# Relationship between Vitamin and Calcium Supplement Use and Colon Cancer[1]

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## Abstract

**The relationship between vitamin supplement use and colon cancer was assessed in a population-based case-control study among men and women aged 30–62 years. Cases were 251 men and 193 women diagnosed with colon cancer in 1985–1989 in three counties in the Seattle metropolitan area who were identified from the Surveillance, Epidemiology, and End Results cancer registry. Controls were 233 men and 194 women identified by random digit dialing. Supplement use was assessed by questions on frequency, duration, and dose per day (for individual supplements) or type (for multivitamins) during the 10-year period ending 2 years before diagnosis. All results were adjusted for age and sex and were not confounded by other measured behaviors. The average daily intake of supplemental vitamins A, C, E, folic acid, calcium, and multivitamins during the reference period were each associated with reduced risk of colon cancer (all *P* for trend <0.03). The strongest associations were for use of vitamin E (odds ratio, 0.43; 95% confidence interval, 0.26–0.71 for ≥200 IU/day *versus* none) and multivitamins (odds ratio, 0.49; 95% confidence interval, 0.35–0.69 for daily use *versus* no use; both *P* for trend <0.001). These two associations were also significant using a stricter test of trend limited to supplement users, which reduces the effect of colinearity among these exposures. Because almost all vitamin D supplementation comes from multivitamin pills, the association of vitamin D use with colon cancer could not be distinguished from that of multivitamin use. Clinical trials or cohort studies with long-term assessment would be needed before public health recommendations could be made about supplement use.**

## Introduction

There is substantial evidence that vitamin and mineral intake may be related to colon cancer risk. Studies of diet and colon cancer provide consistent evidence that consumption of fruits and vegetables is associated with decreased risk of colon cancer (1–3). Although the specific dietary factors responsible for this protective effect have not been clearly identified, fruits and vegetables contain vitamins and minerals that may influence the likelihood of cancer.

Laboratory studies suggest a variety of biological mechanisms by which micronutrients may prevent colon cancer. Most attention has been given to antioxidant micronutrients (including vitamins C and E) as protective agents for cancer (2, 4, 5). Functions proposed for antioxidants include protection of cell membranes and DNA from oxidative damage and scavenging and reduction of nitrites. In addition, vitamins C and E have been shown to inhibit experimental colon tumors (6, 7) and to reduce human fecal mutagenic activity (8). Diets deficient in folic acid may result in hypomethylation of DNA, which might also be a factor in colon carcinogenesis (9). Calcium may bind intraluminal bile acids, thereby preventing their toxic effects and the resultant compensatory hyperproliferation (10) or may function to directly reduce cell proliferation by inducing terminal cell differentiation (11). Similar evidence exists for vitamin D in lowering colon cancer risk, because it controls the availability and intracellular functions of calcium (4).

Studying the effect of vitamin and mineral intake from supplements in relation to cancer is of interest for several reasons. First, supplement use can lead to a higher intake of some nutrients than can be obtained from food, which could lead to a steeper and therefore more detectable gradient of risk. Second, supplement intake can be more easily assessed over time than food intake, and long-term nutrient intake is likely to be a greater predictor of cancer risk than intake at a single reference point. Finally, if supplements prove to reduce cancer risk, increasing intake of micronutrients by use of vitamin supplements rather than food may be an attractive public health strategy. Community and worksite interventions to increase fruit and vegetable consumption have had only modest success (12). In contrast, large numbers of Americans are taking supplements (13), although supplement use has not been explicitly recommended by scientific or government agencies.

Although there is a substantial body of research on diet and colon cancer (1–3), fewer studies have investigated the association of supplement use with colon cancer (14–24), and none of the observational studies have assessed supplement intake as cumulative or average dose over a long time frame. We present the association of multivitamin supplements and specific micronutrients from supplements with colon cancer risk from a population-based case-control study in Washington State. Detailed assessment of multivitamin and individual supplement use over a 10-year reference period was used to estimate the dose of supplemental vitamins A, C, E, folic acid, and calcium.

## Materials and Methods

**Selection of Cases and Controls.** All incident cases of adenocarcinoma of the colon diagnosed between July 1985 and

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September 1989 among residents of King, Pierce, or Snohomish County aged 30–62 years were identified through the Seattle-Puget Sound Surveillance, Epidemiology, and End Results registry. Ineligible for the study were patients with adenocarcinoma of the appendix, the rectosigmoid junction, or the rectum; those with carcinoma *in situ*; and those with carcinoid tumors, sarcoma, or lymphoma of the colon. A population control group was selected by a random digit dialing method based on the one-step Waksberg procedure for survey sampling. Inclusion criteria were similar for cases and controls, in particular, the absence of antecedent colon or rectal cancer, polyposis, or inflammatory bowel disease; residence in a private household in one of the three selected counties; and ability to communicate in English. Because of the small percentage of minorities in the area, the study was limited to whites.

A total of 659 cases were identified. Of these, 102 died before being approached for the study. Among the remaining cases, 55 were ineligible (11 had prior colorectal cancer, 10 had polyposis or inflammatory bowel disease, 10 had no phone or lived outside the Seattle-Puget Sound area, 6 had participated in a prior study, and 4 were not able to communicate adequately). For 39 cases, permission to contact was not granted by the treating physician, 16 cases refused to participate in the study, and 3 were not reachable. Thus, 84.5% of identified cases were alive, and 88.4% (444 of 502) of alive, potentially eligible cases completed the interview for an overall estimated case response proportion of 74.7% (0.845 × 0.884).

Among the controls, household screening to determine eligibility was successful for 9051 of the 9384 households identified. Of those screened, 549 were selected by stratified random sampling to approximate the age, sex, and residence distribution of the cases. Of these, 2 were deceased, and 26 were ineligible (19 were nonwhite, 3 had colorectal cancer, 3 had colorectal diseases, and 1 could not communicate adequately). Ninety-four potentially eligible controls refused at the initial screening, refused the interview, or were not reachable. Thus, 96.5% of residential phone numbers were screened for eligibility, and 82.0% (427 of 521) of potentially eligible controls completed the interview for an overall estimated control response proportion of 79.1% (0.965 × 0.820).

**Exposure Measurement.** A structured telephone interview focused on a reference period that was defined as the 10-year period prior to 2 years before diagnosis for the cases or prior to a corresponding date for the controls. The interview assessed supplement use, sociodemographic characteristics, medical antecedents, medications, physical activity, height and weight, bowel habits, and beverage consumption. Subjects also completed a self-administered food frequency questionnaire, the results of which have been presented previously (25, 26).

Information on supplement use, including multivitamin supplements and individual supplementation with vitamins A, C, E, and calcium, during the 10-year reference period was ascertained in the interview. The average daily dose of nutrients from supplements (summed across multivitamins and individual supplements) over the 10-year period was calculated from questions on years of use of each type of supplement, days per week of use during those years, and formulation of usual type of multivitamin (for multivitamin supplements) or dose per day for vitamins A, C, E, and calcium. We classified multivitamins into three groups: (*a*) a "one-a-day" type; (*b*) a therapeutic/high potency type; and (*c*) a "stress" multivitamin, which represented the major types of multivitamin supplements in the years of exposure. The formulations used were the 1982 formulations of One a Day plus Minerals (Miles; 5,000 IU of vitamin A, 60 mg of vitamin C, 30 IU of vitamin E, 400 μg of folic acid, and 130 mg of calcium), Theragran (Squibb; 10,000 IU of vitamin A, 200 mg of vitamin C, 15 IU of vitamin E, and no folic acid or calcium), and Stresstabs (Lederle; 5,000 IU of vitamin A, 600 mg of vitamin C, 30 IU of vitamin E, 400 μg of folic acid, and no calcium), respectively (28). Vitamin B complex pills and B complex plus C were not considered to be multivitamins because they contained no vitamin A, E, or calcium and little (100 μg) or no folic acid (27). Vitamin B complex plus C was coded as 300 mg of vitamin C. The use of calcium containing antacids (Tums), for any purpose, was included in the supplemental calcium dose, based on questions on years of use, frequency of use, and brand name.

The average daily dose of each supplemental nutrient was categorized as no use and two or three levels of use. Because 13% of the subjects took a one-a-day-type multivitamin for the 10-year period, this group sometimes formed a single category of use, *e.g.*, 5000 IU of vitamin A per day is identical to use of a one-a-day-type multivitamin daily for 10 years, as is use of 100 mg of calcium per day. For each nutrient except folic acid, the cutoff for the highest category was selected to represent use greater than that from taking a one-a-day-type multivitamin daily for the 10-year reference period. For vitamin A, the highest level (>5000 IU/day) could only be achieved by use of a therapeutic type of multivitamin or use of individual vitamin A supplements; for vitamin C, the highest level of use (≥500 mg/day) could only be achieved by taking stress-type multivitamins or individual vitamin C supplements; for vitamin E, the highest category (≥200 IU/day) represents the equivalent of 5 years or more daily use of the common dose (400 IU) of vitamin E individual supplements; and the highest level of calcium (>100 mg) could only be achieved by individual use of calcium. The highest category of use of folic acid (≥400 mg/day) is identical to use of a one-a-day or stress-type multivitamin for 10 years.

**Data Analysis.** The relationship between supplement intake and colon cancer was evaluated among the 444 cases and 427 controls who completed the interview. Unconditional logistic regression (28) was used to estimate the OR[3] for colon cancer and its 95% CI associated with each of the levels of each supplemental nutrient. All analyses were adjusted for age by inclusion of five age categories (ages, in years, 30–44, 45–49, 50–54, 55–59, and 60–62) in the model. Analyses of men and women combined were also adjusted for sex. No other measured factors confounded the associations presented (see "Results"). The association of each supplement variable to colon cancer risk was assessed by a test for trend, using the logistic regression analogue to the Mantel extension test (*i.e.*, a test based on the significance of a single trend variable coded as the category of exposure). A second test for trend was also conducted limited to users of the supplemental nutrient, as suggested by Breslow and Day (29).

The relation of nutrients from supplements to colon cancer within certain subgroups of the population (*e.g.*, age groups) was modeled by including interaction terms between indicators of each category of supplement use and the subgroup of interest. The presence of effect modification was tested by use of an interaction term between the supplement trend variable and the group variable.

[3] The abbreviations used are: OR, odds ratio; CI, confidence interval; RDA, recommended daily allowance.

*Table 1* Use of multivitamin or individual vitamin supplements among colon cancer cases and controls by sex[a]

| | Men | | Women | |
|---|---|---|---|---|
| | Cases ($n$ = 251) $n$ (%) | Controls ($n$ = 233) $n$ (%) | Cases ($n$ = 193) $n$ (%) | Controls ($n$ = 194) $n$ (%) |
| Multivitamin use[b] | | | | |
| None | 169 (67) | 141 (61) | 111 (58) | 86 (44) |
| One-a-day | 60 (24) | 76 (33) | 56 (29) | 77 (40) |
| Therapeutic type | 20 (8) | 16 (7) | 24 (12) | 26 (13) |
| Stress type | 2 (1) | 0 (0) | 2 (1) | 5 (3) |
| Use of individual supplements | | | | |
| Vitamin A | 10 (4) | 5 (2) | 5 (3) | 9 (5) |
| Vitamin C | 46 (18) | 61 (26) | 47 (24) | 53 (27) |
| Vitamin E | 29 (12) | 38 (16) | 24 (12) | 31 (16) |
| Calcium[c] | 37 (15) | 35 (15) | 42 (22) | 43 (22) |

[a] Regular use for at least 1 year in the reference period (the 10-year period ending 2 years prior to diagnosis for cases and a comparable period for controls).
[b] Based on formulation of subject's most commonly used brand or type (see "Materials and Methods").
[c] Includes use of calcium-containing antacids.

## Results

Table 1 shows the types of supplements used by cases and controls. Overall, 27% of subjects used a one-a-day-type multivitamin for at least 1 year during the 10-year reference period, 10% used a therapeutic-type multivitamin, and few used a stress-type multivitamin. Individual supplementation with vitamins C, E, and calcium was common (12–27%), whereas individual use of vitamin A was rare (5% or less). Most users of individual supplements also used multivitamin supplements.

The relationship between intake of multivitamins and supplemental vitamins A, C, E, folic acid, and calcium and risk of colon cancer is given in Table 2. Because most types of multivitamins contained 400 IU of vitamin D and because individual vitamin D pills are rarely taken, our results for supplemental vitamin D intake are virtually identical to those for multivitamins; therefore, they are not presented separately. There was a significant relation between multivitamin use and supplemental intake of each of the five nutrients of interest and colon cancer risk for men and women combined (all $P$ for trend $<0.03$). These relations were consistent for men and women considered separately, except supplemental vitamin A intake and calcium intake were not associated with colon cancer among men. The strongest associations were with multivitamins and supplemental vitamin E ($P$ for trend $<0.001$). Men and women who used multivitamin supplements daily for the entire 10-year reference period had one-half the risk of colon cancer compared with those who never used multivitamins during this time period (age-adjusted OR, 0.49; 95% CI, 0.35–0.68). Those who averaged 200 IU or more of vitamin E per day over the 10 years had a 57% reduction in risk compared with non-users of vitamin E (OR, 0.43; 95% CI, 0.26–0.71).

Much of the consistency across the exposures in Table 2 is due to the fact that most multivitamin pills contain all or most of the nutrients of interest. For this reason, we defined the highest category of use (except for folic acid) as one that can only be achieved by substantial use of individual supplements or of a type of multivitamin other than a one-a-day type (see "Materials and Methods"). Furthermore, we also tested for trend (or difference) across levels of use limited to users of the supplemental nutrient. Using this stricter test, only for vitamin E (among women and both sexes combined) and for multivitamins was there a clear gradient of risk ($P < 0.02$) among users (Table 2). For supplemental intake of vitamin A, vitamin C, and calcium there was not a dose-response trend among users; in particular, the highest level of use was not clearly associated with lower risk than intermediate levels.

When both supplemental vitamin E and multivitamin use were simultaneously entered into a model for men and women combined, the odds ratios for the highest levels of use of each supplement were only moderately attenuated, but there was less precision (OR, 0.65; 95% CI, 0.29–1.42 for daily use of multivitamins, $P$ for trend = 0.05; and OR, 0.50; 95% CI, 0.24–1.07 for vitamin E $\geq$200 IU/day, $P$ for trend = 0.16).

No measured factors confounded the associations presented in Table 2, including correlates of supplement use such as education and smoking (13, 30, 31, 32), or other predictors of colon cancer in this study, including intake of alcohol, water, the nutrients of interest from food, fruits and vegetables, breads and cereals, or fiber; hormone replacement therapy; body mass index; constipation; or physical activity (26, 27, 33). After adjustment for each of these factors, the odds ratios did not change to the tenths place.

We examined whether the associations of multivitamin use and supplemental vitamin E with colon cancer differed by subgroups categorized by the factors listed above. Only water intake was a significant ($P < 0.01$) effect modifier of the multivitamin-colon cancer association. Those with a low intake of water ($\leq$2 glasses per day, about one-half of the study population) had less reduction in risk from 10 years of daily use of multivitamins (OR, 0.73; 95% CI, 0.46–1.14) than those with higher intake (OR, 0.31; 95% CI, 0.18–0.54). There were no clear effect modifiers of the supplemental vitamin E-colon cancer association. There were no important differences in the association of supplemental nutrients to colon cancer by anatomical subsite (data not shown).

## Discussion

We found daily use of multivitamins for 10 years to be associated with one-half the risk of colon cancer among men and women combined compared with no use of multivitamins. Multivitamins generally contain 100% of the United States RDA for vitamin A, vitamin C, vitamin D, vitamin E, folic acid, other B vitamins, and often include minerals including small amounts of calcium and 100% of the RDA of iron and zinc. Supplemental vitamin E use was associated with a reduced risk of colon cancer with a clear dose-response trend, even when we restricted the trend test to users of the supplement. Vitamins A, C, folic acid, and calcium also were associated with reduced risk of colon cancer using standard methods to test for associations but not when tested for trend among users only. Our results on vitamin D could not be separated from those on multivitamins because almost all supplemental vitamin D comes from multivitamin pills, and our results on calcium are limited by relatively low levels of supplementation in the population studied [the cutoff for our highest category of use (100 mg/day) is only equal to 10% of the RDA].

As noted in the introduction, reviews of epidemiological studies of diet and cancer indicate that fruit and vegetable intake reduces the risk of colon cancer. However, few reviewers have attempted to summarize these studies in relation to the effects of specific micronutrients. Potter *et al.* (34) reviewed the epidemiological literature on nutrient intake and colon cancer, and Enger *et al.* (35) reviewed similar studies on colon adenomas. Although some studies found inverse associations with vitamins A, C, D, E, folic acid, or calcium, there was little consistency across studies. Based on dietary intake data col-

*Table 2* Relationship of colon cancer to average daily intake of multivitamins and supplemental vitamins A, C, E, folate, and calcium[a]

| | Men | | | | Women | | | | Both | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cases *n* (%) | Controls *n* (%) | Age-adjusted OR | 95% CI | Cases *n* (%) | Controls *n* (%) | Age-adjusted OR | 95% CI | Cases *n* (%) | Controls *n* (%) | Age- and sex-adjusted OR | 95% CI |
| Multivitamins (pills) | | | | | | | | | | | | |
| Never used | 169 (67) | 141 (61) | 1.00 | | 111 (58) | 86 (44) | 1.00 | | 280 (63) | 227 (53) | 1.00 | |
| <1/day | 44 (18) | 35 (15) | 1.10 | (0.67–1.82) | 46 (24) | 42 (22) | 0.84 | (0.51–1.40) | 90 (20) | 77 (18) | 0.97 | (0.68–1.39) |
| 1/day | 38 (15) | 57 (25) | 0.55 | (0.34–0.88) | 36 (19) | 66 (34) | 0.43 | (0.26–0.71) | 74 (17) | 123 (29) | 0.49 | (0.35–0.69) |
| *P* for trend | | | 0.03 | | | | 0.001 | | | | <0.001 | |
| *P* for difference among users | | | 0.02 | | | | 0.04 | | | | 0.001 | |
| Vitamin A[b] (IU/day) | | | | | | | | | | | | |
| None | 167 (67) | 140 (60) | 1.00 | | 111 (58) | 87 (45) | 1.00 | | 278 (63) | 227 (53) | 1.00 | |
| <5000 | 42 (17) | 42 (18) | 0.86 | (0.53–1.40) | 46 (24) | 49 (25) | 0.74 | (0.45–1.21) | 88 (20) | 81 (21) | 0.81 | (0.57–1.14) |
| 5000 | 24 (10) | 35 (15) | 0.58 | (0.33–1.02) | 19 (10) | 36 (19) | 0.43 | (0.23–0.81) | 43 (10) | 71 (17) | 0.51 | (0.33–0.78) |
| >5000 | 18 (7) | 16 (7) | 0.97 | (0.47–1.98) | 17 (9) | 22 (11) | 0.59 | (0.29–1.19) | 35 (8) | 38 (9) | 0.75 | (0.46–1.24) |
| *P* for trend | | | 0.22 | | | | 0.01 | | | | 0.009 | |
| *P* for trend among users | | | 0.94 | | | | 0.46 | | | | 0.46 | |
| Vitamin C[b] (mg/day) | | | | | | | | | | | | |
| None | 161 (64) | 126 (54) | 1.00 | | 97 (50) | 77 (40) | 1.00 | | 258 (58) | 203 (48) | 1.00 | |
| <60 | 27 (11) | 29 (13) | 0.73 | (0.41–1.29) | 28 (15) | 32 (17) | 0.69 | (0.38–1.25) | 55 (12) | 61 (14) | 0.71 | (0.47–1.07) |
| 60–499 | 36 (14) | 45 (19) | 0.65 | (0.40–1.08) | 42 (22) | 49 (25) | 0.69 | (0.41–1.15) | 78 (18) | 94 (22) | 0.67 | (0.47–0.96) |
| ≥500 | 27 (11) | 33 (14) | 0.63 | (0.36–1.11) | 26 (14) | 36 (19) | 0.58 | (0.32–1.04) | 53 (12) | 69 (16) | 0.61 | (0.40–0.91) |
| *P* for trend | | | 0.04 | | | | 0.04 | | | | 0.004 | |
| *P* for trend among users | | | 0.71 | | | | 0.62 | | | | 0.53 | |
| Vitamin E[b] (IU/day) | | | | | | | | | | | | |
| None | 163 (65) | 133 (57) | 1.00 | | 106 (55) | 77 (40) | 1.00 | | 269 (61) | 210 (49) | 1.00 | |
| <15 | 36 (14) | 31 (13) | 0.96 | (0.56–1.63) | 43 (22) | 46 (24) | 0.67 | (0.40–1.12) | 79 (18) | 77 (18) | 0.81 | (0.56–1.17) |
| 15–199 | 36 (14) | 47 (20) | 0.64 | (0.39–1.05) | 34 (18) | 46 (24) | 0.56 | (0.33–0.96) | 70 (16) | 93 (22) | 0.61 | (0.42–0.87) |
| ≥200 | 16 (6) | 22 (9) | 0.59 | (0.30–1.18) | 10 (5) | 25 (13) | 0.27 | (0.12–0.59) | 26 (6) | 47 (11) | 0.43 | (0.26–0.71) |
| *P* for trend | | | 0.04 | | | | <0.001 | | | | <0.001 | |
| *P* for trend among users | | | 0.21 | | | | 0.05 | | | | 0.02 | |
| Folic acid[c] (mcg/day) | | | | | | | | | | | | |
| None | 189 (75) | 157 (67) | 1.00 | | 135 (70) | 112 (58) | 1.00 | | 324 (73) | 269 (63) | 1.00 | |
| <400 | 36 (14) | 39 (17) | 0.79 | (0.48–1.30) | 39 (20) | 43 (22) | 0.75 | (0.46–1.25) | 75 (17) | 82 (19) | 0.77 | (0.54–1.10) |
| ≥400 | 26 (10) | 37 (16) | 0.59 | (0.34–1.01) | 19 (10) | 39 (20) | 0.44 | (0.24–0.80) | 45 (10) | 76 (18) | 0.51 | (0.34–0.77) |
| *P* for trend | | | 0.04 | | | | 0.007 | | | | <0.001 | |
| *P* for trend among users | | | 0.36 | | | | 0.17 | | | | 0.08 | |
| Calcium[d] (mg/day) | | | | | | | | | | | | |
| None | 168 (67) | 138 (59) | 1.00 | | 110 (57) | 93 (48) | 1.00 | | 278 (63) | 231 (54) | 1.00 | |
| <100 | 33 (13) | 41 (18) | 0.67 | (0.40–1.13) | 43 (22) | 39 (20) | 0.94 | (0.56–1.57) | 76 (17) | 80 (19) | 0.81 | (0.56–1.16) |
| 100 | 22 (9) | 28 (12) | 0.65 | (0.36–1.20) | 12 (6) | 29 (15) | 0.38 | (0.18–0.80) | 34 (8) | 57 (13) | 0.52 | (0.33–0.83) |
| >100 | 28 (11) | 26 (11) | 0.88 | (0.49–1.57) | 28 (15) | 33 (17) | 0.71 | (0.40–1.26) | 56 (13) | 59 (14) | 0.78 | (0.52–1.18) |
| *P* for trend | | | 0.25 | | | | 0.05 | | | | 0.03 | |
| *P* for trend among users | | | 0.50 | | | | 0.30 | | | | 0.81 | |

[a] Intake averaged over a 10-year period ending 2 years prior to diagnosis for cases and a comparable period for controls.
[b] From multivitamins and individual supplements.
[c] From multivitamins.
[d] From multivitamins, individual supplements, and calcium-containing antacids.

lected in the present study, we found relative risks of colon cancer in the range of 0.3 to 0.55 for upper *versus* lower quartile of intake of vitamin E, folate, and calcium from food among women only (26).

Only one randomized trial of micronutrient supplements, the Physicians' Health Study (14), had large numbers of colorectal cancer end points ($n = 341$). This study found no difference in colorectal cancer incidence between those randomized to 50 mg of β-carotene (a vitamin A precursor) on alternate days *versus* placebo. The Alpha-Tocopherol, Beta-Carotene Study (15) found a 20% reduction in colorectal cancer incidence among the men randomized to 50 mg of α-tocopherol (vitamin E), although this result was not statistically significant, and the number of cases was small ($n = 149$).

Randomized placebo-controlled trials of the recurrence of sporadic colorectal adenomas have tested vitamins A, C, E, and β-carotene supplements. Trials of β-carotene found either no effect (36) or increased risk of new adenomas (37). Roncucci *et al.* (38) found a large reduction in new adenomas for patients randomized to a supplement containing vitamins A, C, and E (relative risk, 0.16; $P < 0.001$), but other trials of vitamins C and E (36, 39) including a large, multicenter trial (36), found no effect.

Observational studies of vitamin supplements and colon cancer include studies of five large cohorts. Shibata *et al.* (16) found an inverse association between vitamins A and C and colon cancer only among women in the Leisure World Cohort. In the Iowa Women's Health Study, Bostick *et al.* (17, 18) found a significantly reduced risk with supplemental vitamins A and E (17) and suggestive but nonsignificant results for vitamin D and calcium supplements (18). Kampman *et al.* (19) found no association between calcium supplements and colon

cancer in the Netherlands Cohort Study. In the Health Professionals Follow-up Study, colon cancer risk was inversely associated with dose of supplemental vitamin D (20) but not with years of folic acid use (21). In the Nurses Health Study, the use of multivitamin supplements for 15 years or more was associated with a nonsignificant 25% reduction in colorectal cancer (22). Of two case-control studies that reported on vitamin supplements and colon cancer, one found a significant protective effect of vitamins A and C (23), whereas the other found some evidence of reduced risk with use of calcium or vitamin D but not with total vitamin use (24). A case-control study of vitamin supplements and colorectal adenomas found a reduced risk of incident adenomas among those who used vitamin C or multivitamins for long duration but no reduction in recurrent adenomas (40).

Interpretation of the prior observational studies and of the present study should take into account that it is difficult to separate the effects of multivitamin supplement use from the effect of specific supplemental nutrients. Because multivitamins contain several nutrients, this leads to colinearity among the supplemental intake variables. Vitamins A, D, and folic acid are usually ingested as part of a multivitamin and rarely as individual supplements; therefore, results presented for these micronutrients might actually reflect an effect of multivitamins (or of some other micronutrient in multivitamins). Thus, this study and prior research support an effect of vitamin supplements on colon cancer risk but are limited in their ability to identify the specific nutrient(s) that may affect risk.

To reduce the colinearity in this study, we attempted to create supplement variables so that those in the highest dose category represented a particular multivitamin with high potency or use of the individual supplement as opposed to use of a one-a-day-type multivitamin. Thus, one test of the effect of a specific nutrient on colon cancer risk would be that risk of colon cancer at the highest level of supplement use was lower than the intermediate levels, which represent multivitamin users. We also applied a stricter dose-response trend by limiting the test to users of the supplement only. This tests for the effect of the exposure among those exposed, rather than the usual dose-response trend in which the difference in disease risk between those exposed and unexposed contributes to the significance of the trend (30). Only multivitamins and supplemental vitamin E were associated with colon cancer using the stricter test.

One limitation of our study is that supplement users may be more health conscious than nonusers and, therefore, more likely to practice other disease prevention behaviors, which may reduce their risk of disease (31). Studies have shown some differences in smoking, exercise, and diet between supplement users and nonusers (13, 31, 32). However, we found no measured factors that confounded the associations presented. Furthermore, the test for trend among users only allows users to be compared among themselves, which should reduce confounding by factors that differ between users and nonusers. Conversely, there is also concern that certain health conditions may lead people to take supplements (31). To account for this, we ended our 10-year reference period 2 years before diagnosis for cases (and a comparable time for controls) to reduce any effects of symptoms of colon cancer on supplement use.

It is unlikely that screening differences between supplement users and nonusers could have biased our results. Colon cancer screening would have two divergent effects on disease risk. Screening that leads to earlier diagnosis of invasive colon cancer would artificially appear to increase the risk of disease by moving diagnosis to an earlier age, whereas screening that prevents the occurrence of disease by removal of adenomas would appear as a protective factor. The former is unlikely to have biased our results because supplement users are more likely to participate in cancer screening than nonusers (32), and the latter would have little impact because only 3% of the study cases and 2% of controls reported having had a polyp removed. We also found no differences by anatomical subsite, as may have occurred if screening were a confounder.

Case-control studies of supplement use and cancer incidence may also suffer from selection bias and from differential measurement error. Selection bias may have occurred in this study if supplement users were more likely to agree to be controls than nonusers, perhaps because they are more interested in health issues. Selection factors among cases are less likely to have biased our results, unless cases who died before interview were more likely to use supplements than those who were interviewed. Differential measurement error could have occurred if individuals with cancer remember and report their exposure to supplements differently from controls.

Nondifferential measurement error could have occurred in this study due to poor recall by subjects, limitations of our multivitamin supplement database, and our choice of a reference period. We did not attempt to develop a comprehensive supplement database because the formulation of multivitamins changed over time within some brands, and because subjects often cannot name a single brand. However, a major advantage of our measurement of supplements compared with past research is that we collected sufficient details of use to estimate the average daily dose over a 10-year time period. However, our choice of reference period was by necessity somewhat arbitrary.

In summary, the use of supplements was associated with reduced risk of colon cancer in this study, with multivitamin use and use of supplemental vitamin E showing the greatest reduction of risk. Large clinical trials or cohort studies with detailed, long-term exposure assessment would be needed before any public health recommendations could be made about the benefits and risks of supplements.

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