Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial

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Summary

Background Some epidemiological studies have suggested that high dietary intake of calcium and fibre reduces colorectal carcinogenesis. Available data are not sufficient to serve as a basis for firm dietary advice. We undertook a multicentre randomised trial to test the effect of diet supplementation with calcium and fibre on adenoma recurrence.

Methods We randomly assigned 665 patients with a history of colorectal adenomas to three treatment groups, in a parallel design: calcium gluconolactate and carbonate (2 g elemental calcium daily), fibre (3·5 g ispaghula husk), or placebo. Participants had colonoscopy after 3 years of follow-up. The primary endpoint was adenoma recurrence. Analyses were by intention to treat.

Findings 23 patients died, 15 were lost to follow-up, 45 refused repeat colonoscopy, and five developed severe contraindications to colonoscopy. Among the 552 participants who completed the follow-up examination, 94 stopped treatment early. At least one adenoma developed in 28 (15·9%) of 176 patients in the calcium group, 58 (29·3%) of 198 in the fibre group, and 36 (20·2%) of 178 in the placebo group. The adjusted odds ratio for recurrence was 0·66 (95% CI 0·38–1·17; p=0·16) for calcium treatment and 1·67 (1·01–2·76, p=0·042) for the fibre treatment. The odds ratio associated with the fibre treatment was significantly higher in participants with baseline dietary calcium intake above the median than in those with intake below the median (interaction test, p=0·028)

Interpretation Supplementation with fibre as ispaghula husk may have adverse effects on colorectal adenoma recurrence, especially in patients with high dietary calcium intake. Calcium supplementation was associated with a modest but not significant reduction in the risk of adenoma recurrence.

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Introduction

There is clear evidence that diet has a major role in colon carcinogenesis. Some experimental and analytical studies have suggested that the consumption of dietary fibre, vegetables, whole-grain cereals, and calcium may have a protective effect against colorectal cancer[1] and adenomas,[2] but results from epidemiological studies have been inconsistent.[3–6] Adenomas are thought to be precursors of most colorectal cancers in more developed countries and could be a target for primary prevention. Several arguments support the notion that the adenoma-carcinoma sequence is a multistep process.[7] Cancer could be prevented at the stage of adenoma appearance, growth, or transformation into carcinoma. Attractive carcinogenesis hypotheses can be tested in intervention studies, the most appropriate way to assess the feasibility and efficacy of preventive measures. Two intervention studies have provided some evidence of a protective effect of calcium alone or with antioxidants on adenoma recurrence,[8,9] but findings of trials on the effects of a low-fat, high-fibre diet[10] and wheat-bran supplementation have been disappointing.[11] No intervention study has investigated the effects in human beings of soluble fibre such as ispaghula husk, a mucilaginous substance, which has potent antitumour activity in animal models of colon carcinogenesis. The European Cancer Prevention Organisation (ECP) Intervention Study, started in 1991, was a placebo-controlled trial aimed at assessing the efficacy of ispaghula husk and calcium supplementation in the prevention of adenoma recurrence over 3 years.

Methods

Participants

The ECP Intervention Study involved 21 centres from ten countries (Belgium, Denmark, France, Germany, Ireland, Israel, Italy, Portugal, Spain, and the UK). Between 1991 and 1994, we enrolled patients with colorectal polyps who met the inclusion and exclusion criteria.[12] The inclusion criteria were: a complete index colonoscopy showing at least two adenomas or one adenoma of diameter more than 5 mm, based on the diagnosis of the local pathologist; age between 35 and 75 years; no debilitating or life-threatening disease; and ability to follow the study protocol. Reasons for exclusion were: a history of large-bowel disease (familial polyposis coli, ulcerative colitis, or Crohn's disease, colonic resection, or invasive carcinoma in any of the removed polyps); contraindications to calcium or fibre (such as malabsorption syndromes, kidney stones, hypercalcaemia, or treatment with a digitalis glycoside); current calcium treatment that could not be stopped; and fibre supplementation that the patient refused to interrupt. All patients gave written informed consent. The protocol was approved by the regional ethics committee.

Design

We randomly assigned eligible patients to treatment groups after stratification according to centre, in a three-group parallel design. Randomisation was balanced every

six patients: two were allocated the calcium treatment, two the fibre treatment, one the calcium placebo, and one the fibre placebo. The two active treatments were 2 g elemental calcium (calcium gluconolactate and carbonate), administered twice daily in the form of two sachets to be diluted in a glass of water, and 3·5 g ispaghula husk, administered in the form of one sachet of orange-flavoured effervescent granules to be diluted in water and drunk immediately. Two placebos made up of sucrose and of the same excipient as the active treatments were used, one with the appearance and the taste of the calcium supplement (four sachets per day) and the other as one sachet similar to the fibre supplement. Patients, staff in the clinical centre, and study investigators were not aware of the treatment assignments. Treatments were allocated by an independent randomisation centre, which was responsible for checking inclusion and exclusion criteria, for randomisation, and for the preparation and distribution of treatment packages. The randomisation centre agreed to break the treatment code only after the main results had been obtained.

Treatment compliance and side-effects were assessed every 6 months by means of a standard interview. At follow-up visits, participants returned any unused sachets, were encouraged to continue the study, and were given a further 6-month supply of treatment. The degree of compliance was calculated as the number of sachets consumed by the patient during a given period as a percentage of the number that should have been taken during this period. Furthermore, at the 1-year examination, 24 h faecal collections were obtained for measurement of faecal calcium, as an indicator of calcium treatment compliance. 100 mg freeze-dried faeces was mixed with 2 mL concentrated nitric acid in a tightly sealed glass bottle. The bottles were placed in a heating block at 120°C for 1 h. On cooling, 1 mol/L hydrochloric acid (10 mL) was added, then total calcium in the supernatant fluids was measured by atomic absorption spectrophotometry.

The study protocol entailed a follow-up colonoscopy 3 years after the qualifying colonoscopy. At both the initial and 3-year examinations, all parts of the colon had to be thoroughly examined; if the colonoscopy was incomplete, the parts not examined had to be viewed by a further colonoscopy within 3 months. Randomisation was done only after a complete examination had been obtained (see below, second endpoints). The original protocol specified that all polyps should be removed, except for one small polyp (diameter <5 mm) in the sigmoid colon or rectum. At both the initial and the 3-year colonoscopies, the endoscopist numbered the polyp and described its size and location. At the initial examination the endoscopist recorded whether or not it was removed. For polyps left behind at the initial examination, the endoscopist also recorded the distance from the anal margin. These polyps were resected at the 3-year examination. All removed polyps were forwarded to the local department of pathology in numbered containers. To ensure standard pathological diagnosis of polyps removed at both examinations, one numbered slide of each polyp was sent to one of two preassigned experts for assessment of the histological type, architecture, and degree of dysplasia according to a standard protocol. The experts were not aware of the diagnosis made by the local pathologist or of treatment assignment. In cases of disagreement, the diagnosis of the expert pathologists was retained after checking of the discrepancies. Furthermore, when one expert had difficulties in the interpretation of a slide, the doubtful slide was examined by both experts during working sessions specially organised at the annual meetings. Endoscopic examinations between the initial and the 3-year colonoscopy were not recommended unless they were essential to the patient's health. Polyps found at interim colonoscopies were diagnosed only by the local pathologist.

At enrolment and at the end of the study, diet was assessed by a standard, previously validated,[13] questionnaire adapted to the dietary habits of each country. A European food composition table that used data from available food composition tables and additional information from the food industry was established for the purpose of the study. So that each participant was interviewed in a standard way, a strict protocol was set up, including training in Dijon (France) and tests before the start of the study. The interview lasted about 1·5 h. Dietitians were unaware of the treatment assignments. The final interview was undertaken without referral to the initial one.

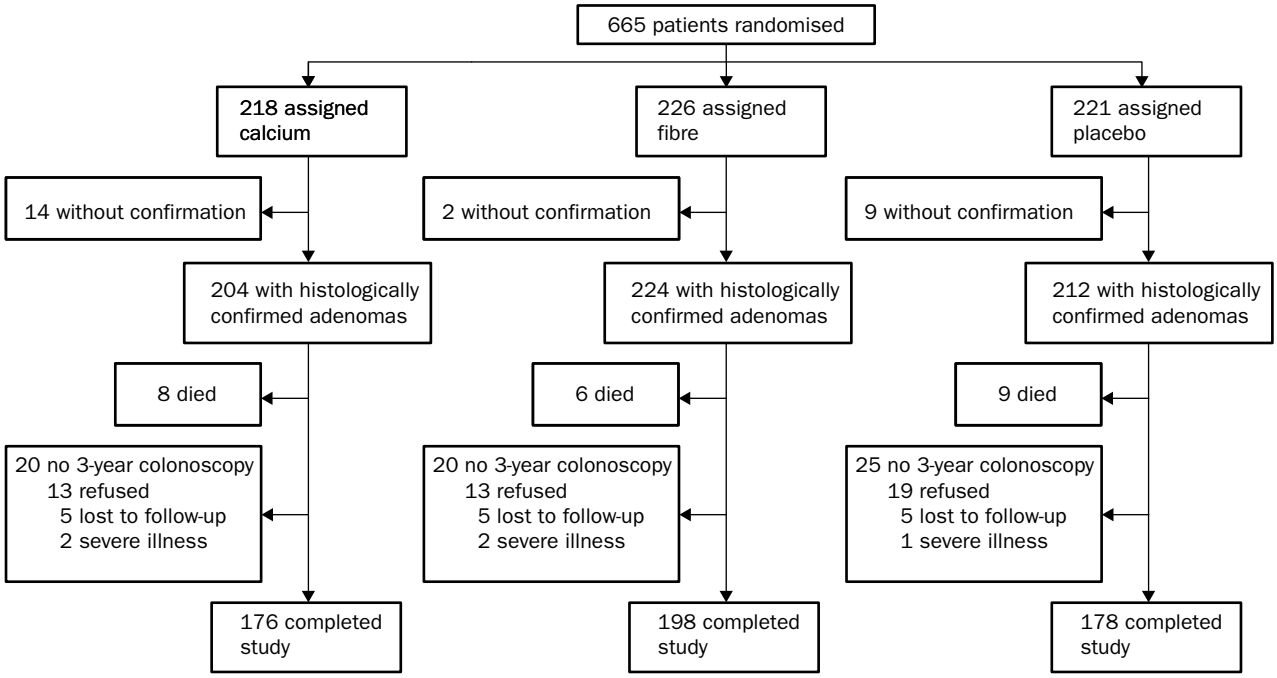
The primary study endpoint was the occurrence of new adenomas at the 3-year colonoscopy. When interim endoscopic examinations were undertaken (13 patients), polyps removed less than 12 months after the qualifying colonoscopy were not counted as endpoints because we could not exclude the possibility that they were present but not seen at the initial examination. This question arose for only one patient, who had one hyperplastic polyp. By contrast, adenomas removed between 1 year and 3 years after the initial colonoscopy were included with those removed at the final colonoscopy (five patients).

The initial protocol also included as a second endpoint the adenoma growth of small polyps (<5 mm) in the sigmoid colon and rectum. This outcome measure was given up because most clinicians in the study centres were reluctant, for ethical reasons, to leave small polyps behind. Only 16 patients had small polyps left behind. These remaining polyps were easily located at the 3-year examination, so they were not counted as recurrent polyps.

Statistical analysis

With the assumption of an annual adenoma recurrence rate of around 10%, the 3-year recurrence rate was estimated to be 27%. The study was initially designed to have at least 90% power to detect an absolute reduction of 10% in the recurrence rate in a two-sided test at 5% significance. 400 participants per group should have been included during an 18-month period. However, recruitment was slower than expected and had to continue for 3 years. The low rate of recruitment was due, in some countries (Germany, Israel), to geopolitical problems resulting in difficulties in obtaining grants. In other countries (mainly in France and in southern European centres), the characteristics of patients recruited in endoscopy units from large hospitals changed over time—increasing numbers of patients were judged ineligible (especially very old or severely ill patients and those who did not speak the country's language). When recruitment was stopped in 1994 for financial reasons, only 665 patients had been randomised. This sample size gave 80% power to detect an absolute difference of 12% in the recurrence rate.

Standard procedures from BMDP software (version 7.0) were used for univariate and multivariate statistical analyses. The main analyses were by intention to treat. For descriptive analysis, differences between treatment groups in qualitative and quantitative variables were tested by χ^2 tests and ANOVA, respectively. Logistic



Trial profile

regression was used to estimate the crude and adjusted risk (odds ratio) of adenoma recurrence associated with the calcium and fibre treatments. Baseline characteristics significantly related to adenoma recurrence were introduced into the regression models as covariates and their interaction with both treatments was systematically tested.

Results

Among the 640 patients who had histologically confirmed adenomas at inclusion, 13 underwent interim colonoscopy (five calcium group, six fibre group, two placebo group) and 552 underwent the 3-year colonoscopy (figure). A complete colon examination was obtained in 539 patients, of whom 21 had undergone a control colonoscopy. In 13 other patients (2·3%), only a limited examination could be obtained. This examination reached at least to the transverse colon for eight patients. The proportion with final colonoscopies did not differ among treatment groups (176 of 204 in the calcium group, 198 of 224 in the fibre group, and 178 of 212 in the placebo group; p=0·41). Of the 88 patients who did not complete the study, 23 died, 15 were lost to follow-up, 45 refused the follow-up colonoscopy, and five developed severe illnesses contraindicating colonoscopy.

There were no significant differences between the three groups in age, sex, history of adenomas, geographical area of recruitment, or in the characteristics of adenomas at inclusion (table 1). The mean dietary intake of energy, lipids, calcium, fibre, carbohydrates, and proteins was similar in the three groups (data not shown).

94 patients stopped the assigned treatment prematurely, in most cases during the first year (table 2), but the proportions who stopped prematurely did not differ significantly between treatment groups. Treatment cessation was primarily due to the occurrence of side-effects (n=50) or to lack of motivation (n=37). Side-effects were reported by 26 of 176 patients in the calcium group, 19 of 198 in the fibre group, and 12 of 178 in the placebo group (p=0·043). Major side-effects such as severe diarrhoea or abdominal pain were observed in 12 patients (six in the calcium group and three each in the fibre and placebo groups). The proportion of poor compliers (compliance <80%) was higher in the calcium group than in the other groups. Analysis of faecal calcium at the 1-year examination showed that the proportion of participants with calcium values above the median of the study sample (24 mg/g) was much higher in the calcium group than in the fibre and placebo groups (105 of 128 *vs* 37 of 134 and 50 of 134, p<0·0001). In the calcium group, the proportion of patients with high faecal calcium values was significantly higher in good compliers than in poor compliers (99 of 108 *vs* six of ten, p=0·009).

During the 3-year study period, at least one adenoma developed in 28 (15·9%) participants in the calcium

	Calcium (n=176)	Fibre (n=198)	Placebo (n=178)
Age (years)*	58·8 (8·8)	59·1 (8·9)	59·3 (8·4)
Sex			
Male	116 (65·9%)	128 (64·6%)	107 (60·1%)
Female	60 (34·1%)	70 (35·4%)	71 (39·9%)
History of adenoma			
No	145 (82·4%)	175 (88·4%)	148 (83·1%)
Yes	31 (17·6%)	23 (11·6%)	30 (16·9%)
Geographical area			
Southern Europe and Israel	34 (19·3%)	40 (20·2%)	37 (20·8%)
Western Europe	72 (40·9%)	86 (43·4%)	70 (39·3%)
Northern Europe	70 (39·8%)	72 (36·4%)	71 (39·9%)
Number of adenomas at inclusion			
One	104 (59·1%)	138 (69·7%)	118 (66·3%)
Two or more	72 (40·9%)	60 (30·3%)	60 (33·7%)
Size of adenomas			
At least one adenoma ⩾10 mm	99 (56·3%)	105 (53·0%)	105 (59·0%)
At least one adenoma ⩾20 mm	36 (20·5%)	25 (12·6%)	30 (16·8%)
Family history of colorectal cancer†			
No	129 (80·6%)	152 (85·4%)	144 (84·7%)
Yes	31 (19·4%)	26 (14·6%)	26 (15·3%)

Data are mean (SD)* or number of patients. †Information on family history was lacking in 44 participants.

Table 1: **Baseline characteristics of patients who completed the study**

	Number of patients			p
	Calcium (n=176)	Fibre (n=198)	Placebo (n=178)	
Stopped treatment				
Total	36 (20·5%)	33 (16·7%)	25 (14·0%)	0·27
During first year	30 (17·0%)	21 (10·6%)	18 (10·0%)	0·09
Compliance*				
<50%	40 (22·7%)	28 (14·1%)	21 (11·8%)	
50–79%	14 (8·0%)	13 (6·6%)	11 (6·2%)	
⩾80%	122 (69·3%)	157 (79·3%)	146 (82·0%)	0·044

*Number of sachets consumed by the patient as a percentage of the number that should have been taken during a given period.

Table 2: **Treatment compliance according to treatment group**

group, 58 (29·3%) in the fibre group, and 36 (20·2%) in the placebo group. One patient in the placebo group was diagnosed with an invasive adenocarcinoma. The risk of recurrence was significantly increased in patients receiving the fibre treatment (odds ratio 1·63 [95% CI 1·01–2·64]), whereas non-significant reduction in risk was found in the calcium group (0·75 [0·43–1·29]; table 3). Adjustment for age, sex, history of adenoma, and number and location of adenomas at inclusion had little effect on these results. Information about family history of colorectal cancer and use of aspirin and non-steroidal anti-inflammatory drugs could be obtained in 508 and 451 patients, respectively. Further adjustment for these variables provided very similar estimates of treatment effects (data not shown). The exclusion of the few participants with interim colonoscopies (among them, four patients in the fibre group and one patient in the calcium group had recurrent adenomas) did not greatly affect these results. The adjusted odds ratio was 0·64 (0·36–1·14; p=0·13) in the calcium group and 1·57 (0·94–2·60; p=0·08) in the fibre group.

Treatment compliance did not significantly influence the effects of calcium or fibre supplementation (table 3).

	Calcium		Fibre	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
All patients				
Crude	0·75 (0·43–1·29)	0·29	1·63 (1·01–2·64)	0·042
Adjusted*	0·66 (0·38–1·17)	0·16	1·67 (1·01–2·76)	0·042
Treatment compliance				
<80% (n=127)	0·53 (0·17–1·72)	0·29	1·06 (0·34–3·33)	0·93
⩾80% (n=425)	0·70 (0·36–1·36)	0·29	1·91 (1·08–3·35)	0·023
Interaction test	p=0·57		p=0·35	
Age†				
<65 years (n=395)	0·67 (0·34–1·35)	0·26	1·50 (0·80–2·80)	0·20
⩾65 years (n=157)	0·72 (0·26–2·01)	0·33	2·24 (0·92–5·47)	0·07
Interaction test	p=0·99		p=0·49	
Sex†				
Men (n=351)	0·58 (0·29–1·18)	0·13	2·05 (1·11–3·78)	0·019
Women (n=201)	1·01 (0·37–2·73)	0·99	1·11 (0·43–2·88)	0·83
Interaction test	p=0·45		p=0·28	
Adenoma history†				
No (n=468)	0·66 (0·35–1·27)	0·21	1·76 (1·01–3·09)	0·044
Yes (n=84)	0·85 (0·24–2·99)	0·79	1·77 (0·49–6·38)	0·37
Interaction test	p=0·93		p=0·77	
Adenomas at inclusion†				
One (n=360)	0·50 (0·21–1·18)	0·11	1·73 (0·90–3·34)	0·096
Two or three (n=192)	0·85 (0·38–1·89)	0·68	1·60 (0·72–3·55)	0·24
Interaction test	p=0·39		p=0·93	
Adenoma of right colon at inclusion†				
No (n=438)	0·97 (0·50–1·89)	0·92	1·95 (1·06–3·56)	0·028
Yes (n=114)	0·26 (0·08–0·84)	0·019	1·19 (0·44–3·20)	0·73
Interaction test	p=0·054		p=0·32	

*Adjustment for age, sex, adenoma history, and number and location of adenomas inclusion. †In analyses by subgroups, adjustment for all variables listed except for the subgrouping variable.

Table 3: **Risk of adenoma recurrence associated with fibre or calcium treatment**

	Calcium		Fibre	
	Odds ratio (95% CI)*	p	Odds ratio (95% CI)*	p
Baseline dietary calcium†				
Below median	0·51 (0·22–1·18)	0·11	1·04 (0·49–2·18)	0·92
Above median	0·65 (0·43–2·30)	0·99	2·81 (1·33–5·92)	0·005
Interaction test	p=0·12		p=0·028	
Baseline dietary fibre†				
Below median	0·80 (0·34–1·87)	0·60	1·78 (0·83–3·79)	0·13
Above median	0·65 (0·29–1·46)	0·29	1·77 (0·87–3·61)	0·11
Interaction test	p=0·90		p=0·80	
Baseline dietary fat†				
Below median	0·63 (0·27–1·45)	0·27	1·50 (0·72–3·13)	0·27
Above median	0·77 (0·33–1·76)	0·53	2·08 (1·00–4·36)	0·047
Interaction test	p=0·74		p=0·17	

*Adjusted as in table 3. †Baseline dietary assessment was missing in 29 patients; median dietary intake 918 mg per day for calcium, 19 g per day for fibre, and 87 g per day for total fat.

Table 4: **Risk of adenoma recurrence associated with fibre or calcium treatment according to baseline intake of calcium, fibre, and total fat**

There was no significant interaction between the treatment effects and age, sex, history of adenomas, or characteristics of adenomas at inclusion. However, there was a trend for a modifying effect of the location of adenoma at inclusion on the risk of recurrence associated with calcium treatment (interaction test, p=0·054). The calcium treatment was associated with a significant reduction in the recurrence risk when adenomas of the right colon were present at inclusion; there was no evidence of benefit in patients without right-colon adenomas.

There was no significant modification of the treatment effects by baseline intake of fibre or fat (table 4). However, there was some evidence that baseline dietary calcium intake might interfere with the effects of fibre treatments: the adverse effect of fibre treatment was significantly stronger in patients with dietary calcium intake above the median than in those with dietary calcium intake below the median (interaction test, p=0·028). The beneficial effects of calcium treatment were more pronounced, though not significantly so, in patients with dietary calcium intake below the median than in those with dietary calcium intake above the median (interaction test, p=0·12).

Dietary assessment was completed at both initial and final examinations among 397 patients; 87 of them had developed at least one new adenoma. In these patients, the odds ratios for recurrence were 0·74 (0·37–1·48; p=0·39) for calcium treatment and 2·24 (1·24–4·03, p=0·007) for fibre treatment after adjustment for age, sex, adenoma history, and number and location of adenomas at inclusion. In the three treatment groups, there was a general trend towards a decrease in dietary intake after 3 years without any significant differences between treatment groups (table 5). However, although dietary fibre intake decreased in the calcium and placebo groups, it increased slightly in the fibre group. Further adjustment for 3-year changes in dietary intake of total calories, calcium, and fibre did not change the effects of calcium and fibre treatments on adenoma recurrence. The odds ratio for recurrence was 0·71 (0·35–1·45; p=0·35) for calcium treatment and 2·27 (1·25–4·11; p=0·006) for fibre treatment.

70 patients developed at least one adenoma with a diameter of 0·5 mm or larger. The adjusted odds ratio for these larger adenomas was 0·76 (0·37–1·60) for calcium treatment and 1·86 (0·99–3·50) for fibre treatment. Only a few patients developed adenomas with a diameter of 10 mm or larger (eight fibre group, five calcium group,

Daily intake	Baseline assessment				3-year assessment			
	Calcium (n=116)	Fibre (n=145)	Placebo (n=136)	p	Calcium (n=116)	Fibre (n=145)	Placebo (n=136)	p
Energy (MJ)	9·40 (2·78)	9·57 (3·14)	9·77 (3·16)	0·62	9·25 (3·01)	9·49 (3·17)	9·16 (2·90)	0·64
Calcium (mg)	944 (364)	985 (396)	1023 (404)	0·28	917 (358)	951 (371)	979 (398)	0·44
Fibre (g)	20·1 (7·1)	21·4 (9·3)	21·7 (8·5)	0·25	19·4 (6·7)	21·9 (10·0)	20·6 (7·8)	0·06
Total fat (g)	88·3 (28·3)	91·7 (34·6)	92·3 (30·5)	0·56	86·8 (30·9)	88·8 (30·1)	86·5 (26·6)	0·78
Carbohydrates (g)	248 (90)	255 (102)	259 (109)	0·71	245 (97)	255 (105)	244 (101)	0·59
Proteins (g)	83·1 (24·6)	86·1 (27·2)	87·5 (26·9)	0·42	82·1 (27·6)	85·8 (28·6)	82·9 (25·4)	0·50

Table 5: **Mean (SD) baseline and 3-year daily intake among participants who completed the study**

and four placebo group) or tubulovillous adenomas (seven in the fibre group, five in the calcium group, and three in the placebo group). No villous adenomas were found at the 3-year examination. New adenomas developed on the left colorectum (including and distal to splenic flexure) in 81 patients and on the right colon (proximal to the splenic flexure) in 62. The adjusted odds ratio for recurrence on the left colorectum was 0·88 (0·46–1·69) for calcium treatment and 1·70 (0·95–3·00) for fibre treatment. The adjusted odds ratios for new adenomas on the right colon were 0·48 (0·22–1·07) and 1·39 (0·72–2·68), respectively.

Discussion

This randomised intervention study showed that calcium supplementation for 3 years had a slight but not significant beneficial effect on adenoma recurrence, whereas fibre supplementation by a mucilaginous substance resulted in a significant increase in the recurrence rate.

The rate of final colonoscopy was high and similar in all treatment groups, and the baseline characteristics of the patients who completed the study did not differ between treatment groups. We do not believe, therefore, that our results can be explained by selection biases. As in most nutritional intervention studies, a proportion of patients prematurely stopped treatment or consumed only part of the prescribed treatment. Overall, about 77% of the patients reported that they had taken more than 80% of the prescribed sachets and our objective assessment of treatment compliance (faecal calcium analyses) gave no evidence that compliance was exaggerated by patients. Treatment compliance was similar in the fibre and placebo groups. On the other hand, the lower compliance in the calcium group could have reduced the statistical power of the study and may partly explain the weakness of the association between calcium treatment and adenoma recurrence. Furthermore, the number of participants was lower than planned, contributing to a decrease in statistical power.

The adverse effect of the ispaghula fibre supplementation was observed overall and in most subgroups of patients, which suggests that it cannot be attributed to chance alone. This conclusion is supported by the finding that fibre treatment had little effect in participants with poor compliance. The increased risk of adenoma recurrence was found for both small and larger adenomas and without noticeable variations according to the colon subsites. Furthermore, there was no evidence that it could be explained by differential changes in dietary intake by treatment groups during the trial. Our findings do not accord with the hypothesis of a protective effect of fibre on the risk of colon cancer. A review of the evidence from 37 observational studies showed that only half were strongly or moderately supportive of the protective effect of fibre against colon cancer.[14] A meta-analysis of 13 case-control studies of colon cancer was compatible with a beneficial effect of dietary fibre,[15] whereas more conflicting results emerged from large prospective studies on colorectal cancer[3,4] and adenomas.[4,16]

These conflicting findings reflect the complexity of nutritional epidemiology and emphasise the potential usefulness of intervention studies. The interventional approach has the advantage of avoiding measurement errors inherent in dietary assessment and allows adequate control for the confounding factors to and precise definition of time of exposure. Published randomised trials on the effect of fibre supplementation on adenoma recurrence have had disappointing results.[10,11,17–19] None found a significant overall difference between treatment groups. The Australian Polyp Prevention Trial actually suggested an increased risk of recurrence for adenomas of any size;[19] a significant reduction in the rate of recurrence of large adenomas (⩾10 mm) was found only when a low-fat diet was combined with wheat-bran supplementation. However, this result needs to be interpreted cautiously because of the small number of patients involved. Despite the lack of an overall effect of wheat-bran supplementation on adenoma recurrence, a larger trial also suggested an adverse effect on the number of recurrent adenomas.[11] In our study, there was no differential effect of ispaghula fibre according to the size of recurrent adenomas, and this effect was not modified by the dietary intake of fat. However, because very few patients developed large adenomas, we cannot exclude the possibility of a beneficial effect of ispaghula husk on later stages of carcinogenesis, such as adenoma growth and malignant transformation.

The reasons why fibre supplementation by a mucilaginous substance may have adverse effects on adenoma recurrence are unclear. Up to now, dietary fibre has been postulated to be protective against colon carcinogenesis by increasing stool bulk, by decreasing transit time and hence the contact of carcinogens with the colonic epithelium, by binding bile acids and carcinogens, by decreasing colonic pH, or by increasing the production of short-chain fatty acids.[20] We chose ispaghula husk because it is known to have stool-bulking properties and to decrease faecal pH. Furthermore, it is widely used as a laxative agent and only negligible side-effects have been reported. In animal models of colon carcinogenesis, this agent has been one of the most effective soluble fibres in tumour prevention.[21,22] However, other soluble fibres such as pectin, guar gum, agar, and carrageenan increase tumour development in rodents.[21] The detrimental effects of soluble fibre in animal experiments could be due to an increasing production of short-chain fatty acids by bacterial fermentation and an excessive acidification, which may stimulate proliferation of epithelial cells.[21,23] However, the significance of hyperproliferation in relation to the carcinogenesis process is unclear.

The role of dietary calcium intake in the prevention of colorectal cancer and adenomas is debated.[5,6] A recent meta-analysis of 24 case-control and cohort studies did not support the hypothesis of substantial protection against colorectal neoplasia.[5] Most previous clinical trials on calcium supplementation have dealt with intermediate biomarkers of colorectal carcinogenesis. The results of studies on rectal epithelial-cell proliferation have been

conflicting, showing a beneficial effect of calcium in some studies but not in others.[24] A reduction in faecal concentrations of total and secondary bile acids has been observed in some studies[25] but not in others.[26,27] Our overall results did not reach statistical significance, probably because of a lack of power. However, they are consistent with those of one previous trial that showed a significant reduction in adenoma recurrence after 4 years of calcium supplementation.[8] Another trial also reported that a mixture of calcium and antioxidants had a beneficial effect on adenoma recurrence, though not on adenoma growth;[9] the effects of calcium could not be disentangled from those of antioxidants. Calcium may protect against colon carcinogenesis by binding secondary bile acids and fatty acids to form insoluble soaps in the bowel lumen, thus reducing their proliferative effect on colonic cells.[28] Changes in bile-acid metabolism could selectively increase the risk of right colon cancer.[29] Interestingly, our results suggest that calcium supplementation may be particularly beneficial in patients with low dietary calcium intake and in those who initially had adenomas on the right colon. Furthermore, in contrast to the fibre supplementation, calcium treatment seemed to have beneficial effects whatever the degree of treatment compliance. Although this finding must be interpreted cautiously because of the small sample size, it suggests that even low doses of calcium and a short duration of treatment might be effective in the prevention of adenoma recurrence.

Our study was not designed to examine the interaction between calcium and fibre supplementation. We have no evidence that dietary fibre intake may interfere with the effects of calcium supplementation. On the other hand, we found that the adverse effect of ispaghula fibre supplementation was significantly stronger in patients with a high dietary calcium intake than in those with a low calcium intake. This finding was unexpected, and we cannot rule out that it was due to chance alone. In a previous controlled study on faecal bile acids in patients with colorectal adenomas, the combined effect of high-dose fibre and high-dose calcium treatment was less than the effects observed for each taken alone.[25] One explanation for our puzzling finding is that ispaghula husk fibre binds more strongly to calcium than to faecal bile acids, so secondary bile acids can exert toxic effects on the colonic mucosa. We cannot yet say whether the adverse effects of ispaghula husk should be ascribed to mucilages or to nutritional characteristics specific to our European population (high dietary calcium intake). However, our results emphasise the complexity of dietary interventions. Many nutritional factors, as well as other environmental or genetic factors, should probably be taken into consideration before supplements are added to foods.

We cannot draw any conclusions about other types of fibre or the effects of fibre supplementation on later stages of carcinogenesis. However, our study, along with the two American trials,[10,11] suggests that low-fat, high-fibre diet and supplementation with wheat-bran fibre or ispaghula husk may not be effective strategies for the prevention of colorectal adenoma recurrence. However, our findings should not prevent recommendations for high consumption of vegetables, fruits, and cereals, because this approach has potentially beneficial effects on other chronic disease, especially coronary heart disease.

Contributors

C Bonithon-Kopp coordinated the collection of data, did statistical analysis, and wrote the first draft of the paper. O Kronborg, A Giacosa, and U Räth were involved in the study design, in the coordination of data collection in their country, and in the revision of the report. J Faivre was the principal investigator who initiated and coordinated the running of the trial, and contributed to the writing of the paper.

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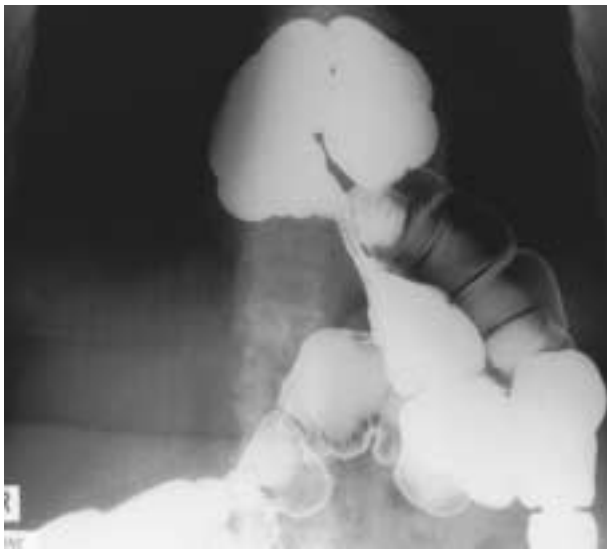
Clinical picture

Constipation and hiatus hernia

Garrett Smith, Mary Dempsey, Gregory Falk



A 65-year-old woman presented with constipation of 4 weeks duration. She complained of no foregut symptoms. A barium enema revealed herniation of transverse colon through a large paraoesophageal hiatus hernia (PHH). This defect was repaired and her symptoms resolved. Patients with large PHH may present with various symptoms, most typically retrosternal and epigastric pain and reflux. The presence of a large mediastinal mass could lead to these symptoms mimicking primary cardiorespiratory pathology, and thus to delay in diagnosis. The complications of these hernias are life-threatening and all patients with symptoms should be considered for repair, which can generally be done laparoscopically.

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