Calcium, Vitamin D, and the Occurrence of Colorectal Cancer Among Women

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**Background:** Despite evidence from animal studies for a protective effect of higher calcium and possibly vitamin D intake against colorectal cancer, epidemiologic studies have been inconclusive. **Purpose:** We investigated the associations between the intake of calcium and vitamin D and the occurrence of colorectal cancer. **Methods:** In a prospective study, 89,448 female registered nurses who were free of cancer responded to a mailed, semiquantitative food-frequency questionnaire in 1980; dietary information was updated in 1984 and 1986. Through 1992, 501 incident cases of colorectal cancer (396 colon and 105 rectal cancers) were documented. As measures of exposure, we used nutrient intake in 1980 and also two measures of long-term intake on the basis of the three questionnaires: the average of intakes from the three questionnaires and consistent intakes, which were defined as high if women were in the upper tertile on all questionnaires and low if they were in the lower tertile on all questionnaires. To further characterize long-term intake, we conducted analyses excluding women who reported a change in their consumption of milk (primary source of calcium and vitamin D) in the 10 years prior to 1980. **Results:** On the basis of the data from the 1980 questionnaire alone, the multivariate RR for colorectal cancer for women in the upper versus the lower quintile were 0.80 (95% CI = 0.60-1.07) for dietary calcium, 0.84 (95% CI = 0.63-1.13) for dietary vitamin D (from foods only), and 0.88 (95% CI = 0.66-1.16) for total vitamin D (from foods and supplements). After the exclusion of women who reported a change in their milk intake, the RRs for colorectal cancer for the highest versus the lowest categories of average intake were 0.74 (95% CI = 0.36-1.50) for dietary calcium, 0.72 (95% CI = 0.34-1.54) for dietary vitamin D, and 0.42 (95% CI = 0.19-0.91) for total vitamin D. The corresponding RRs for the consistency analyses were 0.70 (95% CI = 0.35-1.39) for dietary calcium, 0.59 (95% CI = 0.30-1.16) for dietary vitamin D, and 0.33 (95% CI = 0.16-0.70) for total vitamin D. **Conclusions:** These findings do not support a substantial inverse association between calcium intake and risk of colorectal cancer, but an inverse association between intake of total vitamin D and risk of colorectal cancer was suggested. **Implications:** Available evidence does not warrant an increase in calcium intake to prevent colon cancer, but longer-term studies of both calcium and especially vitamin D in relation to colorectal cancer risk are needed. [J Natl Cancer Inst 1996;88:1375-82]

Diet is thought to be a major etiologic factor in developing colorectal cancer (1), but inconsistencies exist in findings for the specific dietary components. In numerous epidemiologic studies, a high intake of fruits and vegetables and a low intake of red meat has been associated with a reduced risk of developing colon cancer (2-5). A possible protective effect of calcium against colon carcinogenesis has been suggested by animal studies; calcium binds bile acids and free fatty acids and may thus diminish their proliferative effect on the colon mucosa (6-9). An alternative hypothesis, on the basis of in vitro studies in human epithelial cells (10), suggests that calcium might inhibit the proliferation of colonic epithelial cells directly by inducing terminal differentiation. Experimental findings in humans and animals suggest that vitamin D inhibits cell proliferation, possibly because of a direct effect of vitamin D or perhaps indirectly by increasing calcium absorption (11-14). Intervention studies (10,15-20) in humans on the effect of calcium on cell proliferation have yielded inconsistent findings. Although ecologic studies (21-24) support an inverse association between calcium and colon and rectal cancers, results of case-control and cohort studies that have addressed the role of calcium (25-
43) and vitamin D (25,28,29,31,35,41,43) in relation to colorectal cancer are inconsistent.

Despite the considerable number of studies in humans, in cultured colonic malignant cell lines, and in experimental animal models, the possible roles of calcium and vitamin D as colorectal anticarcinogens remain unclear. The inconclusive findings of analytic epidemiologic studies may partly be due to misclassification of intake of these nutrients because the dietary assessment has been at only one time period. In the present study, we investigated the associations between intakes of calcium and vitamin D and the occurrence of colorectal cancer in a prospective study of U.S. women. One strength of this study lies in the use of three dietary questionnaires collected prospectively over 6 years. We have previously reported results that did not support an association between the intake of calcium and the diagnosis of colorectal adenomatous polyps but did suggest an inverse association with vitamin D, particularly for rectal polyps, in this population (44).

Methods

Study Cohort

In 1976, 121,700 female registered nurses aged 30-55 years were enrolled in the Nurses' Health Study by use of a mailed questionnaire. Every 2 years, follow-up questionnaires are mailed to the participants to update information on risk factors and major medical events that have occurred. Dietary intake data were collected in 1980, 1984, and 1986 by means of a mailed, self-administered, semiquantitative food-frequency questionnaire. Women who completed the 1980 dietary questionnaire and who had no history of cancer (except nonmelanoma skin cancer), ulcerative colitis, or Crohn's disease at the beginning of the follow-up period were eligible for analysis (n = 89,448). In 1992, more than 94% of the participants had responded to follow-up questionnaires. The 12-year follow-up analyses of 89,448 women included 501 incident cases of colorectal cancer (396 colon and 105 rectal cancers).

Case Ascertainment

The ascertainment of cases of colorectal cancer has been described in detail elsewhere (45). On each biennial follow-up questionnaire, we asked whether cancer of the colon or rectum had been diagnosed during the previous 2 years. We also used the National Death Index and the Postal Service to identify fatalities; we estimate that more than 98% of the deaths were ascertained (46). When a participant (or next of kin for decedents) reported a diagnosis of cancer elsewhere on each biennial follow-up questionnaire, we asked her (or next of kin) for permission to obtain hospital records and pathology reports regarding this diagnosis. Study physicians blinded to the exposure information reviewed the medical records to extract information on the histologic type, the anatomic location, and the stage of the cancer. Cancers other than adenocarcinoma were excluded. We included 52 cases with missing information for anatomic location, and the stage of the cancer. Cancers other than adenocarcinoma were excluded. We included 52 cases with missing information for anatomic location, since analyses limited to colon cancer cases with complete information yielded results virtually identical to those of analyses excluding these cases.

Dietary Assessment

In 1980, the Nurses' Health Study semiquantitative food-frequency questionnaire included 61 food items, the 1984 questionnaire was increased in length to 121 items, and the 1986 questionnaire included 136 items. In each questionnaire, participants were asked how often, on average during the past year, they consumed a specified, commonly used portion of each food. There were nine possible responses, ranging from almost never or less than once per month up to six or more times per day. In 1980, the questionnaire included seven specific dairy foods: skim or low-fat milk, whole milk, ice cream, yogurt, cottage cheese, hard cheese, and butter. The 1984 and 1986 questionnaires included these seven items and four more: cream, sour cream, sherbet or ice milk, and cream cheese. Nutrient intakes were computed by multiplying the frequency of intake of each unit of food by the nutrient composition of the specified portion size according to composition values from U.S. Department of Agriculture sources (47) supplemented with other sources (48). Analyses were conducted with energy-adjusted nutrient intakes based on the residuals from the regression of nutrient intake on total caloric intake (49). Nutrient values were computed with and without vitamin and mineral supplements. All three questionnaires included questions about vitamin and mineral use. However, information on calcium supplements was ascertained only in the 1984 and 1986 questionnaires; women were asked to record their calcium supplement dose in the following categories: less than 400, 400-900, 901-1300, and 1301 mg or more per day. Twenty-eight percent of the women reported current multivitamin use in 1980, 37% in 1984, and 35% in 1986. The percentage of participants who reported use of calcium supplements was 28% in 1984 and 52% in 1986; this question was not included on the 1980 questionnaire.

Assessment of the reproducibility and validity of the food-frequency questionnaire indicates that this dietary instrument provides useful information about intake of a wide variety of nutrients and foods consumed over an extended period of time (50,51). At the time of the original validation study, diet recall values for vitamin D were not available. However, the major food sources of vitamin D (dairy products, especially low-fat or skim milk) were measured reasonably well. Pearson correlation coefficients between the dietary record data and the 1980 food-frequency questionnaire were 0.67 for skim or low-fat milk and 0.54 for whole milk, whereas those for the 1984 questionnaire were 0.79 for low-fat or skim milk and 0.62 for whole milk (50). Pearson correlation coefficients between dietary record data and the 1986 food-frequency questionnaire were 0.64 for energy-adjusted total calcium and 0.75 for calcium without supplements (Sampson L.; personal communication).

Data Analysis

Nutrients were analyzed with the use of quintiles of nutrient intake, according to the distribution in the study population, and as continuous variables. Calcium and vitamin D intake were considered with and without supplements. Since no information on calcium supplements was collected in 1980 and the results for dietary and total calcium were not appreciably different, we focused primarily on data for dietary calcium. Total vitamin D refers to the total nutrient derived from foods and supplements. Dietary vitamin D refers to the nutrient derived from foods only, which largely includes vitamin D from fortification of dairy products. For each participant, person-months of follow-up were computed from the month of return of the 1980 questionnaire to the date of colorectal cancer diagnosis, death from any cause, or May 31, 1992, whichever came first. Person-months of follow-up were allocated according to exposure status in 1980. Relative risks (RRs) and their 95% confidence intervals (CIs) were calculated using the lowest quintile of intake as the reference. The Mantel extension test was used to evaluate linear trends across categories of nutrient intake. In the multivariate analyses, the trends were tested with the use of the medians of the quintiles of nutrient intake as a continuous variable in the logistic model. The P values for the trends are two-sided.

We used multiple logistic regression models to control simultaneously for several potentially confounding variables (52). Covariates that are a priori potential risk factors for colorectal cancer were included in the models. In the multivariate models, we included age (in six categories), history of colorectal cancer in a parent or sibling, body mass index (in quintiles), smoking (pack-years of smoking >35 years before diagnosis), physical activity (metabolic equivalents per week), aspirin use (times per week), and quintiles of intake of red meat and alcohol. To investigate the possibility that calcium intake might reduce risk of colorectal cancer among women with higher intake of fat, we examined the association between calcium intake (in tertiles) and colorectal cancer risk within tertiles of total or saturated fat.

To assess long-term nutrient intake, two types of analyses were conducted that used of all three dietary questionnaires. First, for the analysis of colon and colorectal cancers, the average nutrient intake from the three questionnaires was computed and grouped into seven categories to examine a wide range of nutrient intake. For rectal cancer, for which there were fewer cases, the average nutrient intakes were categorized into quintiles. Second, nutrient intakes from each questionnaire were categorized into tertiles. Participants were then categorized into the high (or low) group if they fell in the highest (or lowest) tertile on all three questionnaires. All of the other women were included in the middle category. This analysis was not conducted for rectal cancer because of the small number of
available cases. The follow-up period for the analyses using all three questionnaires was 1986 to 1992, which included a cohort of 88 985 women.

In the 1980 questionnaire, nurses were asked whether their intake of each food category had significantly increased or decreased in the previous 10 years. We used this information to conduct additional analyses, excluding women who reported a significant change in their milk intake during this period of time. This was used a priori as a marker for consistent, long-term intake of calcium and vitamin D.

**Results**

During 1 012,280 person-years of follow-up over a 12-year period (1980 through 1992), we documented 396 cases of colon cancer and 105 cases of rectal cancer. Table 1 presents age-standardized risk factors for colorectal cancer according to intake of total calcium and vitamin D in 1980. Compared with women with the lowest intake of energy-adjusted calcium and vitamin D, women with the highest intake had a higher intake of phosphorus and dietary fiber and a lower intake of alcohol and animal fat. Women in the higher category were less likely to be current smokers and more likely to be multivitamin users. A higher proportion of women in the highest quintile of vitamin D used aspirin compared with those in the lowest quintile. There were no appreciable differences in body mass index, level of physical activity, proportion of women with a family history of colorectal cancer, or proportion with previous colorectal polyps among the categories of calcium or vitamin D intake.

**Colorectal Cancer**

On the basis of the 1980 questionnaire and follow-up from 1980 through 1992, the multivariate RRs for individuals in the upper quintile of dietary calcium intake were 0.80 (95% CI = 0.60-1.07) compared with those in the lower quintile (Table 2). Similar weak, nonsignificant inverse associations were seen for dietary vitamin D intake (RR = 0.84; 95% CI = 0.63-1.13) and total vitamin D intake (RR = 0.88; 95% CI = 0.66-1.16). The tests of trend for these associations were not statistically significant. The exclusion of women who reported a change in their milk intake in the 10 years prior to 1980 (n = 26,980) resulted in somewhat stronger RRs. This was especially noted for total vitamin D and colorectal cancer where a significant RR of 0.67 (P for trend = .02) was observed.

With women who reported a change in their milk intake prior to 1980 excluded, analyses based on the averages of the three questionnaires for dietary calcium and vitamin D intakes in relation to colorectal cancer risk were virtually identical to those based on the 1980 questionnaire (Table 3). However, a stronger RR was observed for the highest category of average total vitamin D intake compared with the lowest category (RR = 0.42; 95% CI = 0.19-0.91). Similarly, in the consistency analysis, the RR for women in the high category compared with the low category of total vitamin D intake was 0.33 (95% CI = 0.16-0.70).

**Colon and Rectal Cancers Examined Separately**

To examine the associations with colon and rectal cancers separately, we modeled the nutrients as continuous variables (Table 4). For calcium intake, there were no material differences between the results for colon cancer and those for colorectal cancer on the basis of the data from either the 1980 questionnaire or the 1980 through 1986 average. For dietary and total

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**Table 1. Characteristics* of the study population according to quintiles of calcium and vitamin D intake based on the 1980 Nurses' Health Study dietary questionnaire**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quintile</th>
<th>Quintile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total calcium</td>
<td>Total vitamin D</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>No. of participants</td>
<td>17 903</td>
<td>17 871</td>
</tr>
<tr>
<td>Mean daily intake†</td>
<td>1618</td>
<td>1597</td>
</tr>
<tr>
<td>Total energy, kilocalories</td>
<td>380</td>
<td>543</td>
</tr>
<tr>
<td>Dietary calcium, mg</td>
<td>170</td>
<td>217</td>
</tr>
<tr>
<td>Phosphorus, mg</td>
<td>911</td>
<td>1021</td>
</tr>
<tr>
<td>Animal fat, g</td>
<td>56.5</td>
<td>53.6</td>
</tr>
<tr>
<td>Dietary fiber, g</td>
<td>14.5</td>
<td>16.4</td>
</tr>
<tr>
<td>Alcohol, g</td>
<td>8.8</td>
<td>7.3</td>
</tr>
<tr>
<td>Family history, ‡</td>
<td>7.9</td>
<td>7.8</td>
</tr>
<tr>
<td>Previous polyp, %</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Mean body mass index§</td>
<td>24.3</td>
<td>24.3</td>
</tr>
<tr>
<td>Metabolic equivalents/wk</td>
<td>24.6</td>
<td>25.1</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>33.7</td>
<td>30.2</td>
</tr>
<tr>
<td>Aspirin use, %</td>
<td>32.2</td>
<td>34.2</td>
</tr>
<tr>
<td>Multivitamin use, %</td>
<td>26.7</td>
<td>30.5</td>
</tr>
</tbody>
</table>

*Standardized for age at baseline.
†Adjusted to total energy intake by regression analysis.
‡History of colorectal cancer in parent or sibling.
§Weight (kg)/height (m)².
IIUse in 1980.
vitamin D, stronger inverse associations were seen for rectal cancers, except for total vitamin D according to the 1980 dietary assessment. However, the CIs were wide in the subanalysis. Stronger, but less precise, inverse RRs for calcium and vitamin D were observed for colon and rectal cancers after exclusion of women who reported a change in their milk consumption in the 10 years prior to 1980 (data not shown).

Additional Analyses

As noted previously, calcium supplement use in participants increased from 28% in 1984 to 52% in 1986; we did not ask about this in 1980. When we assessed total calcium intake in the analyses using the three dietary questionnaires, the results were not appreciably different from those for dietary calcium presented in Table 3. After excluding women who reported a change in their milk intake, the RR for colorectal cancer for the highest versus the lowest quintile of average total calcium intake was 0.71 (95% CI = 0.37-1.35). In the consistency analysis, women in the high category had an RR for colorectal cancer of 0.76 (95% CI = 0.38-1.52) compared with those in the low category.

Dairy products contributed to 91% of dietary calcium intake and to 82% of dietary vitamin D intake in this study population.

When we conducted analyses of dairy sources of calcium and vitamin D based on the 1980 questionnaire, the results were consistent with those from all food sources. The RR for colorectal cancer for individuals at the highest compared with the lowest quintile was 0.92 (95% CI = 0.69-1.21) for calcium from dairy sources and 0.85 (95% CI = 0.64-1.12) for vitamin D from dairy sources. When intake of milk was assessed, women who reported two or more servings of milk per day in 1980 had an RR of 0.89 (95% CI = 0.65-1.19) compared with those in the lowest tertile. The RR for colorectal cancer of 0.88 (95% CI = 0.65-1.19) compared with those consuming less than one serving per month. In the analysis of average intake, women with an average milk intake of more than two servings per day in 1980 had an RR for colorectal cancer of 0.88 (95% CI = 0.65-1.19) compared with those consuming less than one serving per month. In the consistency analysis, the RR for women who fell in the highest tertile of milk intake on all questionnaires was 0.77 (95% CI = 0.57-1.08) compared with those whose intake was less than one per month.

There was no clear evidence that dietary fat modified the relationship between calcium intake and risk of colorectal cancer. An inverse trend was observed for dietary calcium when fat intake was examined in tertiles, but with wide CIs. The RR for colorectal cancer for individuals at the highest compared with the lowest tertile was 0.90 (95% CI = 0.56-1.45) compared with those in the lowest tertile.

To determine whether high levels of calcium intake can reduce risk of colorectal cancer among persons with high dietary fat intake, we examined the association of calcium (in tertiles) and the risk of colorectal cancer within tertiles of dietary fat. There was no clear evidence that dietary fat modified the relation between calcium intake and risk of colorectal cancer. An increase in risk was seen with decreasing calcium intake in the highest versus the lowest quintile of average total calcium intake. The RR for colorectal cancer for individuals at the highest compared with the lowest quintile was 0.66 (95% CI = 0.46-1.04) compared with those whose intake was less than one per month.

In the consistency analysis, the RR for women who fell in the highest tertile of milk intake on all questionnaires was 0.86 (95% CI = 0.69-1.08) compared with those consuming less than one serving per month. In the analysis of average intake, women with an average milk intake of more than two servings per day in 1980 had an RR for colorectal cancer of 0.88 (95% CI = 0.65-1.19) compared with those consuming less than one serving per month. In the consistency analysis, the RR for women who fell in the highest tertile of milk intake on all questionnaires was 0.77 (95% CI = 0.57-1.08) compared with those whose intake was less than one per month.

Additional Analyses

As noted previously, calcium supplement use in participants increased from 28% in 1984 to 52% in 1986; we did not ask about this in 1980. When we assessed total calcium intake in the analyses using the three dietary questionnaires, the results were not appreciably different from those for dietary calcium presented in Table 3. After excluding women who reported a change in their milk intake, the RR for colorectal cancer for the highest versus the lowest quintile of average total calcium intake was 0.71 (95% CI = 0.37-1.35). In the consistency analysis, women in the high category had an RR for colorectal cancer of 0.76 (95% CI = 0.38-1.52) compared with those in the low category.

Dairy products contributed to 91% of dietary calcium intake and to 82% of dietary vitamin D intake in this study population.
### Table 3. Relative risk (RR) and 95% confidence interval (CI) of colorectal cancer according to category of average and consistent intake of dietary calcium and dietary and total vitamin D among women who did not change their milk intake in the 10 years prior to 1980: The Nurses’ Health Study

<table>
<thead>
<tr>
<th>Dietary calcium</th>
<th>Dietary vitamin D</th>
<th>Total vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/day</td>
<td>IU/day</td>
<td></td>
</tr>
<tr>
<td>&lt;500</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>500-600</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>601-650</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>651-750</td>
<td>31</td>
<td>33</td>
</tr>
<tr>
<td>751-850</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>851-1000</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>13</td>
<td>&gt;280</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.36-1.50</td>
<td>0.34-1.54</td>
</tr>
<tr>
<td><em>P for trend</em></td>
<td>.21</td>
<td>.29</td>
</tr>
</tbody>
</table>

*Adjusted for age, body mass index, physical activity, family history of colorectal cancer, aspirin use, cigarette smoking, red-meat intake, and alcohol consumption.

†Average intake of the 1980, 1984, and 1986 dietary questionnaires.

‡CI for the upper compared with the lower intake.

§*P for trend calculated by using the median of each category of intake as a continuous variable in the multiple regression model for the average intake.

Women were categorized in the low or high category if they consistently fell in this category on all three of the 1980, 1984, and 1986 dietary questionnaires.

Because many women began using calcium supplements during the course of this study, this would have induced some misclassification. We therefore conducted analyses of the 1980 through 1992 cohort that excluded women who reported using calcium supplements in 1982, 1984, or 1986. Although the number of colorectal cancer cases was reduced (n = 298), no important differences emerged when these results were compared with the results in the total population. In this analysis, women in the lower (RRs = 1.00, 1.49, and 1.74) and the upper (RRs = 1.00, 1.10, and 1.18) category of total fat but not in the middle category (RRs = 1.00, 0.88, and 0.89). When saturated fat was used as the fat variable, a similar pattern was observed.

### Table 4. Relative risk (RR) and 95% confidence interval (CI) of colon and rectal cancers according to intake of energy-adjusted† dietary calcium and dietary and total vitamin D modeled as continuous variables: The Nurses’ Health Study

<table>
<thead>
<tr>
<th>Dietary calcium</th>
<th>Dietary vitamin D</th>
<th>Total vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980 intake</td>
<td></td>
<td>1980-1986 average intake†</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>Rectal cancer</td>
<td>Colon cancer</td>
</tr>
<tr>
<td>n = 396</td>
<td>n = 105</td>
<td>n = 170</td>
</tr>
<tr>
<td>RR§</td>
<td>0.87</td>
<td>0.74</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.62-1.17</td>
<td>0.38-1.38</td>
</tr>
<tr>
<td>Dietary vitamin D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR§</td>
<td>0.96</td>
<td>0.45</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.72-1.28</td>
<td>0.25-0.83</td>
</tr>
<tr>
<td>Total vitamin D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR§</td>
<td>0.81</td>
<td>1.16</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.63-1.05</td>
<td>0.73-1.82</td>
</tr>
</tbody>
</table>

*Adjusted for age, body mass index, physical activity, family history of colorectal cancer, aspirin use, cigarette smoking, red-meat intake, and alcohol consumption.

†Energy-adjusted by regression analysis.


§RR for an increase of 800 mg of dietary calcium, 250 IU of dietary vitamin D, and 500 IU of total vitamin D.
When we included total vitamin D and dietary calcium simultaneously in the models for colorectal cancer, where the stronger effects were seen, the relation for calcium was weaker, whereas that for vitamin D was unchanged. We also conducted analyses comparing women in the highest quintile of both dietary calcium and total vitamin D to those in the lower quintiles. The RR for women who were in both the high calcium and vitamin D quintiles was 0.81 (95% CI = 0.52-1.26) compared with those in the lowest quintiles of both calcium and vitamin D.

Since the results for total vitamin D were more suggestive of an inverse association with colorectal cancer than those for dietary vitamin D, we explored the possibility that something other than vitamin D in multivitamins might protect against colorectal cancer. When we conducted the analysis using only supplemental vitamin D from the 1980 questionnaire, the RR for the users was 0.95 (95% CI = 0.79-1.15) compared with the nonusers. When we looked at the duration of use of multivitamins, women who used multivitamins for 15 years or more had an RR of 0.76 (95% CI = 0.50-1.16) compared with the nonusers. In the consistency analysis of multivitamin use, women who reported taking multivitamins on all three questionnaires had an RR for colorectal cancer of 0.81 (95% CI = 0.56-1.17) compared with those who reported no use on all three questionnaires. When we included the consistency variables for total vitamin D and multivitamin use in the same model, the RR for vitamin D became stronger (RR = 0.62; 95% CI = 0.31-1.21 for women in the upper compared with the lower category), whereas that for multivitamin use was attenuated (RR = 0.99; 95% CI = 0.61-1.60 for consistent users compared with nonusers). When we assessed the relation between supplemental vitamin D and risk of colorectal cancer within quintiles of dietary calcium, there was no evidence of a stronger reduction in risk from vitamin D from supplements among women with a low intake of vitamin D from food.

There was a weak positive association between energy intake and colorectal cancer. The age-adjusted RR for the highest compared with the lowest quintile of energy intake was 1.18 (95% CI = 0.89-1.57). When we conducted analyses using calcium and vitamin D intakes not adjusted for energy intake, there was no suggestion of stronger associations with colorectal cancer.

**Discussion**

Results from this study do not support any major inverse association between calcium intake and risk of colorectal cancer. While a weak, nonsignificant RR of 0.80 was observed for the association of dietary calcium and colorectal cancer from the 1980 dietary questionnaire, we saw no evidence of a dose-response relation, and data from the three dietary questionnaires did not suggest an association for calcium intake. The results for vitamin D are somewhat suggestive of an inverse association with colorectal cancer. The strongest RRs for colorectal cancer were observed for total vitamin D intake on the basis of the average and consistent intake after the exclusion of women who changed their intake of milk. Results for colon cancer were similar to those for colorectal cancer, but the results for rectal cancer are consistent with a stronger inverse association for calcium and vitamin D. However, overall, stronger inverse associations were seen for vitamin D than for calcium. In particular, a significant RR of 0.42 was observed for dietary vitamin D and rectal cancer, based on the 1980 questionnaire. However, this may be a chance finding, since the corresponding results for total vitamin D were weaker (RR = 0.86). Results based on the average of the three questionnaires are consistent with a 50% reduction in risk of rectal cancer for dietary and total vitamin D. These results, however, must be interpreted with caution because they are based on a small number of cases (n = 46).

Epidemiologic studies that have examined the association between calcium as a risk factor for colorectal cancer have been inconsistent. There is some evidence in support of a weak inverse association between relatively high intakes of calcium and risk of colorectal cancer. Thirteen case-control studies (30-42) and six cohort studies (25,28,29,43) have reported results for the association between calcium and colorectal, colon, or rectal cancer. An inverse association was reported in most of these studies (25-34,39,41,42), but this was statistically significant in only three of the case-control studies (31,32,39) and in two of the cohort studies (25,26). A positive, nonsignificant association was reported in five studies (37-40,45), and no estimate of association was reported in one (40).

Epidemiologic data on vitamin D and colorectal cancer are sparse. All four prospective studies (25,28,29,43) have reported inverse associations for dietary vitamin D and colorectal cancer but this was significant only in the Western Electric study (25). In the Iowa Women's Health Study (28) and the Health Professionals Follow-up Study (29), a significant inverse age-adjusted RR was observed for total vitamin D and risk of colorectal cancer, although this was attenuated and no longer significant after multivariate adjustment. Of the three published case-control studies of vitamin D and colorectal cancer, two (32,35) show inconsistent, nonsignificant findings and one (41) reported a statistically significant inverse association.

The hypothesis proposed by Newmark et al. (53) suggests that high levels of calcium are necessary to reduce irritation-driven cell proliferation resulting from free fatty acids and unconjugated bile acids in the colon from a high-fat diet. Our data do not entirely support this hypothesis. It is possible that a greater variation in both nutrients may be needed to fully explore this proposed interaction. However, there was no evidence of a stronger effect of calcium among individuals with high fat intake in two other epidemiologic studies (26,54).

The roles of calcium and vitamin D are closely linked because bioavailability of calcium (e.g., absorption in the gastrointestinal tract and into cells within the body) depends on adequate vitamin D. Vitamin D may protect against colorectal neoplasia, since it reduces epithelial cell proliferation and induces differentiation, and this activity may be mediated through the vitamin D receptor (14). Animal studies (6,7) have indicated that both dietary calcium and vitamin D seem to promote preservation of a favorable histologic pattern in colonic mucosa. It is hypothesized (8,53) that calcium might reduce colon cancer risk by binding secondary bile acids and ionized fatty acids to form insoluble soaps in the lumen of the colon, thus reducing the
The proliferative stimulus of these compounds on colon mucosa. It has also been suggested (15) that calcium can directly affect the proliferative activity of the colon mucosa. Among its several physiologic functions, 1,25-dihydroxyvitamin D, the active form of the vitamin, can induce maturation and differentiation of colonic mucosa. Vitamin D has been shown to reduce risk of carcinogen-induced colon cancer in animals (9, 55), possibly by malignant transformation via K-ras and/or protein kinase C alterations (56). In one study (17), a decrease in the number of tumors in rats with multiple colon tumors and a reduced tumor size was observed after calcium supplementation, but the presence of vitamin D deficiency nullified the protective effect of calcium on colon cancer. The limited analyses combining calcium and vitamin D in our study suggested only a weak positive association for women in the low calcium and vitamin D group compared with those in the other groups.

The median for the upper category of dietary vitamin D among our study participants was 311 IU per day based on the 1980 questionnaire and 322 IU per day based on the average of the three questionnaires. If higher intakes are needed to exert a protective effect for colon cancer, this may explain the stronger RRs seen for total vitamin D where the intakes were substantially higher (median values of 639 and 660 IU per day for the upper categories of the 1980 and the average intake, respectively).

There are several strengths of this study. Besides the prospective nature of the data and the high follow-up rates, this is the first study to combine data collected prospectively from three dietary questionnaires over a 6-year period. This allowed an examination of nutrient intake in various ways. To our knowledge, only one other study (25) has used data from more than one dietary questionnaire. Some published studies did not conduct their analysis with a specific focus on calcium or vitamin D and few had data on dietary vitamin D. In addition, only a few of these studies investigated associations separately for the colon and rectum. The relatively young age of our participants, along with a measurement of diet at three different periods of time, provides a powerful measure of adult lifetime exposure and decreases the possibility of misclassification.

The relatively low number of cases is a limitation of this study. While larger than most studies, the complexity of the analyses addressing the specific hypothesis requires a greater number of cases to detect a weak or modest protective effect. As this cohort continues to age and more cancer cases arise, future analyses will generate more precise risk estimates.

In summary, the results of this study suggest that higher calcium intakes are not associated with a substantially lower risk of colorectal cancer; however, we cannot exclude the possibility that calcium intake has a weak or modest effect on the occurrence of colorectal cancer or that very low intakes of calcium are associated with an increased risk. Our findings for vitamin D are suggestive of an inverse association, particularly for total vitamin D in relation to rectal cancer. However, since most of the support for this protective effect was seen for total vitamin D, we cannot rule out the possibility that something other than vitamin D in multivitamin supplements contributes to this apparent effect. The relation between vitamin D and colorectal cancer may be better elucidated with additional dietary measurements and further follow-up.

References


