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RAPID COMMUNICATION

Folic acid supplementation inhibits recurrence of colorectal adenomas: A randomized chemoprevention trial

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Abstract

AIM: To determine whether folic acid supplementation will reduce the recurrence of colorectal adenomas, the precursors of colorectal cancer, we performed a double-blind placebo-controlled trial in patients with adenomatous polyps.

METHODS: In the current double-blind, placebo-controlled trial at this VA Medical Center, patients with colorectal adenomas were randomly assigned to receive either a daily 5 mg dose of folic acid or a matched identical placebo for 3 years. All polyps were removed at baseline colonoscopy and each patient had a follow up colonoscopy at 3 years. The primary endpoint was a reduction in the number of recurrent adenomas at 3 years.

RESULTS: Of 137 subjects, who were eligible after confirmation of polyp histology and run-in period to conform compliance, 94 completed the study; 49 in folic acid group and 45 in placebo group. Recurrence of adenomas at 3-year was compared between the two groups. The mean number of recurrent polyps at 3-year was 0.36 (SD, 0.69) for folic acid treated patients compared to 0.82 (SD, 1.17) for placebo treated subjects, resulting in a 3-fold increase in polyp recurrence in the placebo group. Patients below 70 years of age and those with left-sided colonic adenomas or advanced adenomas responded better to folic acid supplementation.

CONCLUSION: High dose folic acid supplementation is associated with a significant reduction in the recurrence of colonic adenomas suggesting that folic acid may be an effective chemopreventive agent for colorectal neoplasia.

Key words: Folic acid; Adenoma; Colorectal cancer

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INTRODUCTION

Colorectal cancer is the second most common cancer in the United States[1]. Although the etiology of this disease is related to genetic susceptibility, dietary factors such as vitamins and micronutrients are thought to influence carcinogenesis[2]. Considerable interest has recently been focused on the water soluble vitamin folic acid. Although the specific mechanism(s) by which folate deficiency enhances colorectal carcinogenesis have not been fully elucidated, it has been hypothesized that aberrations in DNA methylation may contribute to abnormalities in DNA synthesis and genomic instability[3].

Several clinical trials have noted an inverse relationship between dietary folic acid and the development of colorectal cancer[4-7]. A folate deficient diet is thought to increase the risk of colonic neoplasia[8-11], whereas supplementation of this nutrient may be chemopreventive[12-15]. However, the timing of folate supplementation may be particularly important since folate intervention after the establishment of microscopic neoplastic foci in the colorectal mucosa may promote

rather than suppress colorectal carcinogenesis[16].

Accumulating data from murine studies have also supported a role for folic acid in the prevention of colon carcinogenesis. Folate deficient rats demonstrate an increased susceptibility to dimethylhydrazine induced colonic neoplasia as compared to folate replete animals[10]. In a similar model, folate supplementation protected against the development of colonic neoplastic lesions in a dose dependent manner[17]. We have previously demonstrated that folic acid supplementation can reduce the age-related susceptibility of murine colorectal mucosa to a colonic carcinogen[18]. In the azoxymethane-induced colon cancer rat model, supplemental folic acid has also been shown to decrease the formation of aberrant crypt foci, which are considered to be precursors of colorectal adenomas and carcinoma[19,20]. Additionally, *in vitro* studies have further demonstrated that supplemental folic acid greatly inhibits proliferation of colon cancer cells[21,22]. Although these studies suggest a chemopreventive role for folic acid in colorectal cancer, to the best of our knowledge, no conclusive long-term clinical trials have been performed to evaluate the efficacy of folic acid in preventing the recurrence of colorectal adenomas. The current 3-year placebo-controlled clinical trial was, therefore, undertaken to test the hypothesis that folic acid will inhibit the recurrence of colorectal adenomas.

MATERIALS AND METHODS

Objectives

The primary objective of this chemopreventive trial is to determine if supplementation of folic acid for 3 years will inhibit the recurrence of colorectal adenomas. The study was initiated in December, 1998 with a 2-year patient accrual followed by a 3-year treatment with folic acid (5 mg/d) or placebo. The study was completed in June, 2005. The study protocol was approved by the Human Investigation Committee of Wayne State University. All subjects provided written informed consent.

Study subjects and treatment

Eligible subjects were male or female, from the age of 18-80 years. However, the youngest subject enrolled in this clinical trial was 44 years of age. All subjects underwent a colonoscopy for colon polyps noted on screening flexible sigmoidoscopy or as routine surveillance for a history of colon polyps at the Detroit VA Medical Center. Prior to colonoscopy, potential subjects agreed in advance to participate if they were found to have at least one adenoma (tubular, tubulovillous, villous) > 0.5 cm, and had no exclusionary factors including hyperplastic histology of the index polyp. The histology of all polyps was examined by a pathologist blinded to the sample coding.

At study entry, all patients completed a lifestyle questionnaire. Nutritional assessment was evaluated by a registered dietitian using a Block Dietary Data System for California, Berkley. Nutrient intakes were computed according to the composition values from the U.S. Department of Agriculture[23], supplemented with other sources[24].

Eligible participants underwent a complete colonoscopy and had all adenomas removed at colonoscopy (with at least one adenoma > 0.5 cm). They were then randomized in a double-blind trial to receive either a 5 mg folic acid tablet (Stanley Pharmaceutical, Toronto, Canada) or one identical placebo tablet (sucrose/fructose base) daily per oral with breakfast for 3 years. Compliance was monitored by both pill count and telephone contact. Patients were seen or contacted by telephone every 90 d by the study coordinator to obtain pill counts, assess adverse events and to renew a 90 d supply of study medication. Patients were required to take $\geqslant$ 90% of their prescribed study treatment. At the end of 3 years, a repeat colonoscopy was performed, and all identified polyps were removed endoscopically. Serum and RBC folate concentrations were monitored at baseline and every 6 mo. During the course of the trial all adverse events including deaths were reported to the Institutional Review Board (IRB).

Choice of folic acid dose

A 5 mg dose of folic acid was chosen on the basis of the previous observations that diets high in folate protect against the development of colorectal neoplasia. Although lower doses of folic acid (0.4-1 mg) resulted in a reduced relative risk of neoplasia, the risk reduction did not achieve statistical significance[12,14]. Kim *et al* noted a significant increase in colonic mucosal and systemic folate concentrations in patients who were treated for 1 year with 5 mg folic acid[25]. Folate supplementation, even at a dose of 15 mg/d, has been rarely associated with gastrointestinal or CNS adverse effects[26]. In addition, the high prevalence of dietary supplementation of folic acid (up to 1 mg/d) in the general population would have been a confounding variable.

Exclusion criteria

Subjects were excluded if they had any of the following criteria: severe co-morbid conditions, such as severe heart disease, cancer, or other diseases causing organ dysfunction or contraindications for colonoscopy and polypectomy. Subjects with gastrointestinal disorders that affect absorption or metabolism of folic acid, B12 deficiency, and hereditary predisposition to colorectal cancer were excluded. In addition, pregnant or nursing mothers were excluded. Sexually active females agreed to use an effective method of birth control. Patients who drank more than 2 alcoholic drinks daily or who were regularly ingesting or anticipating chronic therapy with vitamin, mineral or any other nutritional supplement, steroids and non-steroidal anti-inflammatory drugs (excluding cardiopreventive aspirin doses), antineoplastic agents or folate were also excluded. Patients were asked if they had a family history of familial colorectal cancer syndrome. This question was asked to exclude obvious known history of FAP or HNPCC.

Placebo run-in

Subjects were supplied with a known number of placebo

Table 1 Baseline characteristics of the subjects

Characteristics	Folate group (n = 80)	Placebo group (n = 97)	P
Age (yr)	60.36 ± 10.34	62.64 ± 9.59	NS
Sex (male, %)	93	92	NS
Race			
African American	48%	50%	NS
Caucasian	51%	49%	
Other	1%	1%	
BMI (kg/m^2)	31.62 ± 4.68	29.84 ± 5.71	NS
Dietary intake			
Total calories	2069.58 ± 902.9	1823.53 ± 741.12	NS
Protein (g/d)	79.57 ± 30.07	74.31 ± 36.33	NS
Fat (g/d)	88.89 ± 52.04	75.2 ± 38.38	NS
Carbohydrate (g/d)	237.29 ± 129.32	206.48 ± 86.37	NS
Fiber (g/d)	7.28 ± 5.84	8.51 ± 7.93	NS
Folate (μg/d)	184.45 ± 231.7	162.64 ± 140.23	NS
Calcium (mg/d)	577.14 ± 433.68	569.69 ± 353.75	NS
Aspirin users (≤ 325 mg/d)	24%	24%	NS
Number with advanced polyp (%)	59	53	NS
Adenomas per patient	2.34 ± 1.46	2.06 ± 1.38	NS
Total polyps per patient including hyperplastic polyps	2.88 ± 1.73	2.87 ± 2.21	NS
Current smokers	16 (35%)	19 (39%)	NS
Serum folic acid (ng/mL)	14.53 ± 19.51	11.35 ± 6.65	NS
RBC folate (ng/mL)	446.57 ± 164.81	477.82 ± 148.76	NS
Serum vit B12 (pg/mL)	472.97 ± 456.10	393.02 ± 190.93	NS
Serum calcium (mg/mL)	9.31 ± 0.48	9.33 ± 0.37	NS

NS: Not significant. Advance adenoma: ≥ 2 adenomas, large (> 1 cm) or adenoma with villous component or high grade dysplasia. Number of patients in placebo and folate group represents those who completed the baseline colonoscopy and satisfied the criteria for enrollment. Ninety-four subjects completed the 3-year study.

tablets to be taken daily during breakfast for 4 wk. Those who had taken ≥ 90% of their tablets were randomized.

Randomization and stratification

Participants were randomized to the folic acid or placebo group using a stratified randomization block scheme. There were 3 stratification factors: number of adenomas (1, 2-5 and ≥ 6), size of the largest adenoma (≤ 1 cm, >1 cm) and history of polyps (no, yes). Block randomization was used in a block size of 8 to ensure that at no time during the study would there be a large imbalance between the intervention and control groups. Subject assignment was made in advance and recorded in sealed envelops, numbered consecutively.

Statistical analysis

The statistical analyses were all performed using the Statistical Package for Social Sciences (SPSS, version 8.0; 1997, Chicago, IL). All t-tests were two sided. Initially, the two treatment groups were compared across demographic information using independent t-tests for continuous data and Chi-Square analyses for categorical information. Treatment efficacy was assessed between intervention groups using independent t-tests across classifications of polyp morphology, lateralization, and age grouping. Logistic regression was utilized to assess the incidence of recurring polyps three years post-removal for individuals taking folic acid versus those taking placebo. A contingency table was computed *via* Chi-Square analysis, and Odds Ratios were computed *via* logistic regression analysis.

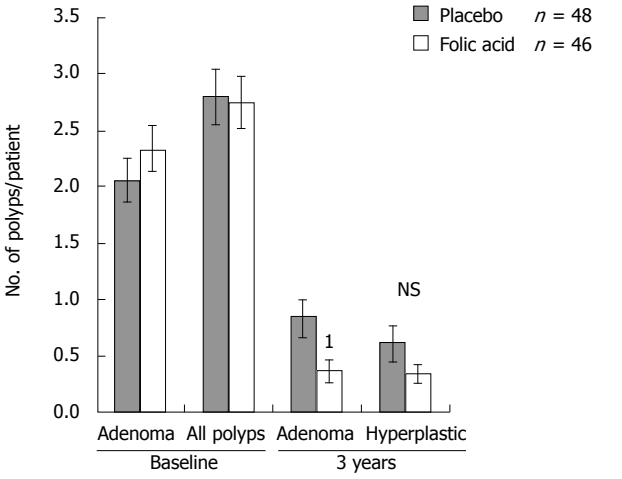

Figure 1 Number of adenomas *versus* treatment. Histograms showing the number of adenomas or all types of polyps in folic acid and placebo-treated groups at baseline and 3 years after treatment. [1]P = 0.02514, compared to the placebo-treated group. Each histogram represents the mean ± SD.

RESULTS

One hundred and thirty seven patients fulfilled the eligibility criteria. Ninety four completed the 3-year follow up colonoscopy and were included in this analysis. There were 43 subjects that dropped out from this study; of which 28 died from various causes unrelated to colon cancer and 15 subjects had geographic relocation precluding further participation. Of those who did not complete the study, there were no statistically significant differences (age, BMI, sex, NSAID/multivitamin, baseline adenoma, RBC folate, deaths) between those assigned to receive folic acid or placebo. Forty nine of the subjects who completed the 3-year follow-up received supplemental folic acid and 45 were given placebo tablets. At post-randomization, there was no statistical difference in the serum levels of folic acid between the two groups (Table 1). Demographic data and other baseline parameters were also comparable between these two groups (Table 1). At the 3-year follow-up colonoscopy, patients in the folic acid group showed a significantly lower number of adenomas per patient (0.36 ± 0.69) with a 64% lower risk ratio, compared to the placebo group (0.82 ± 1.17; odds ratio, 2.77; t = -2.26, P = 0.02514, 95% CI, 0.06-0.84; Chi Square = 11.2, P = 0.00142; Figure 1). The recurrence of adenoma at the 3-year follow-up was twice as high in the placebo group, compared to the folic acid group. There was no significant difference in the recurrence of hyperplastic polyps between the groups (folic acid: 0.44 ± 0.89, placebo: 0.51 ± 0.94; P = 0.74; 95% CI, 0.31-0.43).

Folic acid supplementation caused a significant reduction (P = 0.02335) in the recurrence of adenomas in patients with advanced adenoma [large (> 1 cm)

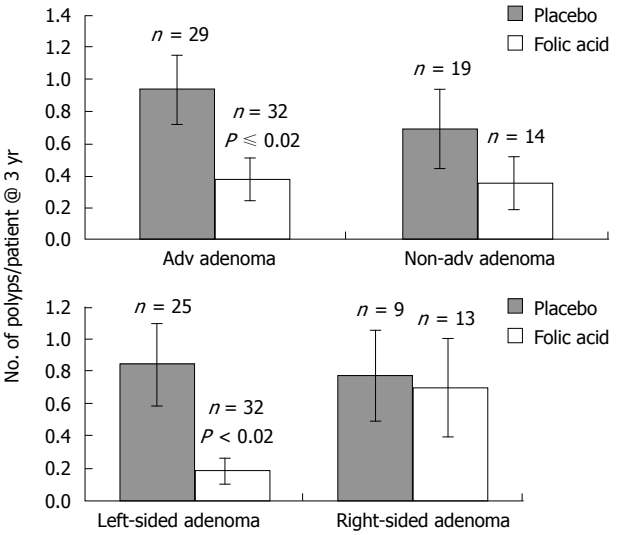

Figure 2 Polyp characteristics and response to treatment. Recurrence of advanced [large (> 1 cm) and polyps with villous component] or non-advanced adenomas (upper panel) as well as right or left-sided adenomas (lower panel) following 3 years of treatment with a high dose of folic acid. The numbers of subjects as well as the levels of significance between the two groups are shown.

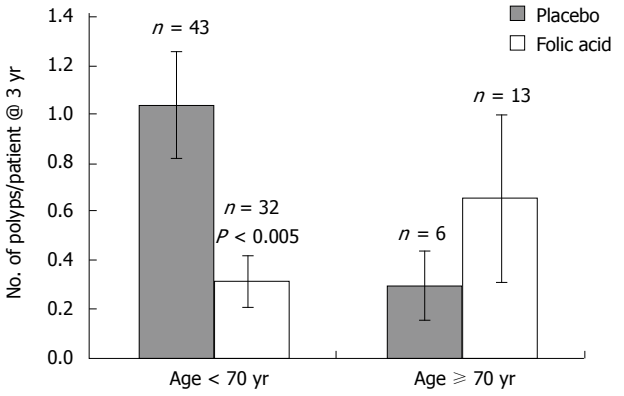

Figure 3 The effect of age on the response to treatment. Recurrence of adenomas in response to 3 years of folic acid treatment in patients over or below 70 years of age in shown. The number of subjects in each group as well as the levels of significance is shown in the figure.

adenoma or adenoma with villous component or high grade dysplasia], compared to the placebo-treated controls (Figure 2, upper panel). Those with non-advanced adenomas also showed a reduction in the recurrence of adenomas with folic acid, compared to placebo controls, but this was not statistically significant (Figure 2, upper panel). On further stratifications, it was noted that subjects with left-sided polyps had a significantly lower ($P = 0.01964$) recurrence of adenomas than those with right-sided polyps in response to folic acid supplementation, when compared with the corresponding placebo-treated controls (Figure 2, lower panel).

Since colorectal cancer is an age-related disease, the data were analyzed to determine the age-related differences in responsiveness to folic acid. We observed that the younger subjects responded better than older subjects in that the recurrence of adenomas was significantly lower ($P = 0.00496$) in younger patients, compared to older patients (Figure 3). This response was maintained until 70 years of age (Figure 3). However, patients older than 70 years of age failed to respond to folic acid supplementation demonstrating a higher recurrence rate of polyps as compared to the placebo group. This difference was not statistically significant (Figure 3). There were more deaths in the folic acid group, compared to the placebo-treated group, but this difference was not statistically significant (19 in folic acid *vs* 9 in placebo, $P > 0.1$).

DISCUSSION

Despite recent advances in medicine, the mortality from colorectal cancer, a leading cause of death in the USA and other Western countries, still remains unacceptably high. Therefore, the search for strategies to prevent the development and progression of colorectal cancer has greatly intensified. Chemoprevention offers a viable option to block neoplastic inception or delay disease progression. Since colorectal cancer is an age-related disease, typically diagnosed after the age of 50, any delay in the onset and subsequent progression of this disease through the use of dietary agents is likely to have significant health benefits. Folic acid has recently emerged as a major contender in the repertoire of promising colorectal cancer prevention agents. A number of animal, as well as a few case controlled human studies, strongly support folic acid as a potentially efficacious chemopreventive agent with a negligible toxicity profile[3]. However, there have been no systematic conclusive studies to examine the effect of supplemental folic acid on recurrence of adenomas in the colon.

Our data, for the first time, show that the daily consumption of a high dose of folic acid over a period of 3 years prevents the recurrence of colorectal adenomas. This reduction could not be attributed to differences in diet or lifestyle. The patients completed a detailed lifestyle questionnaire and nutritional assessment with both study groups demonstrating statistically similar caloric, fiber, fat and protein intake as well as similar baseline BMI, folate, B12 and calcium status. Additionally, the groups were similar with regard to aspirin use and the number and type of adenoma at baseline. Most patients were male which is consistent with the Veterans Affairs based population. Interestingly, patients who had large adenomas or adenomas with a villous component (referred to as advanced adenomas) responded better to high dose folate supplementation, as evidenced by the significantly reduced number of recurrent adenomatous polyps. A similar phenomenon was also observed among patients with left-sided adenomas and those who were less than 70 years of age. Although the reasons for this are not fully understood, it is plausible that the increased responsiveness of these subjects could be a result of greater tissue accumulation of folic acid due to a better active folate transport system. The basis for this inference comes from the observations by Mennan *et al* which suggest that mucosal folate levels may be a determinant factor

in the development of adenomas[27]. They demonstrated that the levels of folate in adenoma, carcinoma as well as normal appearing adjacent mucosa are lower than the corresponding polyp-free controls[27]. Future studies analyzing folate levels in adjacent tissue near recurrent adenomas need to be completed.

Although several clinical trials have suggested a role for folic acid in the prevention of colorectal adenomas, there are no prospective controlled trials addressing this issue at the dose of 5 mg[5-8]. It has also been demonstrated that supplementation of a high dose of folic acid in animals with colonic neoplasia may accelerate the progression of carcinogenesis[16]. A more recent human study showed that supplemental folic acid may not reduce the incidence of colorectal adenomas and in some cases may actually increase the risk[28]. Although the reasons for these controversial issues are not fully understood, one possibility could be attributed to the dual modulatory effect of folic acid on carcinogenesis. It has been demonstrated that the timing and the dose of folate intervention has a promoting effect on the progression of established neoplasms, while it could have a chemopreventive effect if given in premalignant conditions. Data from our clinical trial clearly supports a chemopreventive role of folic acid since supplementation of this vitamin for 3 years inhibits the recurrence of colonic adenomas. More importantly, none of the patients in the folate treatment group were found to have histologically aggressive adenomas or carcinoma at final endoscopy.

The mechanisms by which folic acid exerts its chemopreventive role in colorectal carcinogenesis are becoming increasingly understood. Since folic acid plays a key role in DNA methylation and cellular homeostasis, folate deficiency may result in a variety of cellular consequences including misincorporation of uracil for thymidine during DNA synthesis resulting in an increased spontaneous mutation as well as chromosomal abnormalities and errors in DNA synthesis[29-33]. The restoration of DNA methylation status in patients with colorectal neoplasms treated with supraphysiological doses of folic acid lends further support to the hypothesis. In a recent study, we examined the changes in mutational status of APC, DCC and p53 genes in macroscopically normal appearing rectal mucosa at baseline and after 1 year of treatment with either folic acid or placebo[34]. We have observed that folate supplementation prevented the loss of heterozygosis (LOH) of the DCC gene in 5 out of 5 patients who demonstrated baseline heterozygosis, whereas 2 out of 4 placebo treated patients with baseline heterozygosis demonstrated complete allelic loss. Mucosal protein levels of DCC were also reduced in 70% of placebo treated patients compared to only 10% of folate treated patients[34]. Cell culture studies have further demonstrated that supplemental folic acid and its metabolite 5-methyltetrahydrofolate (5-MTF) inhibit EGF-receptor (EGFR) promoter activity in colon cancer HCT-116 cells by enhancing methylation[35]. Since EGFR is known to play a critical role in the development and progression of a wide variety of epithelial cancers, including colorectal cancer[36,37], the inhibition of basal as well as serum-stimulated EGFR promoter activity by folic acid and 5-MTF suggests that these changes may partly contribute to specific inhibition of growth-related processes in colorectal neoplasia. Supplemental folic acid may also attenuate the downstream events of EGFR signal transduction pathways that are critically involved in modulating growth-related processes. We have observed that in polypectomized patients, supplemental folic acid for 1 year leads to a decreased nuclear translocation of β-catenin[38], which interacts with the T-cell factor 4 (TCF-4) transcription factor to induce expression of specific target genes, including cyclin D1, VEGF and c-myc, which promote cell growth and proliferation[39-42].

The dose of folic acid supplementation may be important when considering the differing effects of supplementation. This has been more explored in the cardiovascular literature in attempting to modulate homocysteine levels where the VISP study showed greater efficacy at higher doses in lowering homocysteine levels[43]. A cogent example of this was the recently published large scale study interventional study of over 1000 men and women who were randomized to receive either 1mg folic acid or placebo. The endpoints were similar to our study, but the 3 year follow up data were very different in that no effect was seen for the dose used[28]. Of interest, there was no effect of gender in that study which may have important implications for our study in terms of applicability to the general population. The timing of supplementation may also be important[44].

In summary, daily consumption of a high dose of folic acid over 3 years prevents the recurrence of colorectal adenomas. Patients below 70 years of age and those with left-sided colonic adenomas or advanced adenomas responded better to folic acid supplementation. We conclude that folic acid is an effective chemopreventive agent for colorectal adenomas, and more specifically for that category of adenomas which are believed to possess the highest risk of cancer progression.

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COMMENTS

Background

Colorectal cancer is one of the major causes of cancer related deaths. In the US and the other developed countries, 50% of the subjects diagnosed with colon cancer die. Therefore, there is a need to prevent the development and progression of colon cancer using chemopreventive agents. Water soluble vitamins, such as folic acid, have shown to have chemopreventive potential for colon cancer. Aim of this investigation was to determine whether folic acid supplementation will reduce the recurrence of colorectal polyps, the precursors of colorectal cancer, we performed a double-blind placebo-controlled trial in patients with polyps.

Research frontiers

Several clinical trials have noted an inverse relationship between dietary folic acid and the development of colorectal cancer. A folate deficient diet is thought to increase the risk of colonic neoplasia, whereas supplementation of this nutrient may be chemopreventive. However, the timing of folate supplementation may be particularly important since folate intervention, after the establishment of microscopic neoplastic foci in the colorectal mucosa, may promote rather than suppress colorectal carcinogenesis. A similar approach using aspirin and similar non-steroidal anti-inflammatory agents have shown promising activity in prevention of colon cancer after resection of colon polyps.

Innovations and breakthroughs

This is a large randomized, single institution, double-blind placebo controlled trial demonstrating the efficacy of folic acid in secondary chemoprevention of colorectal cancer. This is the only study examining high dose supplementation over a period of three years further establishing safety and efficacy of large dose of folic acid. It should also be noted that the present study is the only study of its kind specifically targeting the US veteran population.

Applications

Daily consumption of a high dose of folic acid over 3 years prevents the recurrence of colorectal adenomas. Particularly, patients below 70 years of age and those with left-sided colonic adenomas or advanced adenomas responded better to folic acid supplementation. We conclude that folic acid is an effective chemopreventive agent for colorectal adenomas, and more specifically for that category of adenomas which are believed to possess the highest risk of cancer progression.

Peer review

This is an important study which, for the first time, demonstrates that daily consumption of a high dose folic acid over a prolonged period of time leads to a significant reduction in the recurrence of colonic adenomas. The results suggest that folic acid may be an effective chemopreventive agent for colorectal neoplasia.

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