, including exercising more and consuming more fiber and less saturated fat. Although our results are adjusted for exercise and dietary factors, both exercise and dietary factors may be measured with considerable error, potentially resulting in residual confounding. Confounding by health conscious behaviors, however, would not explain the pattern of results that we observed with respect to timing of multivitamin use. Both participants who reported past multivitamin use and those who reported only recent multivitamin use appeared more health conscious than never users, as shown in table 1. However, there was no suggestion of reduced risk of colorectal cancer among participants who reported only recent multivitamin use.

Potential confounding by history of sigmoidoscopy and/or colonoscopy (whether for screening or for symptoms) is of particular concern because these procedures can result in the detection and removal of precancerous polyps, substantially reducing the risk of colorectal cancer (28). We could not adjust for sigmoidoscopy or colonoscopy in this analysis because no information about these procedures was collected at enrollment in 1992–1993. However, information on sigmoidoscopy and colonoscopy was collected on the follow-up questionnaire in 1997, allowing us to compare the prevalence of these procedures by multivitamin use status. Ever having had a sigmoidoscopy or colonoscopy was only slightly more common among participants who reported regular multivitamin use in 1982 (52 percent) than among participants who reported no multivitamin use in 1982 (46 percent). Therefore, it appears unlikely that confounding by sigmoidoscopy or colonoscopy could fully account for the observed reduction in risk associated with past multivitamin use. No previous study has adjusted for sigmoidoscopy or colonoscopy, although the prevalence of sigmoidoscopy was noted to be virtually identical by multivitamin use in the Nurses’ Health Study analysis (14).

The strengths of this analysis include its prospective design and relatively large size, as well as the availability of information on multivitamin use reported 10 years before enrollment. To our knowledge, this is the largest study of multivitamin use and colon or colorectal cancer incidence. The availability of information on multivitamin use collected 10 years before enrollment allowed us to examine the potential effects of past multivitamin use, without relying on the ability of participants to accurately report past use.
In 1996, the US Food and Drug Administration mandated that all grain be fortified with folic acid (140 µg of folic acid per 100 g) by January 1, 1998 (29). This level of fortification was anticipated to increase daily consumption by approximately 100 µg of folic acid, but improvements in blood folate levels suggest that fortification may be delivering 200 or more µg of folic acid daily (6). Although some folic acid fortification may have begun as early as 1996, it is unlikely that folic acid fortification could have affected results during our study follow-up period, which ended in mid-1997. However, if the reduction in colorectal cancer risk associated with multivitamin use is due to folic acid, multivitamin use may prove to have little effect on colorectal cancer risk in the future in populations where large amounts of folic acid are obtained from fortified foods.

The results of this study and of previous observational studies (13–16) are consistent with an association between multivitamin use and a modest reduction in risk of colorectal cancer after a substantial latency period. The multivitamin component or components that may be responsible remain unclear. Intervention studies using intermediate markers may be useful in clarifying the potential effects of folic acid and other multivitamin components on different stages of colorectal carcinogenesis. There are at least two ongoing randomized trials in the United States examining the effect of folic acid supplementation on recurrence of colorectal polyps (E. Giovannucci, Harvard University, personal communication, 2002; J. Baron, Dartmouth University, personal communication, 2002). It may also be informative to conduct intervention studies using markers of even earlier stages of colorectal carcinogenesis.

In summary, our results are consistent with an association between past, but not recent, multivitamin use and modestly reduced risk of colorectal cancer. The timing of multivitamin use should be examined carefully in future analyses of this association.

REFERENCES