Fecal Bile Acid Concentrations in a Subpopulation of the Wheat Bran Fiber Colon Polyp Trial[1]

David S. Alberts,[2] Janine G. Einspahr, David L. Earnest, Mary F. Krutzsch, Po Lin, Lisa M. Hess, David K. Heddens, Denise J. Roe, Maria Elena Martínez, Gerald Salen, and A. K. Batta

Arizona Cancer Center, University of Arizona, Tucson, Arizona 85724-5024 [D. S. A., J. G. E., M. F. K., P. L., L. M. H., D. J. R., M. E. M.]; Novartis Pharmaceuticals, East Hanover, New Jersey 07936-1080 [D. L. E.]; Eastern Arizona College, Globe, Arizona 85552 [D. K. H.]; and The University of Medicine and Dentistry of New Jersey, Newark, New Jersey 07018-1095 [G. S., A. K. B.]

Abstract

Factors that affect the concentration of secondary bile acids in the aqueous phase of stool may have a greater impact on colon carcinogenesis than those that only modify the total fecal bile acid concentration. This hypothesis was tested using stool samples of a subset of participants enrolled in a Phase III colorectal adenomatous polyp prevention trial, which documented the inability of a 13.5 g/day wheat bran fiber (WBF) supplement to reduce polyp recurrence.

Stool was collected from 68 consecutively consented participants who were enrolled in a Phase III clinical trial of WBF for the prevention of adenomatous polyp recurrence. Nineteen (27.9%) of these fecal bile acid substudy participants were on the low fiber (2.0 g/day) intervention group, whereas 49 (72.7%) were on the high fiber (13.5 g/day) intervention group for ~3 years. Sixty-four participants had both the aqueous and solid phases of stool samples analyzed for bile acid content. Bile acid concentrations, measured in μg/ml for fecal water and μg/mg for dry feces, were determined for lithochilic, deoxycholic, chenodeoxycholic, cholic, ursodeoxycholic, isodeoxycholic, isoursodeoxycholic, ursocholic, 7-ketolithocholic, and 12-ketolithocholic acids.

There were no significant differences between the low and high fiber groups concerning mean or median aqueous phase concentrations of lithocholic or deoxycholic bile acids. In contrast, the median concentrations of deoxycholic acid and other secondary bile acids (including lithochilic, isodeoxycholic, ursodeoxycholic, isoursodeoxycholic, ursocholic, 7-ketolithocholic, and 12-ketolithocholic acids) were significantly lower for the high fiber group in the solid-phase stool ($P < 0.05$).

These results document that a high WBF intervention, taken for a median of 2.4 years, does not significantly reduce aqueous-phase concentrations of secondary bile acids in stool, although their concentrations in solid-phase stool were suppressed. Thus, the inability of the high WBF intervention to reduce colorectal adenoma recurrence may be a consequence of its lack of effect on fecal aqueous-phase secondary bile acid concentrations.

Introduction

A variety of potential treatments to prevent colon cancer have been proposed but have later been found to be ineffective in preventing the recurrence of adenomas; among them is a high-fiber diet. One proposed mechanism of action of fiber, namely a reduction in the concentration of secondary bile acids (*e.g.*, lithochilic, isodeoxycholic, ursodeoxycholic, isoursodeoxycholic, ursocholic, 7-ketolithocholic, and 12-ketolithocholic acids) in stool is an alteration in the effects of secondary bile acids on the colonic epithelium. Other agents, including calcium (1), a low fat diet (2), and nonsteroidal anti-inflammatory drugs (3) may also act via a bile acid mechanism. For example, increased dietary fiber dilutes the concentration of bile acids in stool and reduces bile acid solubility in fecal water (4). Calcium supplementation in the presence of phosphate removes bile acids from solution and decreases their interaction with the colon epithelium (5, 6). Bile acids have been shown to increase arachidonic acid release and its conversion to prostaglandins in colonic mucosa. Nonsteroidal anti-inflammatory drugs (*e.g.*, piroxicam and aspirin) decrease formation of prostaglandin E_2 and other eicosenoids from arachidonic acid. Although these prevention strategies may act through a variety of mechanisms, one common effect is the reduction of adverse effects of secondary bile acids on colonic mucosa.

A variety of lines of evidence drawn from observations in animal and human trials support an important role of fecal bile acids in carcinogenesis. In animal models, the bile acid, cholic acid, acts in the promotion phase of carcinogenesis (7). Furthermore, bile acids increase colonic epithelial proliferation (8). The actual carcinogenic potential of a bile acid was first reported in 1939 for DCA[3] (9). In the ensuing years, additional evidence has accumulated that supports an important role for bile acids as colon cancer promoters (10–13).

The mechanisms by which bile acids promote colon carcinogenesis are not completely understood. The secondary bile acids DCA and CDCA have been reported to be cytotoxic to colonic epithelial cells (6, 14, 15), moderately mutagenic (16),

Received 5/31/02; revised 11/8/02; accepted 12/17/02.
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[1] This work was supported in part by Grant CA-41108 from the NIH.
[2] To whom requests for reprints should be addressed, at Arizona Cancer Center, Tucson, AZ 85724-5024. Phone: (520) 626-7685; Fax: (520) 626-2445; E-mail: dalberts@azcc.arizona.edu.

[3] The abbreviations used are: DCA, deoxycholic acid; CDCA, chenodeoxycholic acid; WBF, wheat bran fiber.

Table 1 Age and gender of participants in substudy ($n = 64$) and overall WBF study ($n = 1240$)

A. Age

Study group	Mean (SD)	*P*
Bile acid substudy	66.8281 (8.7569)	0.2659
Overall WBF study	65.6355 (8.7965)	

B. Gender

Study group	% male	*P*
Bile acid substudy	73.44%	0.278
Overall WBF study	66.53%	

associated with dysplastic changes (17), and antiapoptotic (13). The "cellular toxicity" of fecal water (detected by incubating fecal water with erythrocytes and measuring cell lysis) has been evaluated extensively, and shown to be increased by factors that enhance bile acid solubility and decreased by factors that reduce the DCA concentration (18, 19). However, the reduction in cell membrane injury also may result from decreases in concentration of other membrane-active lipids or toxic substances in fecal water (20). A growing body of knowledge suggests that a reduction in concentration of membrane-toxic bile acids, such as DCA, in fecal water reduces epithelial cell injury and proliferation (21, 22).

Factors that affect the concentration of bile acids (particularly DCA) in the aqueous phase of stool (fecal water) may have a greater impact on colon carcinogenesis than those that only modify the total fecal bile acid concentration (23, 24). This concept is based on the observation that only bile acids that are soluble in fecal water are available to interact with colonic epithelial cells. Dietary modification leads to significant decreases in concentration of DCA in fecal water without changing the total bile acid concentration in the aqueous phase of stool (20). A Phase III clinical trial published recently, finding no effect of WBF on reducing the recurrence of adenomatous polyps, provided an opportunity to investigate this hypothesis (25).

Materials and Methods

Study Participants. Stool was collected from 68 consecutively consented participants who were enrolled in a Phase III clinical trial of WBF for the prevention of adenomatous polyp recurrence. Details of the design and methods of the study have been described previously (26). Briefly, men and women who were 40–80 years of age, who had one or more colorectal adenomas removed during colonoscopy within 3 months before recruitment to the trial, were randomized to either a high (13.5 g/day) or low (2.0 g/day) WBF dietary supplement. An imbalanced randomization scheme was adapted toward the end of the accrual phase of this trial (to equalize numbers of high and low WBF participants completing the original trial), resulting in collection of only 19 (27.9%) of these fecal bile acid substudy participants from the low fiber group, whereas 49 (72.7%) were from the high fiber group. These fecal bile acid substudy participants represented 3.0% of the low fiber and 6.1% of the high fiber groups. Of the 68 substudy participants, 64 had both the aqueous and solid phases of stool samples analyzed for bile acid content. There is no difference in the median period of time of fiber consumption for the two groups ($P = 0.23$). All of the substudy participants provided written informed consent for the 72-h stool collection procedure via an addendum to the original Phase III WBF trial protocol. Substudy participants were counseled to avoid foods that were not part of their regular diets for the 2 days before and through the 3-day stool collection period.

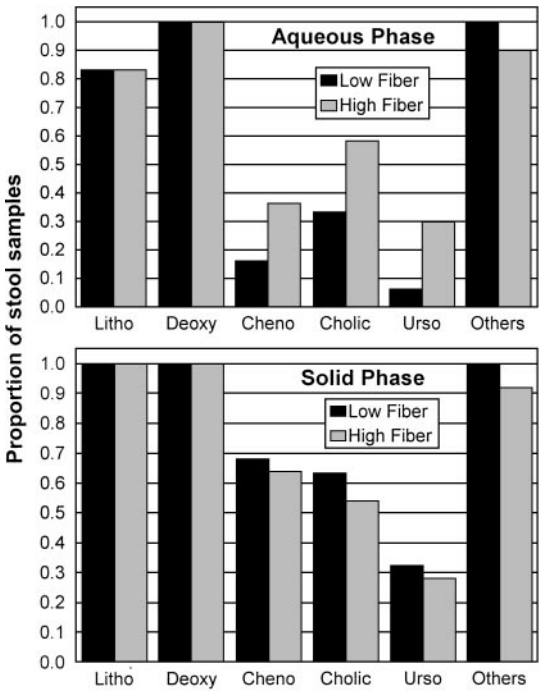

Fig. 1. Proportions of stool samples with detectable amounts of specified bile acids.

Stool Collection. Stool collection dates ranged from October 1996 to January 1998. A 72-h fecal sample was collected from study participants before their third-year (exit) colonoscopy. Each sample was passed into individually labeled specimen containers that were immediately sealed and frozen to minimize bacterial degradation. The stool containers were then placed into large, portable, insulated containers, surrounded by dry ice, and returned to the study clinics.

Bile Acid Measurements. Bile acid concentrations, measured in μg/ml for fecal water and μg/mg for dry feces, were determined for lithochilic, DCA, CDCA, cholic, and ursodeoxycholic acids. In addition, measurements were made for other bile acids (isodeoxycholic, isoursodeoxycholic, ursocholic, 7-ketolithocholic, and 12-ketolithocholic). Details of the method used for measurement of fecal bile acids are described elsewhere (27, 28). Specimens were kept frozen at −80°C until processing at the end of the trial. The specimens were then thawed overnight, and the pH was measured. Samples were weighed, and an equal volume of water was then added, followed by homogenization and then ultracentrifugation at 100,000 × *g* for 1 h. The aqueous portion was separated from the solid portion and stored at −80°C until used for bile acid analysis. The solid portion obtained after ultracentrifugation was freeze-dried and stored at −20°C until used for bile acid analysis. We have observed that stored in this manner, the bile acid composition in the solid and aqueous phases of the stool remains unchanged even after 3 years. The internal standard used was nor-cholic acid.

Statistical Methods. Comparison of demographic characteristics for those participants who participated in stool collection and the remainder of the WBF participants was performed using a χ^2 test and a *t* test. Bile acid detection rates were profiled, and concentrations that were below detectable limits were treated as concentrations of zero. Summary statistics were

Table 2 Mean and median pH, fecal bile acid concentrations, and total bile acid concentration in aqueous and solid phases

Bile Acid	Phase					
	Aqueous (μg/ml)			Solid (μg/mg)		
	Treatment group			Treatment group		
	Low fiber	High fiber	*P*	Low fiber	High fiber	*P*
pH						
Mean	7.03	6.98		7.02	6.99	
Median	7.00	6.90	0.575	7.00	6.90	0.753
SD	0.24	0.40		0.24	0.40	
DCA						
Mean	41.0	59.7		7.07	4.68	
Median	40.0	41.3	0.383	5.17	3.81	0.049
SD	20.0	54.7		5.85	3.78	
Lithocholic acid						
Mean	8.7	14.1		6.85	4.30	
Median	9.2	10.7	0.086	4.71	3.14	0.058
SD	6.2	11.0		7.42	3.44	
CDCA						
Mean	0.5	3.5		0.22	0.30	
Median	0.0	0.0	0.084	0.14	0.15	0.665
SD	1.3	8.8		0.27	0.48	
Cholic acid						
Mean	3.1	17.5		0.42	0.28	
Median	0.0	3.3	0.066	0.16	0.07	0.180
SD	6.5	52.3		0.61	0.79	
Ursodeoxycholic acid						
Mean	0.1	3.7		0.23	0.31	
Median	0.0	0.0	0.034	0.00	0.00	0.686
SD	0.6	9.2		0.53	1.52	
Other bile acids[a]						
Mean	16.9	31.7		3.43	1.63	
Median	11.9	15.4	0.367	2.37	1.13	0.020
SD	16.0	42.4		2.90	1.58	
Total bile acid						
Mean	70.4	130.2		18.21	11.50	
Concentration						
Median	64.1	83.9	0.153	16.18	8.91	0.030
SD	36.7	133.9		14.96	9.11	

[a] Isodeoxycholic, isoursodeoxycholic, ursocholic, 7-ketolithocholic, and 12-ketolithocholic acids.

computed for individual bile acid concentrations, pH, total bile acid concentration, and relative percentage of DCA concentration. The Wilcoxon rank-sum test was used to test for differences in pH, bile acid concentrations, total bile acid concentration, and in relative percentage of DCA levels between treatment groups. This nonparametric statistical test was used because of skewness in the observed values.

Results

In the bile acid substudy, 73.44% of participants were male, similar to the proportion of male participants (66.5%) in the parent Phase III trial ($P = 0.28$). Likewise, the mean age of 66.8 years in the bile acid substudy was similar to those observed in the parent trial (mean age = 65.6; $P = 0.27$; Table 1). Of the 68 substudy participants, 64 had both the aqueous and solid stool phases analyzed. Fig. 1 shows the proportion of samples analyzed that had detectable amounts of the indicated bile acids. There appeared to be little difference in the proportion of low and high fiber-treated participants who had detectable concentrations of the individual bile acids in the solid stool phase (Fig. 1). However, in aqueous-phase stool samples, the high fiber group appeared to have a larger proportion of participants with detectable levels of CDCA, cholic, and ursodeoxycholic acids.

Table 2 provides summary data for mean and median pH, fecal bile acid concentrations, and total bile acid concentration in both the aqueous and solid stool phases. As shown, the median pH did not differ significantly for either the aqueous ($P = 0.575$) or solid ($P = 0.753$) phase. The median fecal aqueous concentrations were significantly higher for ursodeoxycholic acid ($P = 0.034$), but not significantly higher for lithocholic ($P = 0.086$), CDCA ($P = 0.084$), or cholic acid ($P = 0.066$) in the high fiber group of study participants. There were no significant differences between the low and high fiber groups concerning mean or median aqueous-phase concentrations of lithocholic or deoxycholic bile acids, although the values tended to be higher in the high fiber group. In contrast, the median concentrations of DCA and others (isodeoxycholic, isoursodeoxycholic, ursocholic, 7-ketolithocholic, and 12-ketolithocholic acids) were significantly lower for the high fiber group in the solid-phase stool ($P = 0.049$ and $P = 0.020$, respectively). Additionally, median and mean concentrations of lithocholic acid were lower and of borderline significance ($P = 0.058$). Total fecal bile acid concentrations were not significantly higher in the aqueous phase ($P = 0.153$), but were significantly lower in the solid phase ($P = 0.030$) in the high fiber participant group.

In contrast, there were no significant differences in the relative percentage of fecal DCA concentrations between the low and high fiber participant groups for either the aqueous

(median of 59.4% *versus* 56.1%; $P = 0.145$) or solid phases (median of 40.2% *versus* 42.6%; $P = 0.424$).

Discussion

In a prospective, double-blinded, randomized Phase III trial in participants with a history of one or multiple resected colorectal adenomas (≥3 mm in diameter), a high WBF supplement (13.5 g/day for up to 3 years) did not reduce the risk of adenoma recurrence (25). This result is of considerable interest, because prior studies had documented that WBF supplement interventions (13.5–25 g/day for up to 12 months) could significantly lower both total and secondary (*e.g.*, DCA) bile acid concentrations in solid-phase stool (29, 30).

There is increasing evidence that secondary bile acid concentrations in the aqueous as opposed to the solid stool phase are associated with the promotion of colon carcinogenesis (12, 18, 20, 25). It is possible that only secondary bile acids in the aqueous stool phase have adequate contact with colonic epithelial cells to promote carcinogenesis. The results of the present substudy appear to document that the high fiber intervention, taken for a median of 2.4 years, does not significantly reduce phase concentrations of secondary bile acids in stool. In fact, the concentrations of the secondary bile acids tend to be higher (statistically not significant) in the aqueous phase, although their concentrations in solid-phase stool were suppressed. Thus, the inability of the high WBF intervention to reduce colorectal adenoma recurrence may be a consequence of its lack of effect on fecal aqueous-phase secondary bile acid concentrations.

There is a need for well-designed Phase I and Phase II dietary intervention studies before the design and performance of Phase III trials so that end points such as the determination of fecal bile acids can be used as important end points early on, guiding decisions to go into Phase III studies.

Although participants were consecutively consented, the unbalanced randomization in the study during the stool collection period led to an undersampling of low fiber participants. Despite this limitation, the data strongly suggest that a daily WBF supplement of 13.5 g/day does not lower aqueous-phase fecal secondary bile acid concentrations.

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Cancer Epidemiol Biomarkers Prev 2003;12:197-200.