Frontiers in Gastrointestinal Research
Editor: P. Rozen, Tel Aviv

Reprint
Publishers: S. Karger, Basel
Printed in Switzerland

Rozen P, Reich CB, Winawer SJ (eds): Large Bowel Cancer: Policy, Prevention, Research and Treatment. Front Gastrointest Res. Basel, Karger, 1991, vol 18, pp 60–73

Design and Implementation of the Australian Polyp Prevention Project[1]

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Rationale for the Intervention Trial

Higginson and Muir [1], in discussing cancers of suspected but unproved environmental etiology, notably those of the gastrointestinal and endocrine-dependent systems, observed that controversy about the nature of the factors and mechanisms involved had implications for the selection of approaches to cancer research and control. They suggested prudence in the advocacy of marked changes in dietary customs apart from the avoidance of obviously unhealthy habits such as overeating. Willett and MacMahon [2] concluded

[1] Funding and support for this project from the National Health and Medical Research Council, Queensland Cancer Fund, Anti-Cancer Council of Victoria, University of Sydney Cancer Fund, Australian Meat and Livestock Research and Development Corporation, Kellogg's Pty. Ltd. Sydney, Hoffmann-La Roche, Basel.

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that available data were insufficient to serve as a basis for strong specific dietary recommendations. Although Doll and Peto [3] estimated that future research may show between 10 and 70% of cancer to be attributable to diet, Peto [4] does not include diet among reliably established means of preventing deaths from cancer.

Attempts to identify modifiable dietary causes of colorectal cancer (CRC) are increasingly widespread, but are still short of success. The great difficulty with misclassification in nonexperimental observational studies has led to variable results. The most promising leads are being pursued in intervention studies. Clinical trials of ascorbic acid in familial adenomatous polyposis began in the 1970s [5], followed by trials to prevent sporadic adenomatous polyps with ascorbic acid and alpha-tocopherol [6]. Such trials had become feasible with developments in fiberoptic endoscopy. Magnus and Miller [7] pointed out the potential advantages of using precancerous lesions as an end point which included a shorter follow-up period and possibly higher power to detect an effect.

In planning the Australian Polyp Prevention Project we were aware of the inconclusive epidemiological evidence relating dietary factors to the risk of cancers of the colon and rectum. Despite many case-control and some cohort studies, the evidence was inconsistent and it appeared unlikely that further nonexperimental studies would resolve major etiological questions. A randomized trial was therefore considered because of the potential to assess both preventive measures, and at the same time collect data of possible relevance to etiological research. But science being 'the art of the soluble' [8], such a trial would have to be not only relevant to colorectal neoplasia, but also feasible, and this relates directly to the choice of an appropriate end point. Adenocarcinoma would be the most relevant and valid end point in a trial to prevent CRC, but such a trial would require some 40,000 subjects followed over many years. Short-term end points such as measures of intestinal cell proliferation are highly feasible, but of uncertain relevance to cancer prevention. Precursor adenomas were chosen as the option for study because they are common, are removed from the entire large bowel at colonoscopy, follow-up colonoscopy is routine, and new adenomas have a high cumulative incidence.

Australia has an affluent population of some 17 million living mainly in urban areas on the coastal fringe of an arid continent. The population is predominantly Anglo-Celtic and like other similar former British colonies such as Canada, the United States and New Zealand, has very high rates of CRC, with a lifetime risk of 1:25 by age 75. There is government-sponsored

universal health insurance providing access to both private and public medical care including colonoscopy. There is no systematic or widely organized screening for CRC. The Australian Polyp Prevention Project aims to prevent colorectal adenomatous polyps in a collaborative multicenter clinical trial involving 25 colonoscopists in leading clinical units in Brisbane, Sydney and Melbourne. The trial design was developed over several years, leading to the recruitment of the first patient at the end of 1985.

Preventive Measures

At the time of planning our Australian trial in 1982–1984, possible preventive measures considered were: fat reduction; increased dietary fiber, fruits and vegetables; and supplements of beta-carotene, calcium or selenium. Following extensive literature review, the interim dietary guidelines of the US National Research Council's Committee on Diet, Nutrition and Cancer [9] recommended reduced fat intake for the prevention of CRC – an appropriate and practical target was considered to be the reduction of fat intake from a level of approximately 40% to 30% of total calories in the diet. This was considered to be both consistent with good nutritional practice and likely to reduce the risk of cancer. Hence, fat reduction was included in our trial to assess the effects of reduction in intake.

Populations with low CRC risk generally have high intakes of dietary fiber. Limited data suggest that cereal fiber (mainly wheat and rye) is associated with lower risk in Denmark and Finland [10, 11]. Fiber might reduce the promoting effects of fat and associated bile acids by increasing fecal bulk, lowering colonic pH, and/or altering metabolism. It is possible that the risk of a low-fiber diet is conditional upon a high fat intake. Willett and MacMahon [2] stated that although the available epidemiologic data were not entirely consistent, the weight of evidence generally supported the hypothesis that fiber protects against colon cancer. They noted that some difficulty in interpreting simple relations between fiber intake and cancer occurs because foods that are high in fiber may contain other substances that are related to cancer. Hence, we increased cereal fiber intake with a supplement rather than by increasing the intake of food sources.

Several epidemiological investigations have suggested a link between low 'vitamin A' intake and an increased risk of a variety of cancers. The term 'vitamin A' is used as a general term to refer to both ingested vitamin A and beta-carotene, a provitamin that may be converted to vitamin A in vivo. Low

retinol in stored sera from large prospective studies has been associated with subsequent increased cancer risk, but the number of cancers in the large bowel has been too small to estimate risk at this site [12]. A significant inverse association has been found with a heterogeneous group of gastrointestinal cancers [13]. Questionnaire studies of cancer in relation to intake of some beta-carotene-rich vegetables or of 'vitamin A' have been reviewed by Peto et al. [14] who found that intake of certain vegetables rich in beta-carotene is associated with a reduced risk of colorectal cancer. Studies indicate that a deficiency of vitamin A can result in an increased susceptibility to carcinogen-induced neoplasia in some but not all animal models. Retinoids prevent the development of colon carcinoma induced by aflatoxin and dimethylhydrazine [15, 16]. Daily beta-carotene was therefore tested in our trial.

Another reason for selecting beta-carotene was that a practical placebo was available in the form of a capsule taken daily, important for reducing spontaneous dietary change. Although at the time no routine dietary advice was given to patients in whom polyps were found at colonoscopy, there had been considerable speculation in the media on the relationship of diet to cancer. It was considered likely that patients in a trial would be more likely to spontaneously change their diet if they were not actively involved in the trial.

Increased fruits and vegetables as an intervention were considered but the weight of the evidence at the time was not sufficient to justify a more complex trial since a placebo would still be required. Information on the effects of calcium was mainly available from personal communications; and selenium and retinol were considered to be potentially toxic.

Trial Design and Interventions

In deciding whether the purpose of the trial should be pragmatic or explanatory, we felt that it was important to attempt to understand and explain any effects which might occur, e.g. whether or not fat and/or fiber were related to the risk of colorectal neoplasia. Randomized trials are difficult and expensive, and appropriate strategies are needed to maximize their efficiency including the use of factorial designs, appropriate interventions and end points, suitable geographical areas and populations. A factorial design would allow dietary fiber and other factors to be tested in the same trial with great efficiency since all the data are used for estimating the effect of each intervention [17]. We decided to use a $2 \times 2 \times 2$ randomized factorial design, the factors being fat (intake reduced to at least 30% of total energy,

and to 25% if feasible vs. unaltered intake); dietary fiber (25 g additional wheat bran daily vs. unaltered intake); and beta-carotene (20 mg capsule vs. placebo capsule daily). Thus, in those taking beta-carotene, a quarter of the subjects are on reduced fat intake, a quarter on added bran, a quarter on both reduced fat and added bran, and a quarter have no recommended dietary change, with the same proportions in those taking placebo capsules, resulting in 8 groups in all. There are no known toxic effects at the given dose of beta-carotene. There is some experimental evidence that retinoids may be tumor promoters, but there is no possibility of this effect in our trial since although beta-carotene is converted to retinol in the intestine, the conversion is rate limiting and vitamin A toxicity is not reported even with extreme intakes of beta-carotene.

Sample Size and Randomization

The main objectives of the Australian Polyp Prevention Project relate to the independent estimation of rates of new adenomas under the three regimens. The factorial design of the study allows for efficient measures of these effects to be made, as well as for interaction effects of combinations of the factors to be examined. Sample size is a function of rates of new adenomas in the patients, the magnitude of the difference to be detected between preventive treatments, and the desired power of the study to detect such a difference. Even a small difference would reach statistical significance with a large enough sample. Conversely, even large differences might be attributed to chance with a small sample (type II error). The size of a trial should therefore be determined with a view to detecting, if it exists, a statistically significant difference at least as large as a predefined clinically important difference that could be expected between treatments. If no treatment difference exists, then the results of the trial should show this as unambiguously as possible, i.e. the chance of a false-positive result (type I error) should be low.

A reduction of 50% in the rate of new adenomas among those receiving one of the dietary interventions was considered a clinically important difference. In design considerations the type I error rate was set at the conventional 5%, and type II at 1% rather than the more conventional 10 or 20% (with power of 90 and 80%) because of the inconsistency of epidemiological studies and to make this trial as powerful as feasible to detect effects if they were present. The expected proportion of subjects with new lesions at

2 years follow-up was 40%. This was in the middle of the range of clinical experience in participating Australian centers and is approximately the rate since reported by McKeown-Eyssen et al. [18] from a Toronto trial. Given this rate, the assumptions made above, and using an approximate formula for sample size [19] in the comparison of two proportions, a minimum total sample size of 324 (162 receiving each treatment) would be required to detect a 50% reduction in the rates of new adenomas. A smaller reduction of 30% would require a larger sample size to detect with the same power, but with the same sample size the power would be reduced from 99% to the minimum conventional 80%. A lower rate of new lesions would also reduce the power of the trial, but if the rate were 20% in our patient population our sample would still have the conventional 90% power. In fact, to allow for uncertainty, drop-out or a reduced surveillance period, 30% more than the specified minimum number were recruited (n = 424).

Although the detection of interaction effects (e.g. between low fat and high fiber intake) is of great biological (and potentially public health) interest, very large sample sizes may be needed. Interactions might be detected with our sample, but the power of the study to detect modest interaction is low – i.e. they could exist but be missed (by chance, or rejected as a chance phenomenon). Although the study was, thus, not designed with the detection of modest interaction effects as an aim, they will be looked for, and should large effects be present, we would see them.

Randomization objectively distributes both known and unknown prognostic factors between treatment groups, but not necessarily evenly. Known prognostic factors must be taken into account during analysis and statistical sensitivity is reduced if they are not evenly balanced. An approach often used to achieve such a balance is prerandomization stratification with blocking [20]. Stratification has practical limits imposed by the number of subjects. Thus, we limited prerandomization stratification to city, surveillance status at entry (new patient or follow-up) and age (<55, $>= 55$ years). There are, naturally, various other factors which would affect the final estimate of effect. For example, the presence of multiple adenomas has been shown by many investigators to be an important predictor of adenoma incidence. This and other possible prognostic factors will be taken into account during analysis, if necessary, after examining their distribution among the intervention groups. Eligible patients were randomized to treatment groups by the coordinating center (CC) in Brisbane (see below). Randomization within strata was performed in blocks, so that the treatment assignments were exactly balanced among every eight allocations.

Selection of Patients

The internal validity in our trial was enhanced by limiting the categories of subjects included in the trial. We restricted collaborating centers to those with at least 40 new eligible patients per year and where colonoscopists averaged at least 4 colonoscopies per week to reduce the likelihood of misclassification of outcomes. Fundamental eligibility criteria for patients were age (over 30 and under of 75 years); a 'clean' large bowel following colonoscopy (this required the colonoscopist to be confident that all polyps had been removed and that the cecum was reached); furthermore, that there was no spasm or fecal residue in each segment of the colon; histological verification of at least one adenoma, and signed informed consent. Patients seen at surveillance colonoscopy following prior polypectomy were eligible provided they also met the above criteria.

Patients otherwise considered eligible were excluded if they had chronic inflammatory bowel disease such as ulcerative colitis, Crohn's disease, or serious inflammatory diverticulitis; gastrointestinal tract resection (excluding cholecystectomy); familial adenomatous polyposis; diagnosed cancer, excluding nonmelanoma skin cancer, unless symptom-free for 5 years (because of possible effects on diet and nutritional status); medically supervised special diets for renal, liver or gallbladder disease; the colonoscopist felt that it was not in the patient's best interest to have a repeat colonoscopy; the patient was unlikely to be able to complete the trial for medical reasons or others such as place of residence or inability to comprehend English.

Recruitment of suitable patients has been limited by both precolonoscopy eligibility criteria and postcolonoscopy criteria which include confirmed histological diagnosis. Overall, 2,780 polyp patients were registered in project clinics during the period October 1985 to April 1988; 1,304 were potentially eligible for entry at the time of colonoscopy, and 1,476 were ineligible (487 due to place of residence, 339 due to age, 169 due to cancer within 5 years, 150 due to other gastrointestinal disease, 76 for other medical conditions, 157 nonliterate in English, and 14 refusal). Of the 1,304 potentially eligible, 559 were definitely eligible on the basis of histological confirmation of at least one adenoma and confidence by the colonoscopist of a 'clean' colon; 424 (76%) have been recruited with 135 refusals. Of the remaining 745 who were potentially eligible postcolonoscopy, the reasons for nonrecruitment were various and included 282 with nonadenomatous polyp pathology and 136 with other bowel disease. These numbers illustrate the large amount of documentation and screening needed before patients are

recruited into a trial. This process has resulted in a group of participant patients who are highly motivated, and very few have discontinued after entry. All 24-month surveillance colonoscopies were completed by May 1990.

Assessment of Compliance

In order to fully assess the results of prevention trials, it is essential to know the extent to which subjects have complied with each preventive treatment, and also the extent to which controls may have spontaneously changed towards the interventions. In our trial compliance is assessed using data reported by subjects to dietitians and research nurses, and biochemically.

The dietitian and research nurse keep in close personal contact and established good relations with patients throughout the trial by phone and personal contact, thus maintaining motivation. The dietitians collect information with 24-hour recalls, but this method is of limited value in assessing patient compliance with particular food plans since monitoring by the dietitian who gives the dietary counselling has the potential for biased reporting by subjects anxious to demonstrate that they are following the dietary advice. Hence, an assessment of diet for compliance is based on 4-day estimated food records administered by a research nurse independently of the dietitian. These are done by the research nurse at recruitment (prior to dietitian contact) and every 6 months over 2 years for all subjects. Capsule counts are done at the same time.

Biochemical measures of compliance are done on blood samples taken initially and every 6 months, and include beta-carotene, retinol and cholesterol. Other markers of compliance investigated for their utility were: breath hydrogen and plasma acetate as measures of fiber intake; red cell and plasma fatty acids as a measure of reduced fat; and urinary estrogens as a measure of fiber intake and/or reduced fat intake. None was shown to be of value for assessing compliance by sampling of subjects at random times during the trial.

Assessment of Outcome

Surveillance colonoscopy is performed after 2 years in all subjects. This does not preclude earlier examination if this is clinically indicated. The sites

of the large bowel inspected at colonoscopy are recorded together with the location, number and size of adenomas and other pathology. Although desirable, it is difficult for follow-up colonoscopy to be done 'blind' in relation to fat and fiber. In contrast to entry where at least one adenoma must be histologically confirmed, all polyps found at surveillance must be examined with histopathology assessed according to the WHO International Histological Classification of Tumors [21]. One experienced histopathologist, Dr. R. Newland, is reviewing all the material.

Additional Practical Aspects of Trial Implementation

As a clinical trial cannot function without an organizing center, so a multicenter preventive trial must have a coordinating center (CC). The major responsibilities of the latter in a coronary drug trial have been defined [22] as including grant applications, manual of operations and study forms, treatment allocation, data processing, quality control and performance monitoring, data analysis monitoring, and training.

Key Role of the Study Coordinator

The successful implementation of a multicenter trial protocol requires an organized CC. This is only achieved with a committed study coordinator at the helm. Such a person must have strong administrative skills, a paramedical background, and should be a politically neutral figure to the organizations with which the trial deals. Apart from data and day-to-day management, the coordinator has a strong public relations role; the morale of study personnel, clinicians, and participating subjects must always be considered, and regular information bulletins (at various levels) aid in this aspect. The ability to defuse heated debates is desirable.

Grant Applications

Because a trial of this scope and size requires a large number of personnel and resources far above those normally supported by single agencies, grant applications have been made by the investigators to national and state funding sources. Furthermore, funding is often given yearly, at most 3-yearly, and applications for continuing support have to be made before any results are available. This is assisted by detailed progress reports since funding agencies are likely to assist the completion of a well-functioning project in which they have already made a substantial investment.

Manual of Operations and Study Forms and Schedules

Although all epidemiological studies require detailed planning with a study manual specifying how data are to be collected and processed, this is especially important with complex multicenter trials. Table 1 shows the forms and schedules developed by the CC to illustrate the complexity and planning needed for implementation of a large trial. In this project, forms (identified by number) are used for organization and coordination, and for processing of data, whereas schedules (identified by letter) denote instruments used for primary data collection. Each of these documents is accompanied by a set of instructions for its use.

Clinical Recruitment and Protocol Development

Consensus among investigators regarding the documentation to be used is essential and we spent many months developing documents. Early in this phase it was decided to designate clinical coordinators for each city to facilitate problem solving both at the developmental level as well as throughout the recruiting phase. They have proved invaluable. Regular meetings were held in each city to discuss the progress in protocol development, especially document design, with clinical coordinators reporting decisions back to the project coordinator. Later, in the development phase, several meetings of all investigators were held to finalize documentation and recruitment procedures.

Documents were simplified as much as possible to minimize paperwork for clinicians. The project coordinator, along with the research nurse for the city, visited every gastroenterology unit involved in recruiting to ensure that unit staff were familiar with all aspects of the project and recruitment documentation since they were frequently involved in documenting patients.

Patients are screened for precolonoscopy eligibility by completing a questionnaire given out at the endoscopy clinic. If eligible, provisional recruitment is then initiated by the patient's physician (and secretary) who explain the nature and purpose of the trial, and invite voluntary participation. The process is concluded by the research nurse. Detailed recruitment procedures, including informed consent, have been developed.

Randomization Procedure

Unless randomization is done centrally by a group not actively involved in the interventions, the face validity of a project will be compromised. Computerized allocation to intervention was provided for the CC by a customized program which accessed a text file containing a series of random

Table 1. Forms and schedules in the Australian Polyp Prevention Project

Forms		
Recruitment	Form 1	Register of all patients with polyps
	Form 2	Histology log
	Form 3	Letter to eligible patients
	Form 4	Detailed project information
	Form 5	Letter to patient's doctor
	Form 6	Patient consent form
	Form 16	Brief project description
	Form 17	Medical history check
Intervention	Form 7	Patient data log
	Form 8	Dietary compliance
	Form 9	Dietary compliance – food intake
	Form 10	Patient contact and compliance record
	Form 11	Diary of contacts with patients
	Form 18	Change of address/telephone
	Form 19	Record of initial dietary counselling
	Form 21	Letter introducing the capsules
	Form 22	Surveillance colonoscopy reminder
Data management and coordination	Form 12	Data processing record
	Form 13	Clarification request
	Form 14	Capsule mailing record
	Form 23	Data verification record
Finalization	Form 15	Letter of thanks to patient
	Form 20	Recommendations to patient
Schedules		
Recruitment	Schedule A	Precolonoscopic eligibility
	Schedule B	Colonoscopy result
	Schedule D	Self-administered questionnaire
Recruitment and intervention	Schedule C	Histology
	Schedule E	Food diary
	Schedule Fa	Food frequency questionnaire
	Schedule Fb	Record of added items
	Schedule G	Specimen collection record
	Schedule H	Urine collection record
	Schedule I	Acetate questionnaire
Intervention	Schedule J	Results if interval colonoscopy
Data management and coordination	Schedule M	Demographic master

Copies of forms and schedules are available from the CC.

numbers for each of the eight intervention groups. Patients are randomized by the CC after confirmation of eligibility, i.e. that schedules A and B have been adequately completed, at least one polyp has been histologically confirmed as an adenoma, and the informed consent document has been signed by the patient. The program will access the file with treatment allocation only if all of the above criteria have been met. If any one of these criteria is not met, the program automatically terminates; otherwise it will seek the characteristics to determine to which stratum the patient belongs (city, colonoscopy status, age) and access the treatment allocation file to read the next number in that stratum.

Data Management and Quality Control

With the advent of microcomputers with appropriate software, data management has become less tedious, more comprehensive, and affordable by relatively small groups. dBase III Plus (23) was used to define the database management system which runs under FoxBASE+ [24]. Clinical data are held in database files in this system, but dietary data are held in separate files for analysis with a nutrient analysis program.

For any clinical trial, the requirements are for high-quality data efficiently collected with minimal intrusion obvious to patients or the clinical treatment team. To facilitate this, a sensible operations manual which takes account of practical realities is essential, especially for standardization among centers. The manual details the procedures involved in preparing data for entry and analysis, describing how data should be forwarded from the study centers, coding and checking procedures, data entry and update procedures, and the type of filing system to be used.

An enormous amount of paper is used in a trial. Master copies of all forms and most schedules used in the project are produced at the CC, and each center can reproduce much of its own supply. Questionnaires are more complicated and were printed by the CC.

Once completed, all forms and schedules are returned to the research nurse who checks them for completion and accuracy of data collection before returning the forms/schedules to the CC every week. Photocopies of the completed forms and schedules are kept by the research nurse in each center.

Schedules are coded independently and checked in the CC. Any missing, ambiguous, or illegible data which cannot be clarified by phone contact with the research nurse are entered onto a special form which is sent weekly to the research nurse for resolution.

Data verification and logic checks also assist quality control. All data are checked prior to data entry. Because errors also occur during data entry, further verification is necessary. On completion of each verification run, original data are checked to determine the correct entry and corrections made where necessary to each database file preparatory to a further run. Following successful verification further frequency and logic checks are done using customized programs which vary with each database file.

Conclusions

The Australian Polyp Prevention Project is one of many that may be needed to further understand the etiology and prevention of CRC [25]. If the growth rate of adenomatous polyps is reduced, as indicated by their number or size at follow-up, this would allow less frequent colonoscopic surveillance since the risk of malignant change is related to size. Reduced growth would also result in a reduced incidence of visually detectable adenomatous polyps. Reduction in the growth of polyps could also indicate a lower risk for cancer. The interventions being tested are among those currently recommended by cancer societies for the prevention of CRC but without a firm scientific basis.

Prevention trials should not be entered into lightly. The workload is heavy, advanced planning and coordination are needed, and funding is not easy to obtain for what may be 6 or more years before results are obtained. A range of sophisticated skills are needed including experience with computers and data management. Quality control of all aspects of the trial is essential, but because trials are complex, this is not easy to achieve and requires frequent monitoring. The rewards of such prevention trials is that they can help resolve issues in cancer prevention, possibly more validly than many other types of research.

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