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Use of folic acid-containing supplements after a diagnosis of colorectal cancer in the Colon Cancer Family Registry

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Abstract

Background—Supplement use among cancer patients is high, and folic acid intake in particular may adversely affect the progression of colorectal cancer. Few studies have evaluated the use of folic acid-containing supplements (FAS) and its predictors in colorectal cancer patients.

Objective—To assess the use of FAS, change in use, and its predictors after colorectal cancer diagnosis.

Design—We used logistic regression models to investigate predictors of FAS use and its initiation after colorectal cancer diagnosis in 1,092 patients recruited through the Colon Cancer Family Registry (C-CFR).

Results—The prevalence of FAS use was 35.4% before and 55.1% after colorectal cancer diagnosis (p=0.004). Women were more likely than men to use FAS after diagnosis (OR 1.47, 95% CI 1.14-1.89), as were those consuming more fruit (p_{trend}<0.0001) or vegetables (p_{trend}=0.001), and US residents (p<0.0001). Less likely to use FAS after diagnosis were non-white patients (OR 0.66, 95% CI 0.45-0.97), current smokers (OR 0.67, 95% CI 0.46-0.96), and those with higher meat intake (p_{trend}=0.03). Predictors of FAS initiation after diagnosis were generally similar to those of FAS use after diagnosis, though associations with race and vegetable intake were weaker and those with exercise stronger.

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Conclusions—Our analysis showed substantial increases in the use of folic acid-containing supplements after diagnosis with colorectal cancer, with use or initiation more likely among women, Caucasians, U.S. residents, and those with a health-promoting lifestyle.

Impact—Studies of cancer prognosis that rely on pre-diagnostic exposure information may result in substantial misclassification.

Introduction

The B vitamin folate may affect both the development and progression of colorectal cancer, yet information about folate intake among colorectal cancer patients is lacking. Folate mediates the transfer of one-carbon moieties both in the synthesis of nucleotides necessary for DNA synthesis, replication, and repair and in DNA-methylation reactions; these functions may play a role in cancer prevention (1, 2). Folic acid is the oxidized synthetic form of folate used in supplements and fortified foods, with greater stability and bioavailability than naturally-occurring folate (3). Overall, epidemiologic evidence supports an inverse association between high folate intake (from diet and supplements) and risk of colorectal adenomas and colorectal cancer (3-6). Rodent models support the anti-neoplastic effect of folate on colorectal tissue before lesions develop, with modest doses of supplemental folic acid suppressing the development of colorectal cancer (3-7).

However, recent evidence suggests that folic acid may in fact accelerate the progression of existing colorectal cancer precursors. First, in rodents folic acid supplementation promotes the progression of colorectal cancer after early lesions, aberrant crypt foci, are present (3). Second, a clinical trial in patients with a recent history of colorectal adenoma, the Aspirin/Folate Polyp Prevention Study (AFPPS), found no evidence that folic acid prevented development of new colorectal polyps. Instead its use was associated with multiple adenomas and there was a suggestive positive association with advanced adenomas after longer-term treatment and follow-up (6 to 8 years) (8). In this high-risk group of patients, early lesions may have been present but missed or undetectable at baseline colonoscopy, and it has been hypothesized that folic acid could have accelerated their growth (3, 5). Two other trials have recently been completed. A randomized trial of folic acid supplementation among members of the Health Professionals' Follow-Up Study and the Nurses' Health Study with history of colorectal adenoma showed no significant associations between folic acid and recurrent adenomas (any, advanced, or multiple) (9). Similarly, the UK Colorectal Adenoma Prevention trial (ukCAP) found no effect of folic acid supplementation on the occurrence of any, advanced, or multiple new adenomas (10). However, the duration of follow-up and folic acid supplementation for both trials was shorter than for AFPPS, and for ukCAP the folic acid dose was lower and no population-wide fortification program was in place. Because the elevated risk in the AFPPS did not occur until 6-8 years post-diagnosis, additional follow-up in the recent trials is needed to evaluate whether the results are inconsistent.

Both normal and neoplastic colorectal tissues are rapidly dividing with high rates of DNA replication; the provision of nucleotides for DNA synthesis is the most likely mechanism through which folate may both protect normal tissue from DNA damage and carcinogenesis, and accelerate progression of established neoplasia (3, 4, 6, 7). Of concern is that a cancer-promoting effect may also be present for other tissues, as suggested by an increased risk for prostate cancer in the folic acid arm of the Aspirin/Folate Polyp Prevention Study trial (11). A recent analysis of data from a trial in Norway showed an increase in overall cancer incidence and mortality with folic acid supplementation (12). The study's statistical power was inadequate to evaluate individual cancer sites, though hazard ratios for colorectal cancer were close to 1.0.

Consistent with high folate intake promoting growth of established colorectal tumors, anti-folate agents inhibit their growth, an effect exploited in the conventional treatment of colorectal cancer. The chemotherapeutic agent 5-fluorouracil (5-FU), which is widely used in colorectal cancer treatment, inhibits the folate-metabolizing enzyme thymidylate synthase (TS), blocking pyrimidine synthesis, inducing DNA damage, and slowing tumor growth (3, 6, 13, 14). The impact of chronic use of folic acid supplements on 5-FU treatment efficacy is currently unknown.

Nutritional supplement use is high in the U.S. population (3, 15, 16) and higher still among cancer patients (3, 5, 17-19). In the limited number of studies reporting change in supplement use with diagnosis, all showed increases in use. Cancer patients report that they use supplements and other alternative therapies to feel better, gain a sense of control, reduce stress, support their immune systems, and improve chances of a cure (17, 20-22). Interest in research on health behaviors and cancer prognosis is growing (23-26), and thus it is critical to evaluate and quantify lifestyle after a cancer diagnosis in order to design appropriate prognostic studies. Many epidemiologic studies evaluate associations between pre-diagnostic health behaviors and disease outcomes, an approach that may lead to substantial exposure misclassification. Limited information is available on the use of supplements, FAS intake in particular, and determinants of FAS intake among colorectal cancer patients (18, 19, 27). To date, only one study has addressed changes in FAS and other supplement use after colorectal cancer diagnosis (18). Thus, we here evaluate FAS initiation and use after colorectal cancer diagnosis in a large international cohort (n>1000) of colorectal cancer patients, and evaluate a comprehensive set of factors associated with FAS use.

Subjects and Methods

Study Population, Recruitment and Follow-up

The Colon Cancer Family Registry (C-CFR) is an international study of colorectal cancer cases, their family members, and controls recruited by investigators at six sites: Seattle, Washington; the Mayo Clinic in Rochester, Minnesota; a consortium led by the University of Southern California (USC) in Los Angeles; the University of Hawaii; the University of Melbourne in Australia; and Cancer Care Ontario in Toronto. Study protocols were reviewed and approved by institutional review boards at each participating site. Eligibility criteria and sampling schemes differed somewhat by site and have been previously described (28). Briefly, Phase I of recruitment was conducted between 1998 and 2002 and included cases identified both from cancer registries (population-based recruitment) and from clinics serving families with early-onset or multiple colorectal cancer cases (clinic-based recruitment). Response rates varied by study site due to differences in approach protocols. Of those eligible at baseline, between 35% and 78% agreed to participate across the six C-CFR sites. Active follow-up of phase I participants occurred about 5 years after initial enrollment; 22% of cases died before this follow-up, and of the survivors 70-95% completed the follow-up questionnaire.

Questionnaires

Lifestyle and risk factor questionnaires were administered at enrollment, asking about the period before diagnosis, and at follow-up about 5 years later. Data collected included participants' use of supplements and medications, race, ethnicity, and other demographic information, physical activity, height, weight, smoking history, alcohol consumption, and some information on diet. Questions on use of folic acid and multivitamins at enrollment asked if participants had ever taken the supplements regularly (at least twice a week for more than a month), and if they had taken them regularly about two years ago (=use prior to diagnosis). At follow-up, participants were asked if they had taken folic acid or

multivitamins regularly in the interval between baseline and follow-up interviews (=use after diagnosis). Three of the six C-CFR sites, the USC Consortium, Ontario, and Hawaii, also administered a detailed food frequency questionnaire (FFQ) to participants at baseline (29), allowing quantitative assessment of pre-diagnostic folic acid intake for a subset of participants.

The present analysis uses an initial dataset available in 2008 and includes 1,092 colorectal cancer cases recruited during Phase I (28). The subset of 1,092 cases represents all those with data available from questionnaires administered both at enrollment and follow-up, and with data available on covariates such as education, exercise and diet. Compared to Phase I C-CFR cases not included in this subset, cases included had generally similar demographic characteristics and health behaviors. Supplement use was similar between the two groups. Thirty-four percent of those included used multivitamins before diagnosis, compared to 30% of those not included; about 3% of each group used single-supplement folic acid. Those included in our analysis were somewhat younger and more educated, differences likely related to the required survival to follow-up and completion of the follow-up questionnaire.

Statistical Analysis

Nearly all commonly used multivitamins include folic acid, and therefore we included both multivitamins and single-supplement folic acid in our definition of FAS. We first studied the outcome of "FAS use after diagnosis with colorectal cancer", by comparing all patients who used FAS after diagnosis (n=602) to those who did not (n=490). Second, we analyzed "FAS initiation" after colorectal cancer diagnosis by comparing cases who did not use FAS regularly in the two years prior to diagnosis and used FAS after diagnosis ("new use," n=307) to those who used FAS neither immediately before nor after diagnosis ("no use," n=399).

To investigate predictors of FAS use or initiation in colorectal cancer cases, we assessed characteristics that had been associated with supplement use in previous studies (15, 17, 30-32), including age, sex, race (white versus non-white), family history (one or more versus no first-degree relatives with colorectal cancer), study site, education, income, smoking, alcohol intake, diet including intake of fruit, vegetables, and red meat, lifetime exercise, and body mass index (BMI). We chose lifetime rather than recent exercise as better reflecting attitudes towards health rather than current physical capabilities.

We used multivariate logistic regression to evaluate associations between patient characteristics and FAS use or initiation, adjusting each for age, sex, and site as appropriate. For patient characteristics described by multiple ordinal categories, we used Wald trend tests to evaluate any trends apparent in odds ratios across categories. To identify the most important predictors of FAS use or initiation overall, we used forward stepwise regression analyses which evaluated concurrently the covariates listed above, using a significance level of 0.1 for both entering and remaining in the model. To evaluate robustness, we also derived models using the entry and stay criteria of 0.05 and 0.1, respectively. Income and family history were excluded from the forward stepwise analyses because of incomplete data.

Results

Table 1 shows baseline characteristics of the 1,092 colorectal cancer cases. Most were younger than age 60 at diagnosis, and more than a third had a family history of colorectal cancer, reflecting the focus of the C-CFR cohort on recruiting cases more likely to have familial colorectal cancer, including those diagnosed at a young age (28, 33). Nearly a third of cases were from outside the United States. More than a third of cases took a multivitamin at baseline (prior to diagnosis), and 30 (3%) used single-supplement folic acid. Dietary

intake data were available for 424 participants included in this analysis (39%), and showed mean folic acid intake from diet (post-fortification) and supplements of 448 mcg for non-FAS users and 883 mcg for FAS users. Thus, FAS use is a major source of inter-individual variability in folate intakes. For 11%, intake exceeded 1 mg folic acid, the tolerable upper intake level established by the Institute of Medicine to avoid masking vitamin B12 deficiency (34).

The proportion of cases using FAS, including multivitamins, increased substantially after colorectal cancer diagnosis (Table 2). A total of 35.4% of cases reported FAS use prior to colorectal cancer diagnosis, whereas after diagnosis 55.1% reported FAS use (p=0.004). Of those who did not use FAS before diagnosis, 43.5% initiated use after diagnosis (N=307) and 56.5% did not (N=399) (these are the two groups of cases compared in our analysis of predictors of FAS initiation). Former users were more likely to initiate use after a cancer diagnosis than were those who had never used FAS (58.4% versus 36.7%, p<0.0001). Of those cases who were already using FAS before diagnosis, 76.4% maintained use after diagnosis. FAS use was substantially higher, both before and after diagnosis, at U.S. compared to non-U.S. sites (p<0.0001 at both time points), though use increased after diagnosis in all countries studied.

Table 3 shows that women were more likely than men to use FAS after colorectal cancer diagnosis (OR 1.47, 95% CI 1.14-1.89), and non-white cases were less likely than Caucasians to use FAS (OR 0.66, 95% CI 0.45-0.97). Subjects at the Ontario and Australian sites were much less likely to use FAS than were those from U.S sites (ORs of 0.40 [95% CI 0.26-0.61] and 0.16 [95% CI 0.10-0.26] respectively compared to Seattle). Current smokers were less likely to use FAS than were those who had never smoked (OR = 0.67, 95% CI 0.46-0.96). There were positive associations between both higher fruit ($p_{trend} < 0.0001$) and vegetable intake ($p_{trend} = 0.001$) and FAS use, while those who consumed more red meat were less likely to use FAS ($p_{trend} = 0.03$). No strong associations between FAS use and age, family history, education, income, alcohol use, exercise, or BMI were observed. In forward stepwise analysis sex, race, study site, and meat and fruit intake emerged as significant predictors of FAS use after diagnosis (Table 4). Using the more stringent criteria of penter<0.05 and p_{stay}<0.1 resulted in a model in which study site and intake of meat and fruit, but not sex and race, predicted FAS use (data not shown).

The analysis of predictors of FAS initiation after diagnosis (Table 5) gave similar results, with sex, site, smoking, and consumption of meat and fruit showing statistically significant associations. The associations of race and vegetable intake with FAS initiation were weaker than those with FAS use. There was an association between lifetime exercise and FAS initiation that had not been observed for FAS use (OR = 1.48; 95% CI 1.01-2.16 for active versus inactive cases). Forward stepwise analysis showed sex, study site, meat intake, and exercise to be predictors of FAS initiation (Table 6), though exercise did not appear as a predictor in a model using penter<0.05 (data not shown).

Discussion

We observed a substantial increase in the proportion of patients using FAS after colorectal cancer diagnosis compared to use before diagnosis. Those more likely to use FAS included women, Caucasians, U.S. residents, those consuming less meat and more fruit, and possibly nonsmokers and those consuming more vegetables. Predictors of FAS initiation after diagnosis were similar to those of any FAS use, though associations with race and consumption of fruits and vegetables were weaker, and that with exercise somewhat stronger.

Few studies have addressed supplement use among colorectal cancer patients (19, 27); only one has addressed post-diagnostic initiation of FAS use and none has assessed predictors of FAS initiation in these patients. A relatively small study of colon cancer patients (N=278), diagnosed between 1996 and 2000 in North Carolina, assessed change in supplement use after diagnosis (18). It showed that 31% of patients used multivitamins before diagnosis and 1.5% used single-supplement folic acid; two years after diagnosis, the proportions increased to 43% for multivitamins and 7% for folic acid. Our results suggest higher use both before and after diagnosis than did the North Carolina study, particularly at U.S. sites, possibly reflecting geographic differences and/or a time trend; nutritional surveys such as the National Health and Nutrition Examination Survey have generally shown increases in the use of dietary supplements over time (15). In the North Carolina study, factors associated with use of any new supplement after diagnosis included age, female sex, and white race, though predictors of change in FAS use were not reported.

The results of our analyses are in part consistent with earlier analyses of predictors of supplement use in general populations and in cancer patients, which have shown positive associations with female sex, white race, and fruit and vegetable consumption, and inverse associations with smoking and meat consumption (15, 17, 18, 30-32). The results of our multivariate analysis suggest that meat and fruit intake (and geographic location) are more important predictors of FAS use than sex and race. Our results for education contrast with earlier studies of supplement use in both cancer patients and general populations, which showed consistent positive associations; our analysis did suggest that those with more education were more likely to use FAS, but differences were not statistically significant. In a separate analysis of supplement use before diagnosis in our colorectal cancer cases (data not shown), we found generally similar, slightly stronger, associations of FAS use with education and other indicators of socioeconomic status or health-promoting behaviors, consistent with reports from studies of individuals without cancer (15, 30-32).

Our analysis suggests that the use of folic acid-containing supplements among colorectal cancer patients is widespread, with post-diagnostic use substantially higher than pre-diagnostic use. The effect of supplement use and nutrient status on prognosis in cancer patients is an important new area of epidemiologic research (23-26); however, many studies have measured supplement use or nutrient status before cancer diagnosis, rather than during cancer treatment and follow-up. Our results suggest that studies using pre-diagnostic supplement use as a proxy for post-diagnostic use may suffer from substantial exposure misclassification.

FAS use may adversely impact disease course. Results from animal studies and preliminary clinical data indicate that high folic acid intake may accelerate progression of established colorectal adenomas and cancer (3, 8). Effects on disease recurrence and metastasis are unknown. Experimental evidence suggests that folic acid may also alter the efficacy of 5-FU treatment, with effects depending on the timing of its use. The drug leucovorin is a reduced form of folic acid given immediately before 5-FU administration that stabilizes binding of 5-FU to TS and improves response rates (14, 35-37). However, chronic use of folic acid may have the opposite effect. Experimental results in human cancer cell lines and in mouse tumor models suggest that folate deficiency, in culture medium or diet, improves response to 5-FU especially when given with leucovorin (38-40). Mechanisms identified include downregulation of TS expression and activity with low folate status, enhancing inhibition by 5-FU and drug efficacy (39). These results suggest that continuing use of folic acid supplements among colorectal cancer patients receiving 5-FU could reduce treatment efficacy; however, this question has not been studied in a clinical setting (4, 5).

Strengths of our analysis include data from a large, prospective, international study of colorectal cancer cases, with detailed information available on use of specific supplements and on covariates likely associated with this use. The diverse populations from which participants were recruited are a strength of the C-CFR and of our study; however, those included in our analysis still may not fully represent the larger population of colorectal cancer patients. In addition, FAS use among colorectal cancer patients in 2010 may differ from that measured in C-CFR participants between 1998 and 2002, because of media coverage of concerns about the use of folic acid in cancer patients.

Another limitation of the analysis is that data on baseline diet and supplement use were collected at enrollment, asking about intake two years previously, before participants' cancer diagnoses. However, validation studies comparing intake of food and supplements elicited by questionnaire to those obtained by diet record or 24-hour diet recall show comparable correlations for studies of current diet or supplements (41-43), and diet 3-4 years (44) or 10 years (45) in the past. A nested case-control study of long-term dietary recall (46) showed generally similar results for cancer cases and controls, though recall was somewhat poorer for cases with colorectal cancer compared to non-cases.

A further limitation of our data is that FFQs were administered at only three C-CFR sites, and only for the pre-diagnostic time period. Our analysis therefore focuses on qualitative rather than quantitative measures of change in folic acid intake after diagnosis, and on intake from supplements but not from food. However, supplement use is a major source of variation in folate intakes, especially among cancer patients. A pilot study of 176 Ontario CFR participants did collect FFQ data both before and after colorectal cancer diagnosis, and found little change in dietary folate intake after diagnosis, though the subset of participants was not randomly selected and results may not apply to C-CFR participants overall (Gail McKeown-Eyssen, personal communication). Our analysis of 424 CFR participants completing baseline FFQs at three sites showed that pre-diagnostic folic acid intake among FAS users was twice that of non-users, and that intake exceeded 1 mg folic acid for one in ten participants. The data for these subsets of C-CFR participants thus suggest that folic acid from supplements contributes substantially to overall intake, and especially to change in intake after colorectal cancer diagnosis. Intakes were substantial before diagnosis, and though quantitative data on post-diagnostic intake are not available, the results of our qualitative analysis of FAS use suggest that these would be higher still.

The cases in our analysis can only include those surviving five years to follow-up. If FAS use accelerated progression of and death from disease, then post-diagnostic use in all colorectal cancer patients would be higher than our estimate of 55.1%. Some participants were also lost to follow-up or refused to complete the follow-up questionnaire; however, the response rate among survivors was high (82% across all sites). Analyzing the effects of FAS use on survival would address these questions, and such an analysis will be feasible once data on stage at diagnosis, clinical treatment, and mortality are available from all C-CFR sites. A further limitation associated with follow-up five years after enrollment is that our analysis could not assess changes in FAS use directly after colorectal cancer diagnosis, perhaps the most critical time period because of potential interactions with treatment; another is that we cannot exclude secular trends in supplement use as one cause of the increase in FAS use observed.

We here report that FAS use is prevalent among colorectal cancer cases, and identify characteristics of those likely to be using FAS. These findings are important given evidence that folic acid may accelerate progression of colorectal cancer, and the unknown, but plausibly detrimental, effects that FAS intake may have on the efficacy of cancer treatment and on survival. The factors associated with FAS use in our analysis suggest that those who

choose to use supplements may be receptive to information on health-promoting behaviors. However, many cancer patients do not discuss supplement use with their physicians (17). Our research may help clinicians identify patients likely to use supplements after colorectal cancer diagnosis, and allow them to discuss both the benefit and harm that may result. Finally, our study highlights the need to measure supplement use and other critical exposures at time points after diagnosis, to avoid substantial misclassification in studies of cancer prognosis.

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Table 1

Demographic, behavioral and physical characteristics of selected Colorectal Cancer Family Registry study participants at baseline interview, 1998-2002 (N=1,092[a])

		n	%
Age (years)	**<60**	669	61.3
	≥60	423	38.7
Sex	**Male**	517	47.3
	Female	575	52.7
Race	**White**	930	85.2
	Non-white	162	14.8
Family history [b]	**No**	582	61.4
	Yes	366	38.6
Study site	**Seattle**	190	17.4
	Mayo Foundation	273	25.0
	USC[c] **Consortium**	247	22.6
	Ontario	185	16.9
	Australia	163	14.9
	Hawaii	34	3.1
Education	**< High school**	156	14.6
	High school graduate	269	25.2
	Some voc./college	331	31.0
	≥ Bachelor's degree	313	29.3
Income [d]	**< $30,000**	198	24.1
	$30,000 to 44,999	212	25.8
	$45,000 to 69,999	209	25.5
	$70,000 or greater	202	24.6
Smoking	**Never**	466	44.3
	Former	399	38.0
	Current	186	17.7
Alcohol	**No**	500	47.4
(Current use)	**Yes**	556	52.6
Supplement use	**Multivitamin only**	351	32.6
	Folic acid only	8	0.7
	Multivitamin and folic acid	22	2.0
	Neither multivitamin nor folic acid	695	64.6
Red meat intake	**0 to 2**	127	12.0

		n	%
(Servings/week)	**2 to 3**	328	31.0
	3 to 5	257	24.3
	> 5	345	32.6
Fruit intake	**0 to 6**	308	29.3
(Servings/week)	**6 to 7**	282	26.8
	7 to 14	278	26.4
	> 14	185	17.6
Vegetable intake	**0 to 6**	180	16.8
(Servings/week)	**6 to 7**	315	29.3
	7 to 14	301	28.0
	> 14	278	25.9
Physical activity	**Inactive**	241	23.1
(Lifetime) [e]	**Less active**	311	29.8
	Active	258	24.7
	Very Active	234	22.4
Body mass index	**15 to 25**	406	38.8
(kg/m^2)	**25 to 30**	416	39.7
	≥ 30	225	21.5

[a] The subset of C-CFR participants with data currently available from questionnaires administered both at enrollment and follow-up, and data available on epidemiologic covariates analyzed.

[b] First-degree relatives with colorectal cancer: 0 vs. ≥1. Data were missing for 144 participants (13%).

[c] University of Southern California

[d] Data missing for 271 participants (25%).

[e] In average weekly MET hours, where three MET hours = walking at 2 to 3 miles per hour for 1 hour. Inactive = 0 to 6, Less active = 6.1 to 20, Active = 20.1 to 44, and Very active is > 44.

Table 2

Use of FAS [a] before and after a diagnosis of colorectal cancer

Study sites:	Use before diagnosis:[c]	Total % [d] (n)	Use after diagnosis:[b] Yes % [e] (n)	Use after diagnosis:[b] No % [e] (n)
All	**Total**	100% (1092)	**55.1%** (602)	44.9% (490)
	Yes	**35.4%** (386)	76.4% (295)	23.6% (91)
	No	64.7% (706)	43.5% (307)	56.5% (399)
	Former	20.2% (221)	58.4% (129)	41.6% (92)
	Never	44.4% (485)	36.7% (178)	63.3% (307)
U.S.	**Total**	100% (744)	**63.6%** (473)	36.4% (271)
	Yes	**41.0%** (305)	79.0% (241)	21.0% (64)
	No	59.0% (439)	52.8% (232)	47.2% (207)
	Former	21.9% (163)	65.0% (106)	35.0% (57)
	Never	37.1% (276)	45.7% (126)	54.4% (150)
Non-U.S.	**Total**	100% (348)	**37.1%** (129)	62.9% (219)
	Yes	**23.3%** (81)	66.7% (54)	33.3% (27)
	No	76.7% (267)	28.1% (75)	71.9% (192)
	Former	16.7% (58)	39.7% (23)	60.3% (35)
	Never	60.1% (209)	24.9% (52)	75.1% (157)

[a] FAS: folic acid-containing supplements

[b] Use between baseline (1998-2002) and follow-up (2003-2007) interviews

[c] Use two years before baseline interview, conducted between 1998 and 2002.

[d] Column percent, or the number of subjects in this category of pre-diagnostic use as a percent of all subjects

[e] Row percent, or the number of subjects in this category of post-diagnostic use as a percent of this category of pre-diagnostic use

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Table 3

Demographic, behavioral and physical characteristics associated with FAS[a] use after colorectal cancer diagnosis

		FAS use after diagnosis					
		Yes[b] (N=602)		No[c] (N=490)			
		n	%	n	%	OR[d]	95% CI
Age (years)	**<60**	348	57.8	321	65.5	**Ref.**	—
	≥60	254	42.2	169	34.5	**1.13**	0.86-1.48
Sex	**Male**	264	43.9	253	51.6	**Ref.**	—
	Female	338	56.2	237	48.4	**1.47***	1.14-1.89
Race	**White**	519	86.2	411	83.9	**Ref.**	—
	Non-white	83	13.8	79	16.1	**0.66***	0.45-0.97
Family history [e]	**No**	320	61.2	262	61.7	**Ref.**	—
	Yes	203	38.8	163	38.4	**0.98**	0.73-1.31
Study site	**Seattle**	130	21.6	60	12.2	**Ref.**	—
	Mayo Foundation	162	26.9	111	22.7	**0.68**	0.46-1.00
	USC[f] **Consortium**	164	27.2	83	16.9	**0.91**	0.61-1.36
	Ontario	88	14.6	97	19.8	**0.40***	0.26-0.61
	Australia	41	6.8	122	24.9	**0.16***	0.10-0.26
	Hawaii	17	2.8	17	3.5	**0.44***	0.21-0.92
Education	**< High school**	69	11.7	87	18.1	**Ref.**	—
	High school graduate	152	25.9	117	24.3	**1.22**	0.79-1.86
	Some voc./college	184	31.3	147	30.6	**1.16**	0.76-1.75
	≥ Bachelor's degree	183	31.1	130	27.0	**1.44**	0.95-2.20
							p_{tr}=0.11
Income	**< $30,000**	121	24.1	77	24.1	**Ref.**	—
	$30,000 to 44,999	126	25.1	86	27.0	**1.00**	0.67-1.51
	$45,000 to 69,999	131	26.1	78	24.5	**1.13**	0.74-1.70

		FAS use after diagnosis					
		Yes[b] (N=602)		No[c] (N=490)			
		n	%	n	%	OR[d]	95% CI
	$70,000 or greater	124	24.7	78	24.5	**1.01**	0.66-1.55
Smoking	**Never**	267	46.3	199	42.0	**Ref.**	—
	Former	221	38.3	178	37.6	**0.99**	0.74-1.33
	Current	89	15.4	97	20.5	**0.67***	0.46-0.96
							p_{tr}=0.06
Alcohol	**No**	299	51.8	201	42.0	**Ref.**	—
(Current use)	**Yes**	278	48.2	278	58.0	**0.94**	0.72-1.23
Red meat intake	**0 to 2**	89	15.4	38	7.9	**Ref.**	—
(Servings/week)	**2 to 3**	185	32.0	143	29.9	**0.55***	0.35-0.87
	3 to 5	125	21.6	132	27.6	**0.42***	0.26-0.68
	> 5	179	31.0	166	34.7	**0.53***	0.33-0.84
							p_{tr}=0.03
Fruit intake	**0 to 6**	150	25.7	158	33.6	**Ref.**	—
(Servings/week)	**6 to 7**	165	28.3	117	24.9	**1.43***	1.02-2.02
	7 to 14	166	28.5	112	23.8	**1.80***	1.26-2.58
	> 14	102	17.5	83	17.7	**2.11***	1.38-3.23
							p_{tr}<0.0001
Vegetable intake	**0 to 6**	93	15.7	87	18.1	**Ref.**	—
(Servings/week)	**6 to 7**	180	30.4	135	28.0	**1.20**	0.82-1.75
	7 to 14	176	29.7	125	25.9	**1.50***	1.01-2.23
	> 14	143	24.2	135	28.0	**2.00***	1.28-3.13
							p_{tr}=0.001
Physical activity [g]	**Inactive**	122	21.3	119	25.2	**Ref.**	—
(Lifetime)	**Less active**	181	31.6	130	27.5	**1.35**	0.94-1.92

		FAS use after diagnosis					
		Yes[b] (N=602)		No[c] (N=490)			
		n	%	n	%	OR[d]	95% CI
	Active	142	24.8	116	24.6	**1.27**	0.87-1.83
	Very Active	127	22.2	107	22.7	**1.33**	0.91-1.9
							p_{tr}=0.21
Physical activity [h]	**Inactive**	122	21.3	119	25.2	**Ref.**	—
(Lifetime)	**Active**	450	78.7	353	74.8	**1.32**	0.97-1.78
Body mass index	**15 to 25**	233	40.3	173	36.9	**Ref.**	—
(kg/m^2)	**25 to 30**	214	37.0	202	43.1	**0.80**	0.60-1.09
	≥ 30	131	22.7	94	20.0	**0.95**	0.67-1.34

[a] FAS: folic acid-containing supplements

[b] FAS use between baseline and follow-up, about 5 years after enrollment

[c] No FAS use between baseline and follow-up

[d] Adjusted for age, sex, and site as appropriate

[e] First-degree relatives with colorectal cancer: 0 vs. ≥1

[f] University of Southern California

[g] In average weekly MET hours, where three MET hours = walking at 2 to 3 miles per hour for 1 hour. Inactive = 0 to 6, Less active = 6.1 to 20, Active = 20.1 to 44, and Very active is > 44.

[h] Inactive = 0 to 6 MET hours, Active is ≥ 6.1

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Table 4

Independent predictors of FAS[a] use after colorectal cancer diagnosis: results of forward stepwise regression analysis[b]

		Coefficient	SE	Adjusted OR[c]	95% CI
Intercept		0.127	0.108	—	—
Sex	**Male**	—	—	**Ref.**	—
(p=0.070)	**Female**	0.134	0.074	**1.31**	0.98-1.75
Race	**White**	—	—	**Ref.**	—
(p=0.060)	**Non-white**	−0.213	0.113	**0.65**	0.42-1.02
Study site	**Seattle**	—	—	**Ref.**	—
(p<0.0001)	**Mayo Foundation**	0.451	0.152	**0.86**	0.53-1.41
	USC[d] Consortium	0.428	0.154	**0.84**	0.52-1.37
	Ontario	−0.359	0.163	**0.38**	0.24-0.62
	Australia	−1.408	0.196	**0.13**	0.08-0.23
	Hawaii	0.290	0.350	**0.74**	0.30-1.79
Red meat intake	**0 to 2**	—	—	**Ref.**	—
(Servings/week)	**2 to 3**	−0.060	0.122	**0.50**	0.31-0.83
(p=0.002)	**3 to 5**	−0.401	0.131	**0.36**	0.21-0.61
	> 5	−0.165	0.125	**0.45**	0.27-0.76
Fruit intake	**0 to 6**	—	—	**Ref.**	—
(Servings/week)	**6 to 7**	−0.077	0.125	**1.34**	0.92-1.96
(p=0.016)	**7 to 14**	0.159	0.126	**1.70**	1.14-2.52
	> 14	0.289	0.149	**1.93**	1.23-3.05

[a] FAS: folic acid-containing supplements.

[b] $p_{enter} < 0.1$, $p_{stay} < 0.1$

[c] Compares subjects with regular FAS use between baseline and follow-up (N=602), about 5 years after enrollment, to those with no FAS use between baseline and follow-up (N=490)

[d] University of Southern California

Table 5

Demographic, behavioral and physical characteristics associated with FAS[a] initiation after colorectal cancer diagnosis

		New use[b] (N=307)		No use[c] (N=399)			
		n	%	n	%	OR[d]	95% CI
Age (years)	**<60**	191	62.2	260	65.2	**Ref.**	—
	≥60	116	37.8	139	34.8	**0.96**	0.69-1.35
Sex	**Male**	130	42.4	213	53.4	**Ref.**	—
	Female	177	57.7	186	46.6	**1.60***	1.17-2.19
Race	**White**	249	81.1	337	84.5	**Ref.**	—
	Non-white	58	18.9	62	15.5	**0.88**	0.55-1.42
Family history [e]	**No**	160	60.6	217	61.6	**Ref.**	—
	Yes	104	39.4	135	38.4	**0.97**	0.67-1.39
Study site	**Seattle**	52	16.9	49	12.3	**Ref.**	—
	Mayo Foundation	98	31.9	71	17.8	**1.30**	0.79-2.15
	USC[f] **Consortium**	70	22.8	74	18.6	**0.92**	0.55-1.54
	Ontario	51	16.6	84	21.1	**0.57***	0.33-0.96
	Australia	24	7.8	108	27.1	**0.21***	0.11-0.38
	Hawaii	12	3.9	13	3.3	**0.90**	0.37-2.19
Education	**< High school**	38	12.6	80	20.5	**Ref.**	—
	High school graduate	89	29.6	95	24.4	**1.51**	0.90-2.52
	Some voc./college	87	28.9	114	29.2	**1.23**	0.74-2.04
	≥ Bachelor's degree	87	28.9	101	25.9	**1.47**	0.88-2.45
Income	**< $30,000**	59	23.8	66	26.4	**Ref.**	—
	$30,000 to 44,999	70	28.2	70	28.0	**1.27**	0.77-2.10
	$45,000 to 69,999	62	25.0	62	24.8	**1.23**	0.73-2.05
	$70,000 or greater	57	23.0	52	20.8	**1.23**	0.71-2.11

		New use[b] (N=307)		No use[c] (N=399)			
		n	%	n	%	OR[d]	95% CI
Smoking	**Never**	150	49.8	164	42.4	**Ref.**	—
	Former	100	33.2	139	35.9	**0.91**	0.63-1.31
	Current	51	16.9	84	21.7	**0.63***	0.40-0.97
							p_{tr}=0.05
Alcohol	**No**	150	51.2	152	38.9	**Ref.**	—
(Current use)	**Yes**	143	48.8	239	61.1	**0.85**	0.61-1.19
Red meat intake	**0 to 2**	41	13.9	26	6.7	**Ref.**	—
(Servings/week)	**2 to 3**	92	31.1	120	30.7	**0.45***	0.25-0.80
	3 to 5	69	23.3	103	26.3	**0.37***	0.20-0.69
	> 5	94	31.8	142	36.3	**0.38***	0.21-0.70
							p_{tr}=0.01
Fruit intake		90	30.3	132	34.7	**Ref.**	—
(Servings/week)	**6 to 7**	77	25.9	93	24.5	**1.24**	0.81-1.90
	7 to 14	75	25.3	91	24.0	**1.39**	0.89-2.17
	> 14	55	18.5	64	16.8	**1.95***	1.16-3.30
							p_{tr}=0.01
Vegetable intake	**0 to 6**	56	18.6	71	18.2	**Ref.**	—
(Servings/week)	**6 to 7**	86	28.6	111	28.4	**1.01**	0.63-1.60
	7 to 14	92	30.6	98	25.1	**1.42**	0.87-2.30
	> 14	67	22.3	111	28.4	**1.55**	0.89-2.70
							p_{tr}=0.05
Physical activity [g]	**Inactive**	61	21.3	103	26.9	**Ref.**	—
(Lifetime)	**Less active**	96	33.5	105	27.4	**1.59***	1.03-2.48
	Active	68	23.7	90	23.5	**1.41**	0.88-2.25
	Very Active	62	21.6	85	22.2	**1.39**	0.86-2.25
							p_{tr}=0.27

		New use[b] (N=307)		No use[c] (N=399)			
		n	%	n	%	OR[d]	95% CI
Physical activity [h]	**Inactive**	61	21.3	103	26.9	**Ref.**	—
(Lifetime)	**Active**	226	78.8	280	73.1	**1.48***	1.01-2.16
Body mass index	**15 to 25**	112	38.2	138	35.8	**Ref.**	—
(kg/m^2)	**25 to 30**	106	36.2	167	43.4	**0.84**	0.58-1.23
	≥ 30	75	25.6	80	20.8	**1.09**	0.71-1.67

[a] FAS: folic acid-containing supplements

[b] Subject never used or formerly used FAS before diagnosis, and used FAS after diagnosis

[c] Subject never used or formerly used FAS before diagnosis, and did not use FAS after diagnosis

[d] Adjusted for age, sex, and site as appropriate

[e] First-degree relatives with colorectal cancer: 0 vs. ≥1

[f] University of Southern California

[g] In average weekly MET hours, where three MET hours = walking at 2 to 3 miles per hour for 1 hour. Inactive = 0 to 6, Less active = 6.1 to 20, Active = 20.1 to 44, and Very active is > 44.

[h] Inactive = 0 to 6 MET hours, Active is ≥ 6.1

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Table 6

Independent predictors of FAS[a] initiation after colorectal cancer diagnosis: results of forward stepwise regression analysis[b]

		Coefficient	SE	Adjusted OR[c]	95% CI
Intercept		−0.281	0.127	—	—
Sex	**Male**	—	—	**Ref.**	—
(p=0.017)	**Female**	0.218	0.091	**1.55**	1.08-2.21
Study site	**Seattle**	—	—	**Ref.**	—
(p<0.0001)	**Mayo Foundation**	0.794	0.191	**2.01**	1.07-3.77
	USC[d] Consortium	0.266	0.189	**1.18**	0.63-2.21
	Ontario	−0.216	0.189	**0.73**	0.40-1.35
	Australia	−1.187	0.222	**0.28**	0.14-0.55
	Hawaii	0.246	0.370	**1.16**	0.44-3.10
Red meat intake	**0 to 2**	—	—	**Ref.**	—
(Servings/week)	**2 to 3**	−0.074	0.152	**0.41**	0.22-0.77
(p=0.0017)	**3 to 5**	−0.388	0.162	**0.30**	0.15-0.58
	> 5	−0.364	0.155	**0.30**	0.16-0.58
Physical activity	**Inactive[e]**	—	—	**Ref.**	—
(Lifetime)	**Active[f]**	0.198	0.108	**1.49**	0.97-2.27
(p=0.067)					

[a] FAS: folic acid-containing supplements.

[b] $p_{enter} < 0.1$, $p_{stay} < 0.1$

[c] New use versus no use: compares subjects who never used or formerly used FAS before diagnosis, and used FAS after diagnosis (N=307), to those who never used or formerly used FAS before diagnosis, and did not use FAS after diagnosis (N=399)

[d] University of Southern California

[e] Average weekly MET hours = 0 to 6, where three MET hours = walking at 2 to 3 miles per hour for 1 hour

[f] Average weekly MET hours of ≥ 6.1