

The effect of a natural high-fibre diet on faecal and biliary bile acids, faecal pH and whole-gut transit time in man. A controlled study

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Dietary fibre possibly protects against colonic cancer by effects on bile acid metabolism. We investigated the effect of a natural high-fibre diet on secondary bile acid formation. Twelve healthy subjects on an habitual low-fibre diet (for 4 weeks) consumed a high-fibre menu for 10 weeks (experimental group). A control group of 10 subjects consumed their regular high-fibre diet during this period. Faecal and biliary acid composition, faecal weight, faecal pH and gut transit time were studied before and after 6 and 10 weeks of fibre addition. Changes in the experimental group were compared to changes in the control group. The concentration, but not the excretion, of the secondary faecal bile acids was reduced in the experimental group. Faecal weight increased, faecal pH dropped and gut transit time was not altered. The biliary deoxycholic acid content decreased and the cholic acid content increased after 6 weeks, but returned to baseline values after 10 weeks of fibre addition. This study shows that a natural high-fibre diet lowers secondary faecal bile acid concentration through an increase in stool weight. The 7 α -dehydroxylation of primary bile acids is probably not or only transiently inhibited.

Colonic cancer is associated with a high dietary fat and low fibre intake (Walker, 1976; IARC Intestinal Microecology Group, 1977; Jensen, MacLennan & Wahrendorf, 1982; Wynder & Reddy, 1983; Willet & MacMahou, 1984). Epidemiological studies cannot clarify whether this association is causal, and if so, by which mechanisms these dietary factors exert their action. It has been claimed that a high fat consumption can increase bile acid excretion (Cummings *et al.*, 1978), although the results have been controversial (Brussaard, Katan & Hautvast, 1983). Bacterially degraded bile acids in the large intestine such as deoxycholic acid (DCA) and lithocholic acid (LCA) can act as tumour promoters in chemically induced carcinogenesis in rats (Reddy & Watanabe, 1979;

Cohen & Raicht, 1981; Deschner, Cohen and Raicht, 1981) and can influence colonic mucosal proliferation (Lipkin, 1987). A high dietary fibre intake may protect against colonic carcinogenesis by accelerating intestinal transit, diluting colonic contents and reducing colonic pH (IARC Intestinal Microecology Group, 1977; Kelsay, 1978; Walker, Walker & Segal, 1979; Thornton, 1981; Walker, Walker & Walker, 1986).

The influence of dietary fibre on bile acid metabolism has been studied in several ways. In most studies either biliary bile acid composition or faecal bile acids were measured. Supplementation with bran generally reduced biliary DCA (Pomare & Heaton, 1973; Pomare *et al.*, 1976; McDougal *et al.*, 1978; Tarpila, Miettinen

& Metsäranta, 1978; Watts, Jablonski & Touli, 1978; Wicks, Yeats & Heaton, 1978; Huybregts *et al.*, 1980; Arffmann *et al.*, 1983; Marcus & Heaton, 1986), although in two studies no effect was observed (Huybregts *et al.*, 1980; Arffmann *et al.*, 1983). When separate components of dietary fibre were studied, different effects were observed. Pectin had no effect on biliary bile acids in one study (Miettinen & Tarpila, 1977), but increased biliary DCA by 40% in another study (Hillman *et al.*, 1986). Cellulose reduced the biliary DCA content and lignin had no effect (Hillman *et al.*, 1986). A natural high-fibre diet caused a modest decrease in biliary DCA and an increase in cholic acid (CA) content in gallstone patients (Thornton, Emmet & Heaton, 1976). Bran was used in most investigations in which faecal bile acid measurements were performed. In general it caused a decrease in the concentration of bile acids and an unchanged or modestly increased excretion (Eastwood *et al.*, 1973; Jenkins, Hill & Cummings, 1975; Cummings *et al.*, 1976, 1979; Kretsch, Crawford & Calloway, 1979; Kirby *et al.*, 1981; Reddy *et al.*, 1987). The ratio of secondary to primary faecal bile acids did not change in studies measuring individual bile acids.

If dietary fibre does play a protective role in colonic carcinogenesis, then the most physiological way to gain benefit is to increase the natural fibre content of a common average Western diet. Few data are available on simultaneous measurement of biliary and faecal bile acid profiles in subjects in whom the diet was enriched with fibre from various sources.

Moreover, an increase in fibre intake is often accompanied by a decrease in dietary fat consumption, which can influence bile acid metabolism as well (Cummings *et al.*, 1978;

Brussaard *et al.*, 1983). Furthermore, it is not clear whether changes in bile acid metabolism occur on a stable nutrient consumption. Therefore a controlled study was performed in which healthy volunteers consuming a low-fibre diet increased their fibre intake from various sources during 10 weeks. Simultaneously, a control group consumed their habitual high-fibre diet for the same period. Faecal and biliary acids were measured simultaneously, as were whole-gut transit time and faecal pH.

Subjects and methods

Design, subjects and statistics

Healthy subjects were recruited through advertisement in local newspapers. A detailed dietary history was taken and individual food consumption patterns were calculated. Subjects were then divided into a control group and an experimental group. The control group consisted of 10 subjects with an habitual fibre intake of more than 3.5 g/MJ/day (± 30 g/day). They followed their habitual diet for the full 14 weeks of the study. The experimental group consisted of 12 subjects with a low habitual fibre intake (less than 3 g/MJ/day; < 20 g/day). They maintained this habitual low-fibre diet for a baseline period of 4 weeks. They were then switched to a high-fibre diet (planned fibre intake 4 g/MJ/day) for the next 10 weeks. Measurements were made in weeks -3 and -1, and again in weeks +6 and +10. For each subject, baseline (initial) values (mean of weeks -3 and -1) were subtracted from values obtained in weeks 6 and 10 to show individual changes. In the control group, values in week -1 were subtracted from values in weeks 6 and 10. The mean change in the experimental group was compared to the mean change in the control group using the Wilcoxon rank sum test. Both groups were comparable as to age, sex and relative body weight (Table 1).

None of the subjects had gastrointestinal complaints or had undergone gastrointestinal or biliary surgery. Physical findings were normal in all. Liver function tests, blood glucose, and cholesterol/triglyceride levels were within the normal range. No laxatives or antibiotics had been used at least 6 weeks before entry into the study. The study was approved by the hospital Human Research Review Committee and all subjects gave informed written consent.

Table 1. Baseline data on the subjects studied

	<i>Experimental group</i>	<i>Control group</i>
Number (women/men)	12 (6/6)	10 (5/5)
Age (years)	49.1 \pm 4.1	53.9 \pm 1.8
Range	33-71	41-62
Weight (kg)	71.2 \pm 3.3	74.5 \pm 3.3
Height (m)	1.72 \pm 0.02	1.71 \pm 0.03
Body mass index (kg/m ²)	24.0 \pm 1.0	25.4 \pm 0.6

Values represent mean \pm SEM. No significant differences between experimental and control group.

Diets

The increase in fibre intake in the experimental group was derived from cereals, fruit and vegetables. Compliance in individual food intake was checked regularly by visiting the subjects at home and discussing possible problems with them.

All subjects consumed a common average Dutch diet. During the study period the nature and amount of the daily food intake was noted in a specially designed diary for 7 consecutive days (van Staveren *et al.*, 1982). In the control group this was done three times (in weeks -1, 6 and 10) and in the experimental group twice during the low-fibre period (weeks -3 and -1) and after 6 and 10 weeks of a high-fibre diet (see Fig. 1). Individual food consumption data from the diary were calculated using the National Nutrient Data Base NEVO (1985). Care was taken to keep the intake of all food products constant with the exception of dietary fibre in the experimental group.

Parameters studied

Parameters studied included stool wet and dry weight, intestinal transit time, faecal pH, total and individual faecal bile acid concentration and excretion and biliary bile acid composition. Parameters were studied during the weeks food diaries were kept at home.

Whole-gut transit time. On 6 days before and also during stool collection 20 radiopaque pellets were given daily in order to correct for variation in faecal flow (McPherson Kay *et al.*, 1985). On 2 days before stool collection pellets of a different size and shape were given to calculate the whole gut transit time according to Cummings & Wiggins (1976).

Stool collection and faecal flow correction. Stools were collected at home during 3 days at the end of the 3 (control group) or 4 (experimental group) study weeks. After evacuation faeces were immediately frozen in a container with dry ice (frozen CO₂; -70°C). On arrival at the laboratory samples were radiographed and radiopaque pellets counted to calculate the whole-gut transit time. The total number of pellets ingested in 3 days (60) was divided by the number of pellets excreted, and the amount

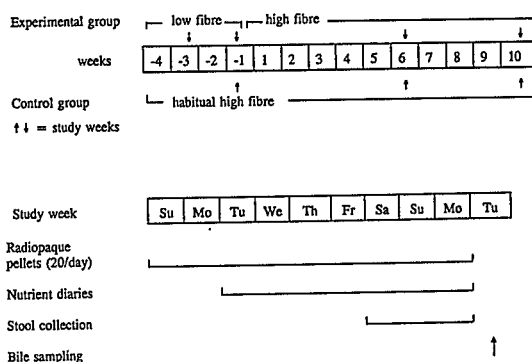


Fig. 1. Experimental design of the study.

of faecal material was multiplied by this value to correct for faecal flow. Samples were then stored at -20°C until analysis.

Faecal pH. The 3-day stool samples were pooled, weighed and homogenized with distilled water. A sample was taken and the pH measured with a pH electrode (Radiometer, Copenhagen, Denmark).

Faecal bile acid analysis. After homogenization of the faeces a sample was freeze-dried and, after extraction, bile acids were measured by gas-liquid chromatography (GLC) as described previously (van Faassen *et al.*, 1985). A modification was included because the individual bile acids were separated on a capillary column (CP Sil 19 CB, Chrompack, Middelburg, The Netherlands). Bile acids were derivatized and injected as trimethylsilyl ethers. Hyodeoxycholic acid was used as internal standard. An automatic solid injection device (Packard Instruments, Delft, The Netherlands) was used to bring the bile acid derivatives on the column. Helium was used as carrier gas. Injection and flame ionization temperature were 300°C. A computerized increment of column temperature from 150°C to 300°C was used to separate the bile acids. Bile acids were eluted at 275°C. In this assay all major bile acids, including the iso-bile acids, can be separated completely.

Biliary bile acid analysis. A fasting duodenal bile sample was obtained at the end of each study week after gallbladder contraction had been induced with cholecystokinin in a dose of 0.5 IDU/kg/body weight. Bile samples were

stored at -20°C until analysis and measured on the same capillary column as the fecal bile acids with 7-keto-deoxycholic acid as internal standard. Bile acids were derivatized and injected as trimethylsilyl ethers. Injection and flame ionization temperatures were 300°C . To separate the bile acids an increment of column temperature from 200°C to 300°C was used. Bile acids were eluted at 280°C .

Results

Since no differences were found in the experimental group for all parameters in the 2 weeks on the low-fibre diet (weeks -3 and -1) the values were averaged and results after 6 and 10 weeks of high-fibre intake compared to this average value, which will be referred to as the 'initial value'.

Dietary assessment

In the control group a stable dietary intake of all food items was achieved, as shown in Table 2. The dietary fibre intake was fixed at about 3.5 g/MJ/day . This was the fibre consumption to which the subjects were accustomed. Body

weight proved to be stable during the study period.

In the experimental group a slight increase in energy intake during the high-fibre period occurred. The dietary fibre intake rose from a mean of 2.3 to 3.7 g/MJ/day after 6 and 3.8 g/MJ/day after 10 weeks. In accordance with the experimental design, more than half of the dietary fibre was derived from vegetables and fruit. The intake of all other nutrients proved to be stable. Body weight did not change during the high-fibre period (Table 2).

Stool weight, whole-gut transit time and faecal pH

Daily stool wet and dry weight, whole-gut transit time and faecal pH proved to be stable in the control group through the study period, as shown in Table 3.

In the experimental group the increase in daily stool wet and dry weight was significant after 10 weeks on the fibre-enriched diet compared to the changes in the control group. The same applied to the decline in faecal pH. With regard to the whole-gut transit time the changes in both groups were not significantly different (Table 3).

Table 2. Nutrient intake and body weight (mean \pm SEM) in the experimental and control groups

	Experimental group (n = 12)			Control group (n = 10) Habitual high-fibre diet		
	Low-fibre diet	High-fibre diet		Weeks		
		Weeks		Initial	6	10
	Initial	6	10	Initial	6	10
Energy (MJ/day)	8.8 ± 0.7	9.4 ± 0.6	9.1 ± 0.6	9.2 ± 0.5	9.0 ± 0.7	9.1 ± 0.7
Dietary fibre ^a						
g/MJ	2.3 ± 0.2	3.7 ± 0.2	3.8 ± 0.3	3.6 ± 0.2	3.5 ± 0.3	3.5 ± 0.3
g/day	20.3 ± 1.7	34.9 ± 2.9	34.6 ± 2.8	32.3 ± 2.5	30.5 ± 2.3	31.1 ± 2.9
% fibres from vegetables/fruit	66 ± 3	58 ± 3	57 ± 3	61 ± 3	58 ± 3	55 ± 3
Cholesterol (mg/day)	349 ± 23	91 ± 23	267 ± 23	310 ± 23	249 ± 24	295 ± 38
Fat (energy %)	37 ± 2	37 ± 1	35 ± 2	37 ± 1	37 ± 1	38 ± 2
Carbohydrates (energy %)	43 ± 2	45 ± 2	46 ± 2	45 ± 2	44 ± 2	46 ± 2
Protein (energy %)	15 ± 1	14 ± 1	15 ± 1	15 ± 1	16 ± 1	15 ± 1
Alcohol (energy %)	5 ± 1	5 ± 2	5 ± 1	4 ± 1	4 ± 1	3 ± 1
Body weight (kg)	71.2 ± 11.3	71.2 ± 11.9	72.1 ± 12.3	74.5 ± 10.3	74.4 ± 10.4	75.4 ± 11.0

^a Dietary fibre measured according to Southgate (1981).

Table 3. Faecal parameters, whole-gut transit time and faecal pH (mean \pm SEM)

	Experimental group (n = 12)		Control group (n = 10)	
	Faecal wet weight	Faecal dry weight	Faecal wet weight	Faecal dry weight
Initial ^a	106 \pm 12	26.9 \pm 1.7	174 \pm 22	36.9 \pm 2.6
Week 6	157 \pm 13	37.2 \pm 2.6	202 \pm 27	42.3 \pm 3.7
Change after 6 weeks	+52 \pm 13	+10.2 \pm 2.1	+27 \pm 24	+5.3 \pm 2.5
Week 10	156 \pm 11	36.2 \pm 2.1	163 \pm 18	36.4 \pm 3.0
Change after 10 weeks	+51 \pm 11*	+9.3 \pm 7.4*	-11 \pm 14	-0.5 \pm 2.3
	Whole-gut transit time	Faecal pH	Whole-gut transit time	Faecal pH
Initial ^a	46.6 \pm 3.6	6.92 \pm 0.11	44.1 \pm 5.7	6.86 \pm 0.07
Week 6	44.2 \pm 3.3	6.80 \pm 0.09	44.8 \pm 4.9	6.84 \pm 0.16
Change after 6 weeks	-2.4 \pm 4.0	-0.12 \pm 0.08	+0.7 \pm 0.8	-0.01 \pm 0.13
Week 10	38.9 \pm 3.6	6.70 \pm 0.10	46.7 \pm 5.6	6.88 \pm 0.14
Change after 10 weeks	-7.7 \pm 3.1	-0.21 \pm 0.16*	+2.6 \pm 3.1	+0.02 \pm 0.09

^a Mean of week -3/-1 in experimental group and week -1 in control group.

* Significantly different from change in control group ($P < 0.05$).

Faecal bile acid analysis

The secondary bile acid concentration (both as $\mu\text{mol/g}$ dry weight and $\mu\text{mol/g}$ wet weight) in the control group showed only minor variations during the study (Table 4). The faecal bile acid excretion increased slightly after 6 weeks and stabilized by week 10. In the individual bile acid pattern no major changes were observed.

In the experimental group the decrease in secondary bile acid concentration was significant by 6 and 10 weeks, compared to the changes in the control group. The total bile acid excretion did not change. The data on individual bile acid concentrations indicate that the decrease after 6 and 10 weeks was significant, compared to changes in the control group. The secondary bile acid fraction did not change in either group (Table 4).

Biliary bile acid composition

As shown in Table 5, a significant increase in biliary DCA and decrease in biliary CA occurred in the control group during the study period. The CDCA content was stable.

In the experimental group the biliary DCA percentage decreased significantly after 6 weeks, compared to the change in the control group, but not after 10 weeks. The CA content did increase significantly after 6 weeks com-

pared to the control group, but at 10 weeks the CA content had returned to the baseline level.

There were no significant differences between both groups with respect to the changes in CDCA content in bile after 6 and 10 weeks (Table 5).

Discussion

Increasing the natural fibre content of the diet seems to be the most physiological and practical way to influence secondary bile acid metabolism and indirectly colonic carcinogenesis. In studies using dietary fibre from several sources (cereals, vegetables and fruit) no effect on total faecal bile acid excretion was found and effects on bile acid concentration were not reported (Raymond *et al.*, 1977; Stasse-Wolthuis *et al.*, 1979). The biliary DCA content was modestly reduced on a natural high-fibre diet, suggesting a decreased formation and/or absorption of DCA in the large bowel; however, in this report faecal bile acids were not measured (Thornton *et al.*, 1976). Our controlled study shows that biliary bile acid composition can be changed on a natural high-fibre diet. These results are in agreement with those of a previous study in gallstone patients (Thornton *et al.*, 1976). However, the reduction of biliary DCA and

Table 4. Individual and secondary faecal bile acid concentration and daily bile acid excretion (mean \pm SEM) in healthy volunteers consuming diets of different fibre content

Bile acid concentration ($\mu\text{mol/g}$ dry weight)	Experimental group (n = 12)				Control group (n = 10)			
	LCA	isoLCA	DCA	isoDCA	LCA	isoLCA	DCA	isoDCA
Initial ^a	7.08 \pm 0.55	3.55 \pm 0.34	10.70 \pm 1.21	3.51 \pm 0.60	4.47 \pm 0.30	2.11 \pm 0.18	8.80 \pm 0.91	2.33 \pm 0.74
Week 6	4.62 \pm 0.52	2.50 \pm 0.25	8.07 \pm 1.16	2.06 \pm 0.33	5.10 \pm 0.29	2.67 \pm 0.44	10.12 \pm 0.79	2.57 \pm 0.61
Change after 6 weeks	-2.5 \pm 0.2*	-1.1 \pm 0.2*	-2.6 \pm 0.7*	-1.4 \pm 0.4*	+0.6 \pm 0.3	+0.5 \pm 0.4	+1.3 \pm 0.6	+0.3 \pm 0.5
Week 10	4.63 \pm 0.46	2.43 \pm 0.23	8.18 \pm 0.94	2.12 \pm 0.36	5.14 \pm 0.36	2.20 \pm 0.22	9.32 \pm 0.99	2.34 \pm 0.66
Change after 10 weeks	-2.5 \pm 0.3*	-1.1 \pm 0.3*	-2.5 \pm 0.6*	-1.4 \pm 0.3*	+0.7 \pm 0.3	+0.1 \pm 0.1	+0.5 \pm 0.8	+0.0 \pm 0.3

Secondary bile acid concentration and total bile acid excretion (mmol/day)	Experimental group (n = 12)				Control group (n = 10)			
	$\mu\text{mol/g}$ dry weight	$\mu\text{mol/g}$ wet weight	total bile acid excretion	% secondary bile acids	$\mu\text{mol/g}$ dry weight	$\mu\text{mol/g}$ wet weight	total bile acid excretion	% secondary bile acids
Initial ^a	24.8 \pm 2.1	6.6 \pm 0.6	0.83 \pm 0.08	97.5 \pm 0.6	17.7 \pm 1.8	4.0 \pm 0.5	0.72 \pm 0.06	97.3 \pm 1.0
Week 6	17.3 \pm 1.8	4.2 \pm 0.5	0.81 \pm 0.09	96.9 \pm 1.4	20.5 \pm 1.2	4.5 \pm 0.3	0.93 \pm 0.14	95.3 \pm 2.1
Change after 6 weeks	-7.5 \pm 0.9*	-2.4 \pm 0.4*	-0.02 \pm 0.08	-0.6 \pm 1.1	+2.8 \pm 0.4	+0.5 \pm 0.1	+0.21 \pm 0.11	-2.0 \pm 1.5
Week 10	17.4 \pm 0.5	4.1 \pm 0.4	0.74 \pm 0.09	95.5 \pm 2.0	19.0 \pm 1.8	4.4 \pm 0.4	0.91 \pm 0.16	95.2 \pm 1.5
Change after 10 weeks	-7.4 \pm 1.1*	-2.5 \pm 0.5*	-0.09 \pm 0.07	-2.0 \pm 1.6	+1.3 \pm 0.3	+0.4 \pm 0.1	+0.19 \pm 0.14	-2.1 \pm 1.3

^a Mean of week -3/-1 in experimental group and week -1 in control group.

* Significantly different from change in control group ($P < 0.05$).

isoLCA: isolithocholic acid; isoDCA: isodeoxycholic acid.

Table 5. Molar percentage of biliary bile acids (mean \pm SEM) in healthy volunteers consuming diets of different fibre content

Bile acid	Experimental group (n = 12)				Control group (n = 10)			
	LCA	DCA	CDCA	CA	LCA	DCA	CDCA	CA
Initial ^a	0.3 \pm 0.3	27.0 \pm 2.4	41.7 \pm 1.7	30.9 \pm 3.2	1.0 \pm 0.3	20.2 \pm 3.6	41.6 \pm 4.2	37.2 \pm 4.3
Week 6	0.2 \pm 0.1	22.9 \pm 2.9	38.7 \pm 1.8	38.1 \pm 3.1	0.8 \pm 0.3	23.6 \pm 3.9	41.4 \pm 3.7	34.2 \pm 4.6
Change after 6 weeks	-0.1 \pm 0.1	-4.1 \pm 1.8*	-3.0 \pm 1.2	+7.2 \pm 2.1*	-0.2 \pm 0.2	+3.4 \pm 3.1	-0.2 \pm 2.5	-2.9 \pm 1.7
Week 10	0.2 \pm 0.1	24.9 \pm 3.4	43.4 \pm 2.5	31.5 \pm 3.3	0.9 \pm 0.3	22.8 \pm 4.7	41.5 \pm 4.8	34.8 \pm 5.4
Change after 10 weeks	-0.1 \pm 0.1	-2.1 \pm 2.1	+1.6 \pm 2.4	+0.6 \pm 2.7	-0.1 \pm 0.1	+2.4 \pm 2.3	-0.1 \pm 3.1	-2.4 \pm 2.5

^a Mean of week -3/-1 in experimental group and week -1 in control group.

* Significantly different from change in control group ($P < 0.05$).

increase in CA content of bile seems to be only transient, since after 10 weeks CA returned to baseline values and the decrease in biliary DCA content diminished compared to the value after 6 weeks. Marcus & Heaton (1986) have shown that administration of a concentrated wheat fibre preparation reduced the proportion of biliary DCA, but that the DCA pool did not change. The input of DCA from the bowel increased. Since the total bile acid pool increased, as did the cholic acid content of bile, these authors assumed that the cholic acid pool increased. If the same effects had occurred in our study, the fall in the molar percentage of biliary DCA could have been explained by an expansion of the cholic acid pool after 6 weeks, thereby reducing the proportion of DCA in bile. However, we did not carry out kinetic experiments. The explanation for the observed effects therefore remains speculative. The changes in biliary bile acid composition were not accompanied by a reduction of the secondary bile acid excretion after 6 weeks, which suggests that secondary bile acid formation was not reduced. These findings are at odds with a previous investigation, in which we demonstrated that lactulose (a non-absorbable disaccharide) can reduce biliary DCA by about 25% and increase the primary bile acid content of the stool to 20%.

This inhibiting effect on DCA formation in the large bowel was probably mediated by acidification of colonic contents (Nagengast *et al.*, 1988). Dietary fibre is only partly digested by the colonic flora (Kelsay, 1978) and, despite the fall in faecal pH in the experimental group, colonic pH probably did not change enough to

inhibit 7α -dehydroxylation of primary bile acids.

The decrease in secondary faecal bile acid concentration (expressed both in dry and wet weight) during extra fibre consumption in the experimental group, compared to the control group, is in agreement with data previously reported in the literature (Eastwood *et al.*, 1973; Jenkins *et al.*, 1975; Cummings *et al.*, 1976; Tarpila *et al.*, 1978; Kretsch *et al.*, 1979; Reddy *et al.*, 1987). However, in contrast to this study bran was used as the main fibre source in most studies. The decrease is caused by the increase in stool output, both in water and dry faecal material. The excretion of bile acids did not change, which is in accordance with some (Eastwood *et al.*, 1973; Walters *et al.*, 1975; Kay & Truswell, 1977; McLean-Baird *et al.*, 1977; Jacobson *et al.*, 1984), but in contrast to other bran studies, in which a dose-related increase was found in faecal bile acid excretion (Jenkins *et al.*, 1975; Cummings *et al.*, 1976, 1979; Spiller *et al.*, 1986).

In conclusion, this study shows that the concentration of the major secondary faecal bile acids can be reduced by adding extra fibre from various sources to the diet. The 7α -dehydroxylation of primary bile acids was probably not inhibited. Whether the observed effects can influence colonic carcinogenesis in a favourable way has yet to be proven. A prospective dietary intervention study in subjects at high risk of developing this disease could elucidate this question.

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