A Randomized Trial of Vitamins C and E in the Prevention of Recurrence of Colorectal Polyps

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ABSTRACT

Because supplements of vitamins C and E had been associated with reduction of fecal mutagen levels, a double-blind randomized trial was designed to examine the effects of these vitamins on the rate of recurrence of colorectal polyps, presumed precursors for colorectal cancer. Two hundred patients believed to be free of polyps after removal of at least one colorectal polyp were randomized to receive a supplement of 400 mg each of ascorbic acid and α-tocopherol, or a placebo. Fifteen patients had to be excluded because a review of pathology indicated that their polyps were not adenomatous. A second colonoscopic examination was planned after 2 yr of supplementation. One hundred thirty-seven people (75% of eligible subjects) completed the study; polyps were observed in the second colonoscopy in 41.4% of 70 subjects on vitamin supplements and in 50.7% of 67 subjects on placebos. After adjustment for differences between groups in demographic and dietary factors before study entry, the relative risk of polyp occurrence was 0.86, with 95% confidence limits from 0.51 to 1.45, in an analysis of 129 subjects with complete information on demographic and dietary factors who had completed the trial. Of the 48 patients who had not completed the study, 7 had died, 33 had not returned to their physician for an examination, and 8 had had a follow-up colonoscopy or sigmoidoscopy. Inclusion of the three polyps found in these eight examinations led to an estimate of relative risk of 0.86 (95% confidence limits, 0.51 to 1.43). The findings of this investigation suggest that any reduction in the rate of polyp recurrence associated with vitamin supplementation is small, and a larger study would be required to ensure that an effect of this size was not a chance finding.

INTRODUCTION

When the present investigation was designed, the possibility that dietary supplementation with vitamins C and E might reduce the rate of formation of adenomatous polyps in the colon and rectum appeared biologically plausible from a number of lines of evidence. Mutagen had been detected in human stool (1) and might be associated with colorectal neoplasia (2, 3). Further, levels of fecal mutagen had been reduced after supplementation with vitamins C and E in 9 of 11 individuals who were mutagen producers (4). Although at the time the mechanism associated with reduced mutagen levels was unknown, it was later established that fecal mutagenicity was caused by fecapentaenes (5, 6), substances which can easily be decomposed in an acidic environment. Thus it is possible that fecapentaenes may be blocked by acids, such as vitamin C, or by unsaturated substances, such as vitamin E, capable of reacting with the conjugated double-bond system of fecapentaenes. In addition, several case-control studies of colorectal cancer have suggested that consumption of vegetables and fruit, natural sources of vitamin C, might be associated with reduced cancer risk (7-13), though these findings have not been reproduced consistently (14-18). Since adenomatous polyps are widely presumed to be precursor lesions of colorectal cancer (19, 20), Bruce and Dion postulated that supplementation with vitamins C and E might reduce the production of mutagens and hence the rate of polyp formation. They therefore undertook a randomized trial to examine the effect of vitamin supplementation on the rate of formation of adenomatous and other polyps in persons who had had at least one adenomatous polyp removed by polypectomy (21).

MATERIALS AND METHODS

Two hundred patients who had at least one polyp in the colon or rectum identified by colonoscopy at two Toronto hospitals between 1979 and 1984 agreed to participate in the study. All participated in a brief dietary inquiry which documented the frequency of usual consumption of bran cereals, whole wheat breads, fruit, green vegetables, fish, poultry, prepared meats, beef, and pork. Basic demographic data were also collected, together with information on current smoking status, usual bowel habits, and history of previous polyps. In addition, patients were asked whether they used supplements of vitamins C or E (free α-D,L-tocopherol), and those who did agreed to discontinue their use for the duration of the study. Otherwise, participants followed diets of their own choosing throughout the study. Participants were randomized to receive a supplement of 400 mg each of vitamins C and E or lactose placebos, over a period of 2 yr. Vitamin supplements and placebos were delivered to the patients every 4 mo. A random urine sample was collected at each visit from which urinary vitamin C levels were assessed as an index of compliance using a dip stick which classified the urine as containing 0 to 40 mg/dl of ascorbic acid on a five point colometric scale. A second colonoscopic examination was performed by the physician who had initially examined the patient and who was blinded to the nature of the supplement received during the study. This examination was planned to take place approximately 2 yr after the initial examination but could be performed earlier if judged clinically necessary. The physician assessed the presence and location of polyps, and any observed were removed and sent for pathology whenever possible.

Demographic and dietary characteristics of subjects assigned to receive vitamins or placebos were compared using χ2 and t tests (22), as appropriate. Kaplan-Meier survival curves (23) were used to estimate the probability of remaining free of polyps and were compared with the log rank test (24). Cox regression (25) was used to examine the association between vitamin supplementation and polyp recurrence, taking account of both the fact and time of recurrence and with adjustment for dietary and demographic factors. Confidence limits for estimates of risk and rate ratios were calculated using Miettinen's test-based procedures (26) and may be somewhat too narrow (27).

RESULTS

Although 200 potentially eligible subjects were initially randomized, a review of the hospital pathology reports revealed that 15 subjects had to be excluded because none of the polyps was adenomatous. Of the 185 subjects with an adenomatous polyp, 96 subjects had been allocated to receive vitamin supplements, and 89 had been allocated to receive placebos. Those receiving vitamins were a year younger on average (57.5 yr) than those on placebos (58.4 yr); most other characteristics did
not differ significantly between the two study groups (Table 1). However, subjects assigned to receive vitamin supplements reported regular use of vitamin C supplements prior to participation in the study significantly more frequently than those who were assigned placebos; they also reported using vitamin E supplements almost twice as frequently as participants on placebos, but this difference did not reach a conventional level of statistical significance. There were no significant differences in the reported diets of participants (Table 2), but those assigned to receive vitamins consumed foods which are postulated to be protective against colon cancer (high-fiber foods such as bran cereals, whole wheat bread, fruit and vegetables, and low-fat sources of muscle protein such as fish and poultry) somewhat more frequently than those assigned to placebos and consumed potentially harmful high-fat foods (such as prepared meats and pork) somewhat less frequently.

Of the 185 eligible subjects, 137 (75%) completed the study with a second colonoscopic examination conducted when most subjects (81.5% of those on vitamins and 82.3% of those on placebos) had been receiving supplements for 12 to 30 mo (Table 3). Demographic and dietary characteristics of subjects who completed the trial were similar to those reported for all eligible subjects in Table 1 and are available on request. During the trial, compliance to the vitamin supplements appeared to be good (Fig. 1), as vitamin C levels of at least 20 mg/dl were detected in the urines of the majority of subjects who were assigned to receive vitamin supplements; in contrast, the majority of subjects assigned to receive placebos had urine ascorbic acid levels under 5 mg/dl, a level expected in persons not receiving supplements (28).

Of the subjects who completed the trial, at least one polyp was found in the second colonoscopic examination in 29 (41.4%) of the subjects receiving vitamins and in 34 (50.7%) of the subjects receiving placebos (Table 4). Based on 29 polyps observed in 120.2 person-years of follow-up in the vitamin supplementation group, the incidence density rate of polyp occurrence was 0.24, and based on 34 polyps in 112.6 person-years of follow-up in the placebo group, the incidence density rate was 0.30, leading to a rate ratio of 0.80 with 95% confidence limits from 0.50 to 1.27. Although the initial and final colonoscopic examinations reached the cecum for the majority of subjects (Table 5), there were two patients, both assigned to receive placebos, in whom the polyp was located in an area of the colon which had not been reached by the initial colonoscopic examination and might therefore have been present prior to study entry. The percentage of subjects remaining free of polyps estimated from Kaplan-Meier survival curves was similar for those assigned to vitamin supplementation and for those assigned to placebos (Fig. 2), and the log rank test revealed no significant difference between the groups (P > 0.30). In both groups the majority of polyps were “neoplastic,” that is, tubular adenomas, tubular-villous adenomas, villous adenomas, or carcinoma in situ (Table 6). The rate ratio of neoplastic polyp formation associated with vitamin supplementation was 0.85 with 95% confidence limits from 0.46 to 1.57, similar to that for all polyps. In about one-third of polyps, no pathological assessment could be obtained because the polyp was cauterized, the biopsy specimen was lost, or the polyp was visualized but not retrieved.

Table 7 reports estimates of relative risk from Cox regression based on 129 persons who completed the study and had complete information on demographic and dietary variables. Relative risks indicate a small reduction in the risk of all polyps and of neoplastic polyps observed in subjects who received vitamins C and E relative to subjects who received placebos, but none of these relative risks reached statistical significance. Relative risks were adjusted for potential confounders identified from among demographic and dietary factors assessed before randomization in forward stepwise Cox regression analyses; factors were considered as confounders if they reached a 10% level of significance. In the analysis of the occurrence of all polyps, age (P = 0.02), frequency of consumption of prepared meats (P = 0.07), and frequency of consumption of fish (P = 0.03) were included as confounding variables but had little effect on the relative risk of polyp occurrence in the vitamin supplementation and placebo groups (Table 7). Similarly, the analysis of neoplastic polyps was adjusted for age (P = 0.02), whether born in Canada (P = 0.08), and frequency of consumption of fish (P = 0.001) with little effect on the relative risk of neoplastic polyp formation (Table 7). Although the use of vitamin C and E supplements prior to study entry differed markedly between subjects randomly assigned to treatment groups (Table 1), comparison of treatment groups is made on selected characteristics at study entry.
Table 3 Follow-up of those who completed study
Distribution is shown of time from study entry to second colonoscopy, by supplement group.

<table>
<thead>
<tr>
<th>Mo from study entry to second colonoscopy</th>
<th>Vitamins</th>
<th>Placebos</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>0-5.9</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>6.0-11.9</td>
<td>9</td>
<td>12.9</td>
</tr>
<tr>
<td>12.0-17.9</td>
<td>14</td>
<td>20.1</td>
</tr>
<tr>
<td>18.0-23.9</td>
<td>21</td>
<td>30.1</td>
</tr>
<tr>
<td>24.0-29.9</td>
<td>22</td>
<td>31.3</td>
</tr>
<tr>
<td>30.0-35.9</td>
<td>3</td>
<td>4.2</td>
</tr>
<tr>
<td>36.0-41.9</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>42.0-47.9</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>48.0-53.9</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>100</td>
</tr>
</tbody>
</table>

* n, number of subjects.

Table 5 Extent of colonoscopy
Location is shown of colon reached by colonoscopy in initial and second colonoscopic examinations, by supplement group.

<table>
<thead>
<tr>
<th>Location reached</th>
<th>Vitamins</th>
<th>Placebos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial examination</td>
<td>Second examination</td>
<td>Initial examination</td>
</tr>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Cecum</td>
<td>59</td>
<td>84.3</td>
</tr>
<tr>
<td>Ascending</td>
<td>5</td>
<td>7.1</td>
</tr>
<tr>
<td>Transverse</td>
<td>4</td>
<td>5.7</td>
</tr>
<tr>
<td>Descending</td>
<td>2</td>
<td>2.9</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Rectum</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total examinations</td>
<td>70</td>
<td>100</td>
</tr>
</tbody>
</table>

* n, number of subjects.

Fig. 2. Percentage of subjects free of polyps at second colonoscopy.

Table 6 Pathology of polyps
Distribution is shown of pathology in persons with polyps, by supplement group.

<table>
<thead>
<tr>
<th>At least one &quot;neoplastic&quot; polyp</th>
<th>Metaplastic polyp only</th>
<th>No pathology</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamins</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Persons with polyps</td>
<td>19</td>
<td>65.5</td>
<td>21</td>
</tr>
<tr>
<td>Placebo</td>
<td>3</td>
<td>3.4</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>100</td>
<td>34</td>
</tr>
</tbody>
</table>

* Neoplastic polyp: adenoma, tubular adenoma, tubular-villous adenoma, villous adenoma, or carcinoma in situ.

Table 7 Relative risks of polyp recurrence in vitamin supplement group compared to placebo group
Relative risks of polyp recurrence are shown among 129 subjects who completed the study and had complete information on confounding variables. For the analysis of all polyps, confounding variables were age and usual frequency of consumption of prepared meats and fish. For the analysis of neoplastic polyps, confounding variables were age, whether born in Canada, and usual frequency of consumption of fish.

<table>
<thead>
<tr>
<th>Relative risk</th>
<th>Any polyp</th>
<th>Neoplastic polyps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>0.87 (0.52, 1.45)</td>
<td>0.86 (0.51, 1.45)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>0.97 (0.51, 1.84)</td>
<td>0.93 (0.48, 1.83)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, 95% confidence limits.
of relative risk of polyp recurrence associated with vitamin supplementation during the trial to be slightly closer to unity.

Of the 185 eligible subjects, 26 of those assigned to receive vitamins failed to complete the study (4 died, 5 moved and were lost to follow-up, and 17 withdrew); of subjects assigned to placebos, 22 did not complete the study (3 died, 4 were lost to follow-up, and 15 withdrew). Deaths occurred from cardiovascular disease (4 subjects), sclerosis of the liver (1 subject), and pancreatic cancer (1 subject); in addition, there was one death whose cause could not be established. The physicians were able to locate charts for 33 subjects (80% of the 41 subjects not known to have died). Only eight (24%) of these patients had returned to the physician for follow-up examination; a colonscopic examination had been performed for six, and a flexible sigmoidoscopy had been performed for two. Seven of the eight patients examined had been assigned to receive vitamins; two of these were found to have a single adenomatous polyp, one (examined by sigmoidoscopy) had a metastatic polyp, and four had no polyps. No polyps were found in the one individual assigned to receive placebos who could be traced. When these data were combined with the information on subjects who had completed the study, estimates of the relative risks based on polyps observed in 172 of the 185 eligible subjects with complete data on confounding variables were similar to those obtained from the subjects who completed the trial, with a relative risk of 0.86 (95% confidence limits from 0.51 to 1.43) for all polyps and 0.85 (95% confidence limits from 0.45 to 1.61) for neoplastic polyps.

DISCUSSION

Subjects assigned to receive the vitamin supplements had somewhat fewer total polyps and fewer neoplastic polyps assessed at final colonoscopic examination than did subjects who were assigned to receive placebos. However, the study had insufficient power to rule out the possibility that the small difference in the observed polyp recurrence rates was a chance finding, and an investigation of larger sample size would be required to detect a difference of this magnitude. A randomized trial involving about 1000 patients and designed to detect a 30 to 40% reduction in polyp recurrence in subjects taking 1 g of vitamin C and 400 mg of vitamin E is being conducted by investigators at Dartmouth Medical School (29). At the time of the design of the present study, a 3-fold reduction in polyp rates had been postulated (21) because of the marked reduction in fecal mutagen levels which had been observed after supplementation with vitamins C and E (4). The estimates of relative risk made here, together with their 95% confidence limits, indicated that the observed results are not compatible with such a large effect. Failure to find a significant effect of vitamin supplementation on polyp occurrence is compatible with the observations of Bussey and coworkers (30) who randomized patients with polyposis coli to receive daily 3 g of ascorbic acid or a sucrose placebo and assessed the number of rectal polyps quarterly for 18 mo. No consistent and significant difference was observed in the proportion of patients who experienced a reduction in the number of rectal polyps.

In the present investigation, several factors must be considered which may have reduced the magnitude of the effect of vitamin supplementation. First, although the polyps seen on second examination were thought to have occurred in the period between the examinations, it is possible that some might have been missed at the initial colonoscopy. Any such errors in diagnosis would be expected to reduce the magnitude of difference that was seen between the study groups, provided the error rates were the same in those receiving vitamins and placebos. As the colonoscopic examinations were performed by physicians who did not know the nature of the supplement taken by their patients, it seems likely that error rates would not be affected by the supplement received.

Also, the total number of subjects who were examined by a follow-up colonoscopic examination was greater for those in the vitamin supplementation group (80.2%) than for those assigned to the placebo group (76.4%). This would be expected to lead to a greater opportunity for the detection of polyps among patients on vitamins and hence to a reduction in the difference seen between the study groups.

Lack of compliance to the vitamin supplements would also reduce the magnitude of the differences which could be seen in the rates of polyp formation. Although urine vitamin C levels suggested that compliance was satisfactory, it must be recognized that this is an index of compliance in the period shortly before the provision of the urine sample, and it is conceivable that this may not have reflected patients’ levels of compliance over periods between sample collections.

Since it has been postulated that dietary fiber and fat, as well as vitamins C and E, may be associated with the risk of colorectal cancer (31), the possible effects of food containing these components must be considered. Logistic arrangements at the beginning of the study made it necessary to randomize the participants to their supplementation group before they had taken part in the initial dietary inquiry, so prior stratification on dietary habits was not possible. Despite the use of strict random allocation, participants assigned to receive vitamins tended to consume potentially protective high-fiber foods more frequently than those assigned to placebos and to consume potentially harmful high-fat foods less frequently (Table 2). There was also a marked difference between the treatment groups in the reported use of vitamin supplements (Table 1) and, for vitamin C supplementation, such a difference would be expected to have occurred only in 3 of 1000 such randomizations of 200 subjects. Further, it should be noted that the imbalance was not caused by the exclusion of the 15 ineligible subjects who had been randomized as none of them reported using vitamin supplements. Account was taken of the differences between the treatment groups in dietary habits and use of vitamin supplements in the Cox regression analysis, and adjustment for reported consumption was found to have little effect on the degree of association between polyp recurrence and vitamin supplementation. In addition to dietary habits before the study, it is also possible that the polyp rates could be affected by diet during the 2 yr of the study. While any dietary change would have the potential for altering the absolute rates of polyps occurrence, the difference in recurrence rates in the two groups would only be affected if different dietary changes took place in those subjects assigned to receive vitamins and those assigned to placebos. As participants were not aware of the nature of their study assignment, such differential dietary change was not expected but was not evaluated.

Two other factors may influence the ability of this study to detect an effect of vitamin supplementation. (a) The study is of polyp occurrence over a period of less than 2 yr for most subjects. Although about 40% of participants had a polyp diagnosed during the period of observation, it may be that the period of follow-up was too short to allow the effects of vitamin supplementation to be observed. This is especially true since it is postulated that the vitamins would block the formation of mutagen and hence the initiation of tumors, rather than affect
promotion. (b) Although a dose of 400 mg of each vitamin was chosen because of the marked reduction in mutagen levels which had been seen in individuals who consumed this level of vitamins (4), it is possible that higher doses, perhaps higher even than the 3 g used by Bussey et al. (30), would be required to produce more marked effects on the occurrence of polyps.

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