Effect of fat, fibre, and beta carotene intake on colorectal adenomas: Further analysis of a randomized controlled dietary intervention trial after colonoscopic polypectomy

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Randomized controlled trials of prevention targeting the biologically relevant intermediate end-points in the adenoma-carcinoma sequence offer important and unusually valid information in a much shorter time frame than if cancer is used as the end-point. We performed a randomized, partially double-blind, placebo-controlled factorial trial to assess whether the following would reduce the incidence of colorectal adenomas in patients after colonoscopic polypectomy for adenomas: (i) a reduction in fat to levels recommended for the prevention of colorectal cancer; (ii) a daily supplement of wheat bran (25 g); or (iii) daily beta carotene (20 mg) supplements. Among the 424 patients who entered into the trial, complete outcome data were collected from 390 at 24 months and from 306 at 48 months. As previously reported, although low fat and added bran had no effect on small adenomas, there was a reduction in the risk of large adenomas in the subgroup with both low fat and added bran. Analyses of outcome in good and poor compliers with the interventions show outcomes consistent with the earlier analyses. In relation to low fat and bran, gender differences were found in the risk of adenomas of any size, most of which were small, but not in adenoma growth as indicated by large adenomas. Our results are consistent with the hypothesis that dietary fat and bran influence, possibly via the metabolism of bile acids, the growth of small adenomas to large adenomas, but have no effect on the incidence of new small adenomas. The latter may be more directly influenced by non-dietary, possibly genetic, factors.

Key words: antioxidants, therapeutic use, carotene, colonic polyps, diagnosis, prevention, control, colorectal neoplasms, dietary fibre.

Introduction

Colorectal cancer develops, in the main, through an adenoma-to-carcinoma pathway, characterized by an accumulation of mutations in oncogenes and tumour suppressor genes. A hyperproliferative mucosal state may precede this. Interventions that can favourably influence these stages in the carcinogenic process promise prevention of malignancy. Randomized controlled trials (RCT) of prevention targeting these biologically relevant intermediate end-points offer important and unusually valid information in a much shorter time frame than if cancer is used as the end-point.

Four RCT of a dietary fibre intervention using adenomatous polyps as the end-point have reported results to date. The De Cosse *et al.* familial adenomatous polyposis (FAP) trial demonstrated a reduction in rectal adenoma numbers in patients randomized to wheat bran (22.5 g fibre supplement), and antioxidant Vitamins C (4 g) and E (400 mg) but only after 24 months and only when analysed on an actual intake basis.[1]

The Toronto Polyp Trial in patients after polypectomy for sporadic adenomas showed no effect of a low fat (< 20% energy as fat), high fibre (total 50 g/day) diet on new adenoma occurrence as assessed by the proportion of patients in the trial who developed one or more adenomas during the average 2-year follow-up.[2] Adenoma size was not considered.

A multicentre USA trial of wheat bran is in progress. Preliminary results of faecal bile acids show a significant reduction in the putatively carcinogenic secondary bile acids especially with the wheat bran intervention.[3] Polyp data are as yet unavailable.

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The Australian Polyp Prevention Project was planned because of the inconclusive epidemiological evidence regarding dietary factors. Because a randomized trial with cancer as the outcome would have been too large to be feasible, the trial was conducted on patients under surveillance for further neoplasia following colonoscopic removal of colorectal adenomas.

The preventive measures assessed in our trial were fat reduction, increased dietary fibre as a wheat bran supplement, and capsules of beta carotene. At the initiation of the trial we judged these interventions to give the optimal balance of likely efficacy with high safety. The trial aimed to assess the effects on the incidence of adenomas of the following: (i) reducing fat to below the 30% level recommended in National Research Council guidelines for cancer prevention:[4] we targeted 25%; (ii) increasing wheat bran intake (25 g daily); and (iii) supplementing with beta carotene (20 mg daily). We have previously reported design and implementation,[5] adenoma outcomes,[6] compliance,[7] changes in serum carotenoids,[8] and changes in serum cholesterol in relation to MN blood group.[9] This paper analyses outcomes of adenomas in relation to sex and level of compliance.

Methods

The design and methods have been presented in detail elsewhere.[5,6]

Subjects

Fundamental eligibility criteria for patients were age (30–74 years); confidence by the colonoscopist following colonoscopy that all polyps had been removed, that the caecum was reached, and that the quality of examination was not compromised by spasm or faecal residue in each segment of the colon; histology report of at least one adenoma; and signed informed consent. Both new patients and patients seen at a surveillance colonoscopy following prior polypectomy were eligible. Patients otherwise considered appropriate were excluded if they had intestinal and other diseases or conditions. Eligible patients were recruited in gastrointestinal units at collaborating centres in Brisbane, Melbourne and Sydney. We prospectively documented 2780 colonoscopies with reported polyps between October 1985 and April 1988: 559 were definitely eligible on the basis of histological report of at least one adenoma and confidence by the colonoscopist of a polyp free colon. Of these, 424 (76%) were recruited.

Study design and interventions

The three interventions were tested in a randomized trial with a 2 × 2 × 2 factorial design. Fat was to be reduced through dietary counselling to a target 25% of total energy (with at most 30%) and was compared with an unmodified diet with respect to fat. Fat reduction was achieved by not adding butter or margarine to foods at the table, by not eating visible fat on meat, by avoiding fried foods and by use of low fat dairy products, but not through major changes to the diet that would affect other household members. Red meat was not excluded in counselling. The fibre supplement consisted of 25 g of finely milled raw wheat bran used for the manufacture of All-Bran by Kelloggs (Australia) Pty Ltd, and containing approximately 11 g dietary fibre. This was added to the diet and compared with nil bran supplement. Finally, all patients took a capsule daily from calendar packs, either 20 mg of beta carotene or an identical-looking placebo supplied by F Hoffmann-La Roche Ltd, Basel, Switzerland.

Eight distinct combinations of interventions were thus available for comparison, with one-half of patients on any one of the three main interventions, one-quarter on any two of the interventions, and one-eighth on the combination of all three. Patients recruited in the first 6 months of the trial and randomized to beta carotene were given placebo capsules until government approval to use this preparation of beta carotene was obtained. Other interventions were not affected. Thus, among patients with a 24-month surveillance colonoscopy, 98% of those randomized to beta carotene had at least 12 months on beta carotene and 74.2% had at least 18 months.

Sample size and randomization

After informed consent was obtained, patients were randomized to one of the eight diet intervention strategies. To make the groups as similar as possible with respect to factors associated with adenoma occurrence, prerandomization stratification was undertaken by age (less than 55 years or 55 years and older), city (Brisbane, Melbourne or Sydney) and surveillance status (initial or follow-up colonoscopy).

Initial dietary assessment and counselling

On recruitment, patients were asked to complete a self-administered 4-day food diary and a comprehensive quantitative food frequency questionnaire asking about intake in the previous 12 months. The diary incorporated two weekdays and the weekend. Initial counselling by a dietitian was based on analysis of the 4-day diary.

Demographic and medical information

These included sex; date and place of birth; height; weight; marital, educational and occupational status; and medical history details.

Monitoring of compliance

Compliance with low fat and bran interventions was monitored by telephone by the dietitian 1 week after counselling and thereafter at regular 3-monthly contacts. These contacts alternated between phone calls and interview and involved the dietitian asking for a detailed recall of intake in the previous 24 h and an approximate intake of food in the previous week. This information was also used for further counselling. Because of the potential for reporting bias to the counselling dietitian, an independent assessment of dietary compliance was based on 4-day diaries, with estimated amounts, administered by a research nurse at recruitment (prior to dietitian contact) and thereafter every 6 months over a 2-year period for all patients. At the same time capsule counts were done and blood was taken by the nurse to measure beta carotene, retinol and cholesterol.

Duration of the trial

Patients were initially recruited for a 24-month trial, although this was subsequently extended in 78.5% of patients to 48 months.

Outcome measures

Surveillance colonoscopy was performed at 24 and 48 months with colonoscopists blinded as to intervention. The location, number and size of all polyps were recorded. Size was estimated by calibration with the open biopsy forceps at the time of colonoscopy. Those polyps retrieved were sent for histology and were subsequently reviewed centrally by the pathologist (RCN), who was blinded as to the intervention status and who also subjectively graded dysplasia in adenomas. Where a colonoscopy was indicated prior to the routine 2-year colonoscopy, histology was recorded on all polyps found in order to be later aggregated with 24 and 48 month colonoscopy data.

Statistical methods

Analyses were based on intention to treat (i.e. on the initial randomization) and included all patients with outcome information irrespective of whether they remained in the trial or the extent of their compliance. Only patients with a colonoscopy at 48 months were included in the 48-month results. Logistic regression was used to estimate the effect of the three dietary interventions simultaneously and to allow for the effect of potential confounders. Models were fitted using EGRET. Estimates of effect are quoted as odds ratios with 95% confidence intervals for the true values based on maximum likelihood estimates of standard error.

Results

Randomization among the eight groups was apparently successful with the eight groups being similarly distributed with respect to demographic, dietary and other variables.[6] Central pathological review failed to confirm an adenoma for 13 of the 424 patients originally considered eligible and recruited to the study. Of the remaining 411, no information on surveillance colonoscopy at 24 months was available for 21, including eight who died and nine who refused to continue. The following results are therefore based on 390 patients (94.9% follow-up) at 24 months and 306 patients at 48 months.

Multivariate analysis found that none of the interventions showed a significant association with total adenomas at the 24- or 48-month follow-up, although with the low fat intervention the odds ratios for large adenomas were 0.4 and 0.3 with confidence limits of 0.1–1.1 and 0.1–1.0, with P-values of 0.06 and 0.05, respectively.[6] Wheat bran appeared to be moderately protective against the risk of moderate plus severe dysplasia, though not significantly (odds ratios and confidence limits of 0.6 (0.2–1.6) and 0.7 (0.2–2.0) at 24 and 48 months). Interactions were found for the outcome of large adenomas between low fat and added bran, there being nil large adenomas in the subgroup with low fat plus added bran.[6] Logistic regression analysis was used to investigate the effects of the low fat and bran interventions and showed the interaction between the low fat and bran interventions to be significant at the 5% level. The analytic model included all three interventions together with potential confounders.

To evaluate the impact of compliance on the estimated effect of the study interventions, outcomes in patients with evidence of high compliance (80% or better) with each intervention in the first 24 months of the trial were compared with those with evidence of less compliance (Table 1). With participants randomized to both low fat and bran interventions there was a slightly higher proportion of small adenomas among good (high) compliers, whereas there were fewer large adenomas and adenomas with moderate or severe dysplasia among good compliers. With beta carotene, there was a higher proportion of both small and large adenomas among good compliers, and a lower proportion with dysplasia. None of these differences was statistically significant.

Although there were no significant interactions among the three interventions for the outcome of an adenoma of any size, there was an interaction between sex and bran intervention ($P < 0.025$). Analyses are presented separately for men and women (Table 2). While all confidence intervals by sex overlap, the point estimates of the odds ratios for total new adenomas were increased in women but not in men in relation to low fat intervention, but this was reversed for added bran. The risk of large adenomas with low fat and with added bran was reduced in both men and women; the reduced risks were of borderline statistical significance for low fat in males only at 24 months.

Discussion

The analyses of outcome in relation to level of compliance considered each intervention singly without adjusting for other interventions. Thus, the placebo group, approximately half of all subjects, comprised 75% assigned to low fat and/or added bran. Low compliers for placebo capsules are likely to have been low compliers for low fat and/or bran. Thus, in the placebo group the differences in outcome of small and large adenomas between low and high compliers are consistent with those in the low fat and bran groups (Table 1). Although

Table 1. Patients with adenomas at 24 months by allocated intervention and expressed by compliance with the intervention

	Intervention							
	Fat reduction*		Bran supplement*		Beta carotene*		Placebo capsule*	
	Poor	Good	Poor	Good	Poor	Good	Poor	Good
No. patients	116	79	90	103	37	161	31	161
Adenoma outcome								
Nil	92	60	69	79	29	119	24	132
< 10 mm (%)	20 (17.2)	18 (22.8)	17 (18.9)	21 (20.4)	7 (18.9)	33 (20.5)	5 (16.1)	23 (14.3)
≥ 10 mm (%)	4 (3.4)	1 (1.3)	4 (4.4)	3 (2.9)	1 (2.7)	9 (5.6)	2 (6.5)	6 (3.7)
Moderate or severe dysplasia present (%)	8 (6.9)	3 (3.8)	5 (5.6)	2 (1.9)	2 (5.4)	7 (4.3)	4 (12.9)	7 (4.3)

*Evidence of compliance with intervention target at least 80% of the time was defined as 'good compliance' while less than 80% of the time was defined as 'poor compliance'.

Table 2. Neoplasia at 24 and 48 months: odds ratios (and 95% confidence intervals) for the effects of the three interventions, by sex

Outcome	Sex	Low fat	Bran	Beta carotene
24 months[a]				
Any adenoma				
	Male[b]	0.7 (0.4, 1.3)	2.0 (1.1, 3.8)	1.2 (0.6, 2.2)
	No. adenomas/No. subjects	30/139	36/132	33/132
	Female[b]	1.7 (0.7, 4.5)	0.6 (0.2, 1.5)	3.2 (1.1, 9.2)
	No. adenomas/No. subjects	13/56	9/61	17/66
Adenoma ≥ 10 mm				
	Male[b]	0.2 (0.1, 1.0)[c]	0.8 (0.2, 2.9)	1.0 (0.3, 3.3)
	No. adenomas/No. subjects	3/139	5/132	6/132
	Female[d]	0.9 (0.1, 6.0)	0.5 (0.1, 3.1)	2.4 (0.4, 15.4)
	No. adenomas/No. subjects	2/56	2/61	4/66
48 months				
Any adenoma				
	Male[b]	0.7 (0.4, 1.2)	1.8 (1.0, 3.4)[d]	1.1 (0.6, 2.0)
	No. adenomas/No. subjects	34/110	39/104	38/108
	Female[b]	1.8 (0.6, 4.9)	0.7 (0.3, 1.9)	2.9 (1.0, 8.7)
	No. adenomas/No. subjects	12/41	10/46	16/48
Adenoma ≥ 10 mm				
	Male[b]	0.2 (0.1, 1.0)[c]	0.9 (0.2, 3.0)	1.9 (0.5, 7.2)
	No. adenomas/No. subjects	3/110	5/104	8/108
	Female[d]	0.5 (0.1, 6.1)	0.5 (0.0, 4.2)	6.0 (0.5, 77.1)
	No. adenomas/No. subjects	1/41	2/46	4/48

[a]Number of patients for each model based on patients with data for all covariates in model; [b]adjusted for the number of adenomas at entry colonoscopy, number of adenomas prior to study entry and history of LBC in first degree relatives; [c]$P = 0.05$; [d]adjusted as for model b, but excluding adenomas prior to entry in order to fit the model. Numbers in parentheses represent 95% confidence intervals.

t statistically significant, this analysis in relation to compliance is consistent with the results of other analyses of outcome, especially of large adenomas in the low fat and added bran and beta carotene intervention groups.

As with previous analyses there was no apparent effect of the interventions on the occurrence of small adenomas.[6] The absence of large adenomas in the subgroup with low fat plus added bran is consistent with the hypothesis that dietary fat and bran influence, possibly via the metabolism of bile acids, the growth of small adenomas to large adenomas, but have no effect on the incidence of new small adenomas.[10] The latter may be more directly influenced by non-dietary, possibly genetic factors.

During the trial measures based on capsule counts and short-term recall indicated that compliance was good to excellent in all arms of the trial (median compliance of individuals averaged 95% or greater for each). This will be reported in detail elsewhere. In summary, a sustained average fold rise in serum beta carotene confirmed the high uptake of this intervention. In the bran intervention group, the diet diary data suggest that the median increase over baseline was about 7 g dietary fibre per day. Changes in the low fat intervention group are more difficult to interpret, with diet diary data showing an apparent median 19 g per day decrease in intake across the first 2 years. However, given the parallel fall in reported energy intake, the absence of substantial weight loss in this group suggests that this figure exaggerates the true decline. Nevertheless, despite the imprecision of measures of compliance, we found lower rates of large adenomas among those estimated to be good compliers with fat and bran interventions. To us, this adds further support to the intention to treat data, indicating protective effects of low fat and added bran.

The gender differences (Table 2) in the incidence of adenomas of all sizes, most of which are small, are unexplained. For fat they are in the opposite direction to those in the Toronto trial which analysed total incident adenomas and did not present separate analyses of large adenomas.[2] However, their outcomes in relation to bran are consistent with our results: lower odds ratios in females. We found no gender differences, for low fat and added bran interventions, in adenoma growth as indicated by large adenomas (Table 2). This is consistent with the hypothesis that non-dietary factors influence the incidence of small adenomas, and dietary factors have a bearing on adenoma growth.

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