

Chemoprevention of Cervical Cancer with Folic Acid: A Phase III Southwest Oncology Group Intergroup Study^{1,2}

Joel M. Childers, Joseph Chu, Lynda F. Voigt, Polly Feigl, Hisham K. Tamimi, Ernest W. Franklin, David S. Alberts, and Frank L. Meyskens, Jr.

University of Arizona Cancer Center, Tucson, Arizona [J. M. C., D. S. A.]; Fred Hutchinson Cancer Research Center, Seattle, Washington [J. C., L. F. V.]; Southwest Oncology Group Statistical Center, Seattle, Washington [P. F.]; University of Washington Medical Center, Seattle, Washington [H. K. T.]; Atlanta Regional CCOP, Atlanta, Georgia [E. W. F.]; and University of California (Irvine), Irvine, California [F. L. M.]

Abstract

Several epidemiological reports and experimental investigations have suggested a preventive role for folic acid in the etiology of cervical cancer. The effect of p.o. folic acid supplementation on the natural history of cervical intraepithelial neoplasia (CIN) was evaluated in a multiinstitutional prospective, randomized, double-blind, placebo-controlled trial. Three hundred thirty-one women with biopsy-proven koilocytic atypia, mild CIN, or moderate CIN were randomized to receive oral folic acid (5 mg) or a similar-appearing placebo daily for 6 months following a 1-month run-in placebo period. Colposcopy, Papanicolaou smear, and serum vitamin levels (folate, retinol, α -tocopherol, β -carotene, and retinyl palmitate) were monitored every 3 months. Demographic, medical, dietary, and sexual history data were obtained from personal interviews. The primary end point of the study was improvement in both Papanicolaou smear and colposcopic picture after 3 and 6 months of treatment as compared to the start of treatment. After 6 months of treatment there was no significant difference between the two study groups in the percentage of patients improved. Median serum folate levels in the treatment arm at 3 and 6 months (29.0 and 20.0 $\mu\text{g}/\text{dl}$) were significantly higher than those in the placebo arm (7.8 and 7.1 $\mu\text{g}/\text{dl}$, respectively). Mean serum levels of retinol, retinyl palmitate, α -tocopherol, and β -carotene did not differ significantly between the two treatment arms. Our data support the conclusion that supplementation with folic acid (5 mg/day) does not enhance the regression of early epithelial abnormalities of the cervix. Whether the correction of folate deficiency prior to the initiation of the CIN process would have any influence on the

outcome is not answered in the current study and will require a different study design.

Introduction

Primary prevention of cancer is an ultimate goal of oncology. Despite the improvements in diagnosis and treatment that have been developed over the last several decades, many thousands of cancer deaths continue to occur annually in the United States. If the sequence of events leading to malignancy could be interrupted by the administration of a chemical agent, not only would many lives be saved, but the heavy demands placed on the health care system would be ameliorated greatly. For this reason, chemoprevention of cancer has been given considerable research attention.

The cervix is an ideal model for the study of chemoprevention in humans (1). The evidence is strong that normal cervical epithelium proceeds through a precancerous stage CIN³ prior to the development of invasive cancer (2, 3). In addition, the anatomical location of the cervix allows magnified visualization via colposcopy, and cytological and histological samples are easily obtained in the office setting.

Epidemiological studies indicate that a deficiency in vitamin nutrition, including folate, may play a role in the etiology of cervical cancer (4-11). Several reports have suggested a protective role for folate in the etiology of cervical neoplasms (10-13). Whitehead *et al.* (12) demonstrated that daily supplementation with 10 mg of folic acid taken p.o. reversed the megaloblastic features observed on Pap smears taken from users of oral contraceptives. Since the cytological changes were not associated with evidence of systemic folate deficiency, these investigators postulated the existence of localized folate deficiency in the cervix as a result of oral contraceptive use. Subsequently, Butterworth *et al.* (10) investigated the possibility of a relationship between folate and oral contraceptives and CIN. Their initial study of oral contraceptive users demonstrated a statistically significant improvement of CIN-I and CIN-II in subjects treated with 10 mg of folic acid p.o. for 3 months. This study also reported a statistically significant lower mean RBC folate concentration in oral contraceptive users compared to nonusers. Even lower RBC folate concentration levels were seen in oral contraceptive users with CIN compared to oral contraceptive users without CIN (12). Additionally, a recent study suggests that inadequate reserves of folate enhanced the effects of other known risk factors such as cigarette smoking, parity, and HPV infection (13).

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³ The abbreviations used are: CIN, cervical intraepithelial neoplasia; PAP, Papanicolaou; HPV, human papillomavirus; OC, oral contraceptive; CIN-I, mild CIN; CIN-II, moderate CIN; KA, koilocytic atypia; FHCRC, Fred Hutchinson Cancer Research Center, SWOG, Southwest Oncology Group.

The purpose of the current investigation was to conduct a randomized double-blind clinical trial to evaluate the hypothesis that prolonged high-dose p.o. folic acid supplementation will improve the regression rate of early stage CIN.

Materials and Methods

Women were recruited primarily from the University of Washington, Atlanta Regional CCOP, and the University of Arizona. Subjects were eligible to participate if two criteria were met. First, colposcopically directed biopsies of the cervix must have confirmed the presence of KA, CIN-I, or CIN-II. Second, colposcopic visualization of the entire squamocolumnar junction as well as a normal endocervical curettage were mandatory. Exclusion criteria included pregnancy, history of diethylstilbestrol exposure *in utero*, or use of any anticonvulsives and/or antimalarial medications, as these compounds can affect folate metabolism.

Informed consent according to individual institutional guidelines was obtained from all subjects prior to a 1-month placebo run-in period. Patients from the Seattle area were registered at the FHCRC before the run-in period. Patients of the Southwest Oncology Group were registered at the SWOG statistical center after successfully completing the run in.

Once the eligibility criteria were satisfied and run in was successfully completed, patients were stratified (KA and/or CIN-I *versus* CIN-II) and randomized. (Institution of origin was also a stratification variable for the non-SWOG patients.) The participants were given a 3-month supply of either 5 mg of folic acid (pteroylglutamic acid) or a similar-appearing inert placebo, both supplied by the National Cancer Institute. One treatment tablet was taken p.o. every day.

The schedule of four patient visits was as follows. At the initial visit, informed consent was obtained, and the patient was given a 1-month packet of placebo pills. The randomization visit was scheduled to occur 1 month later. At that time a Pap smear, colposcopy, and blood samples for serum folate and serum B12 were obtained. After 3 months of treatment with folic acid or placebo, Pap smear, colposcopy, and blood sample for serum folate were obtained again. After this visit, subjects were contacted by a female interviewer from the FHCRC for a 30-min structured, personal interview, which included demographic factor evaluation and medical, dietary, and personal histories. The dietary instrument was developed at the Cancer Prevention and Research Unit at the Fred Hutchinson Cancer Research Center and has been validated (14). The Spearman rank correlation coefficient between dietary folate at interview and serum folate at randomization was 0.11 ($n = 294$; 2-sided $P = 0.059$). After 6 months of treatment, Pap smear, serum folate, and dietary history were obtained, and a colposcopy was performed.

Blood specimens were collected at randomization and at 3- and 6-month treatment visits. If at any time during the study the colposcopic appearance or the Pap smear indicated progression of disease, a colposcopically directed biopsy was performed. The subject was taken off the study if the biopsy confirmed progression of disease.

The primary endpoints of the study were regression of KA, CIN-I, and CIN-II as measured by improvement of Pap smear classification and colposcopic picture. Training sessions to assure uniformity in recording of colposcopy results

were held. The end points were assessed after 3 and 6 months of treatment. The colposcopic pictures and all biopsy and Pap smear reports were sent for blinded review by one of the authors (J.C.)

Serum was frozen at -80°C for testing of retinol, β -carotene, and vitamins C and E at a central lab at the FHCRC. Serum folate was measured at every clinic visit after the run-in period. This was done to compare the treatment and placebo group as well as to measure dosing compliance in the treatment group and to assess for occult folate consumption in the placebo group.

A two-sided P -value was calculated using the χ^2 statistic to compare the proportion of patients improved in the two arms of the trial. The P -value was calculated using the Fisher exact test when there were <5 individuals in a single cell. Logistic regression was used to compute the χ^2 statistic associated with improvement when controlling for potentially confounding variables (15).

Results

Three-hundred thirty-one subjects were randomly assigned: 168 to the folic acid trial arm and 163 to the placebo study arm. The study was activated in December 1988, and all patient follow-up visits were completed in July 1991. Serum vitamin assays were completed in April 1992. More than one-half of those enrolled in the trial were from the Seattle area; approximately 15 and 20% were from the Arizona and Atlanta areas, respectively. A comparison of demographic characteristics shows the treatment and placebo arms of the group to be similar (Table 1). More than one-half of the study subjects were 24 years of age or younger at the time of the study and had annual household incomes of $<\$15,000$. Approximately 90% of the participants were Caucasian. In addition, 35% had a high school education or less. More than one-half of the subjects had five or more lifetime sexual partners and had their first sexual intercourse at <20 years of age (more than 25% had first intercourse at age 15 years or younger) (Table 2). Twenty-five % reported a history of condyloma and 10% a history of genital herpes. More than 90% of the subjects had used oral contraceptives.

Overall compliance with the study protocol was adequate as indicated by the percentage of patients who returned for their follow-up visits (Fig 1). Of those randomized, 91.7% of the folate and 93.3% of the placebo-treated women completed the 3-month treatment visit. Participants (138 or 82.1%) on the treatment arm and 124 (76.1%) participants on the placebo arm completed the 6-month visit. Of the women who completed the 3-month examination, 151 women on the treatment arm and 148 on the placebo arm completed the personal interview. Serum folate was available for 322 of 331 (97.3%) of the participants at randomization, 296 of 306 (96.7%) of the participants who completed the 3-month visit, and 163 of 262 (62.2%) of the participants who completed the 6-month visit. Three of those who had 6-month serum did not have 3-month serum folate available.

Compliance with treatment was excellent, as determined by serum measurements of folic acid. The median folate level in the treatment group ($n = 153$) was 29.0 $\mu\text{g}/\text{dl}$, compared with 7.8 $\mu\text{g}/\text{dl}$ in the placebo group ($n = 143$) at 3 months. At 6 months this trend persisted, showing a median folate level in the treatment group ($n = 85$) of 20.0 $\mu\text{g}/\text{dl}$ compared to 7.1 $\mu\text{g}/\text{dl}$ in the placebo group ($n = 78$). After 3 months of treatment, the serum folate level more

Table 1 Demographic characteristics for patients

	Placebo <i>n</i> = 148		Folic acid <i>n</i> = 151		2-sided <i>P</i> value
	No.	%	No.	%	
Age					
15–19	17	(11.5)	30	(19.9)	.41
20–24	53	(35.8)	51	(33.8)	
25–29	39	(26.4)	33	(21.9)	
30–34	19	(12.8)	23	(15.2)	
35–39	8	(5.4)	7	(4.6)	
40–44	8	(5.4)	4	(2.6)	
45–59	4	(2.7)	3	(2.0)	
Marital status					
Single	37	(25.0)	40	(26.5)	.81
Married	34	(23.0)	33	(21.9)	
Divorced/separated	8	(5.4)	11	(7.3)	
Widowed	2	(1.4)	1	(0.7)	
Living as married	31	(20.9)	24	(15.9)	
Regular partner	36	(24.3)	42	(27.8)	
Race					
White	132	(89.2)	136	(90.1)	.85
Black	6	(4.1)	7	(4.6)	
Other	10	(6.8)	8	(5.3)	
Education					
Less than high school	19	(12.8)	20	(13.2)	.97
High school	36	(24.3)	35	(23.2)	
Post high school	93	(62.8)	96	(63.6)	
Income					
Less than \$15,000	75	(50.7)	85	(56.7)	.67
\$15,000–\$30,000	37	(25.0)	35	(23.3)	
\$30,000–\$45,000	19	(12.8)	18	(12.0)	
More than \$45,000	17	(11.5)	12	(7.9)	
Refused			1		
Smoking history					
Never	72	(48.6)	74	(49.0)	.95
Ever	76	(51.4)	77	(51.0)	

Table 2 Sexual histories

	Placebo <i>n</i> = 148		Folic acid <i>n</i> = 151		2-sided <i>P</i> value
	No.	%	No.	%	
History of condyloma					
Never	105	(71.4)	117	(78.0)	.19
Ever	42	(28.6)	33	(22.0)	
Unknown	1		1		
History of gonorrhea					
Never	141	(95.3)	142	(94.0)	.64
Ever	7	(4.7)	9	(6.0)	
History of genital herpes					
Never	129	(87.2)	133	(91.1)	.28
Ever	19	(12.8)	13	(8.9)	
Unknown	0		5		
No. of sexual partners (lifetime)					
None	1	(0.7)	0		.48
1	9	(6.1)	15	(9.9)	
2–4	52	(35.1)	59	(39.1)	
5–14	63	(42.6)	58	(38.4)	
15+	23	(15.5)	19	(12.6)	
No. sexual partners in reference yr					
None	7	(4.7)	5	(3.3)	.93
1	93	(62.8)	101	(67.3)	
2–4	41	(27.7)	37	(24.7)	
5–14	6	(4.1)	6	(4.0)	
15+	1	(0.7)	1	(0.7)	
Unknown	0		1 ^a		
Age at first sexual intercourse^b					
15 or younger	39	(26.5)	42	(27.8)	.29
16–19	81	(55.1)	91	(60.3)	
20 or older	27	(18.4)	18	(11.9)	
OC use					
Never used OC	12	(8.1)	13	(8.6)	.91
Former OC user	51	(34.5)	55	(36.4)	
Current OC user (using at Dx)	85	(57.4)	83	(55.0)	

^a Lifetime partners was 5–14.

^b One person using placebo reported no sexual partners.

than doubled for 74% (112 of 152) of the patients in the treatment group relative to the value at randomization. For the placebo group, the comparable percentage at 3 months was 6% (8 of 139). After 6 months of treatment, the percentages of patients for whom serum folate doubled were 72% (61 of 85) and 8% (6 of 75) for folic acid and placebo groups, respectively.

Mean serum levels of the other vitamins and nutrients (retinol, α -tocopherol, β -carotene, and retinyl palmitate) were not statistically different between the placebo and treatment groups at the randomization, 3-month, or 6-month treatment visits (results not shown). In addition, mean levels of vitamin A, retinol, β -carotene, vitamin C, or dietary folate based on self-reported food frequencies did not differ between the two treatment arms.

Biopsy results obtained before treatment were very similar in the placebo and treatment groups among women who completed the 3-month examination (Table 3). Cytology was normal for over one-half of the participants in each arm of the trial at the time of the randomization visit (Table 4), reflecting the large number of subjects with low-grade lesions. Two participants in the placebo group and two in the treatment group were dropped from the study between 3- and 6-month visits because of dysplasia progression. An additional person in the treatment group was dropped from

the study during the same period because she underwent cervical conization.

For the purposes of this study, improvement was defined as improvement in both the Pap smear and the colposcopic picture. Improvement was assessed by comparing both the 3- and 6-month visits with colposcopy and cytology at the time of randomization. Three months after randomization, 8.1% of those in the folate group compared to 2.8% of those in the placebo group had improved (2-sided *P*-value; Fisher's exact test = 0.08) (Table 5). Between the 3- and 6-month visits, 28 placebo and 16 folic acid patients left the study. Improvement did not differ between the remaining patients in the 2 groups at the 6-month visit (Table 5).

All four of those in the placebo group who improved in both cytology and colposcopy at 3 months were using OCs at diagnosis, whereas 7 of 12 in the treatment group who improved in both were using OCs at diagnosis. Adjustment for OC use at diagnosis resulted in a 2-sided exact *P* value of .07 for improvement in both cytology and colposcopy (compared to *P* = 0.08 without adjustment). Improvement in both cytology and colposcopy at 6 months did not differ according to OC use at diagnosis. Controlling for serum vitamin levels, dietary vitamin levels, study site, lifestyle

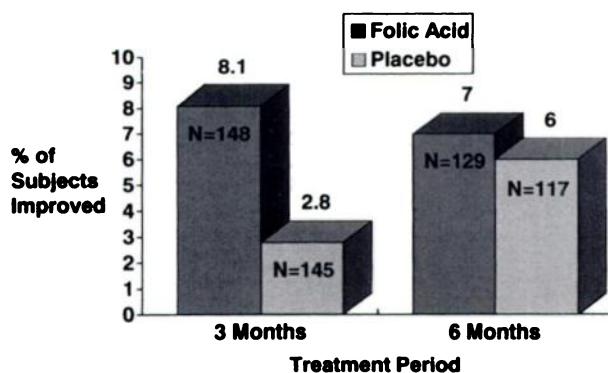


Fig. 1. The percentage of patients whose colposcopic and cytologic evaluations had improved compared to the randomization visit. In the folic acid arm, 154 subjects completed the three-month visit, of whom 138 completed the six-month visit. In the placebo arm, 152 subjects completed the three-month visit, of whom 124 completed the six-month visit. The subjects who were missing cytology or colposcopy at the visits are excluded from this figure (see Table 5).

Table 3 Pretreatment biopsy results: randomized patients^a

	Treatment group	
	Placebo	Folic acid
Koilocytic atypia	1	2
CIN-I	136	132
	15	20
CIN-II		
Total	152	154

^a Includes only patients who completed the 3-month exam.

Table 4 Cytology results at randomization visit^a

	Treatment status			
	Placebo		Folic acid	
	No.	%	No.	%
Normal	81	53.3	82	53.2
Koilocytic Atypia	52	34.2	53	34.4
CIN-I	17	11.2	17	11.0
Missing	2	1.3	2	1.3
Total	152		154	

^a Includes only patients who completed the 3-month visit.

factors, or demographic characteristics did not change the results. There was an insufficient number of subjects at the low end of the serum folate range to determine whether their cervical dysplasia responded differently when contrasted to participants at the high end of folate levels. Since no improvement was possible in both cytology and colposcopy if cytology was normal at the randomization visit, we repeated the analyses excluding these patients. Excluding those with normal cytology at randomization did not change the interpretation of the study results.

Discussion

This multiinstitutional prospective study was designed to test the hypothesis that prolonged high-dose p.o. folic acid

Table 5 Cytology and colposcopy results at 3- and 6-month visits compared to randomization visit

	Placebo		Folic acid		P-value ^a
	No.	%	No.	%	
Change at 3-month visit					
Cyt ^b or Col or both worse	20	(13.8)	29	(19.6)	
Cyt and Col both unchanged	82	(56.6)	68	(45.9)	
Cyt or Col improved, other unchanged	39	(26.9)	39	(26.4)	
Cyt and Col both improved	4	(2.8)	12	(8.1)	0.08
	145	(100.0)	148	(100.0)	
Missing Cyt or Col	7		6		
Change at 6-month visit					
Cyt or Col or both worse	20	(17.1)	28	(21.7)	
Cyt and Col both unchanged	62	(53.0)	59	(45.7)	
Cyt or Col improved, other unchanged	28	(23.9)	33	(25.6)	
Cyt and Col both improved	7	(6.0)	9	(7.0)	0.75
	117	(100.0)	129	(100.0)	
Missing Cyt or Col	7		9		
No visit	28		16		

^a P-values from Fisher's exact test (2-sided) for equality of proportions of patients improving on both Cyt and Col, placebo vs. folic acid

^b Cyt, cytology; col, colposcopy.

supplementation improved the regression rate of CIN. Folic acid (5 mg) given p.o. over a 6-month period appears to have no significant effect on the regression of CIN. This study confirms the results of the single institution trial reported by Butterworth *et al.* (16). There are several shortcomings in the current study: (a) the use of cytology and colposcopic appearance rather than biopsy results as the end points. While expert colposcopists can predict biopsy results in a high percentage of instances, a definitive trial should ideally include biopsy results (17). Without end point biopsy results, epithelial abnormalities could have been missed; and (b) the lack of HPV typing. Conceivably, p.o. folic acid supplementation could have a positive chemopreventive effect on CIN, dependent on HPV type. The false-negative rate of cytology is notoriously high. Indeed, many of our subjects had normal cytologies (despite abnormal colposcopies) before starting the trial.

If vitamin supplementation is unable to exert an effect after the process of malignant transformation is initiated, is it possible that initiation of carcinogenesis can be prevented by avoiding vitamin deficiency? Eto *et al.* (18), in their review of the literature, suggest that folate deficiency is not carcinogenic by itself but that deficient cells are more susceptible to the effects of known carcinogens. Using RBC folate concentration as an indicator of reserves of folate, Butterworth *et al.* (12) has provided evidence that inadequate folate reserves enhanced the effect of cigarette smoking, parity, and HPV-16 infection on CIN risk. The interaction between HPV-16 and inadequate folate reserves was significant. In the current trial we were unable to examine for HPV subtypes, but it is unlikely that the results would be informative regarding therapeutic outcome since the overall results were negative.

This pretreatment/protection relationship between vitamins and carcinogens is supported in a report by Khan *et al.* (19). These investigators demonstrated a direct biochemical basis for a role of retinoic acid in the chemoprevention of HPV-induced cancers. Using human keratinocytes in

culture, they not only demonstrated that retinoic acid reduced the proliferative effect of HPV-16 transformation, but more importantly, discovered that pretreatment of these cells with physiological concentrations of retinoic acid almost completely (95%) suppressed HPV-16-mediated transformation (immortalization) of these cells.

Other chemoprevention agents may be effective after CIN has appeared. A recent Phase III study showed that topically applied all-*trans*-retinoic acid enhanced regression of CIN-II in treated compared to the placebo patients (20). However, the all-*trans*-retinoic acid treatment was ineffective in reversing CIN-III.

Our current study indicates that oral supplementation of folic acid does not produce a chemopreventive effect on cervical intraepithelial neoplasia. The trial has utilized subjects who already have a potentially precancerous condition and does not address whether folate deficiency corrected prior to initiation of the malignant process would be effective. The design of future trials will need to be different from that of the current study to address this question.

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BLOOD CANCER DISCOVERY

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