

## RESEARCH COMMUNICATION

# Study of Prevention of Colorectal Cancer through Lifestyle Modification: an Introduction to the Protocol.

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### Abstract

Previous epidemiological studies have suggested that lack of exercise and a high fat diet increase the risk of colorectal cancer. We planned a clinical trial to test these propositions, using subjects with multiple colorectal adenomas and/or carcinomas. Enrolment in this study was conducted in two stages. First, patients were invited to participate in the dietary modification part of the study. Those agreeing to participate were given dietary advice, and 3 months later all subjects to whom the exercise exclusion criteria do not apply were invited to participate in the exercise part of the study. The subjects were randomized to two groups.

A total of two hundred and eleven patients meeting the entry criteria have been invited to join the trial, of whom 165 (78%) consented to participate in the dietary modification part of the study. After excluding those unsuitable according to the exclusion criteria for the exercise regimen, the remaining 124 subjects were further invited to participate in the exercise regimen part of the study. One hundred and three (83%) subjects have given their consent. Obtaining informed consent in two stages and the free provision of lifestyle modification measures were factors that contributed to this favorable participation rate.

**Key words:** cancer prevention - lifestyle modification - colorectal cancer - randomized control study

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### Introduction

The incidence of colorectal cancer is rising sharply in Japan, and there is a pressing need to develop effective preventive methods. From the results of epidemiological surveys, we know that lifestyle factors such as diet and exercise are strongly linked to the development of colorectal cancer (Moore et al., 1998). A number of case-control studies and cohort studies (Giovannucci et al., 1986; Lee et al., 1991; Thune and Lund, 1996; Gerhardsson de Verdier et al., 1986). suggest the possibility that exercise in particular may prevent the development of colorectal cancer, and the

recommendation of an exercise program is expected to be accepted as a method of prevention. To finalize an exercise-based colorectal cancer prevention regimen, clinical trials will be needed. Such clinical trials have, however, not yet been conducted.

Exercise is known to stimulate the nonspecific immune response, in particular NK cell activity (Brahmi et al., 1985; Nieman et al., 1993; Strasbner et al., 1997; Shinkai et al., 1995; Nieman et al., 1995; Moyna et al., 1996), to alter the bowel transit time, and cure obesity (Honjo et al., 1995). It is thought that through such mechanisms exercise may suppress the development of colorectal cancer, but we were

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unable to uncover any reports of studies into the role of these factors in the etiology of colorectal cancer.

Accordingly, we thought it important to conduct a randomized clinical study into the prevention of colorectal cancer. In Japan, however, only a few randomized clinical studies into the cancer prevention have been attempted (Ishikawa et al., 1995; Tsugane et al., 1996; Tsubono et al., 1997). We therefore planned and conducted a trial capable of scientific assessment, with a high participation rate.

## Subjects and Methods

### Subjects

The subjects were a group of patients at high risk of development of colorectal cancer. The selection criteria were: patients who had undergone colonoscopy at the Osaka Medical Center for Cancer and Cardiovascular Diseases, with two or more lesions diagnosed histologically as colorectal carcinoma or adenoma, and that these lesions should have been resected endoscopically. In the case of colorectal cancer, pathological examination of the specimen removed endoscopically should indicate no need for further treatment. Age at the time of entry into the study was in between 40 and 60 years old, with no regard to gender.

Exclusion criteria were: any patients with a history of large bowel surgery apart from appendectomy, with any malignant disease that had not undergone curative treatment, with any other serious conditions, anyone unable to undergo regular follow-up endoscopies or other follow-up, anyone who had been enrolled in this study, and anyone whose treating doctor deemed them unsuitable for this study.

Exclusion criteria at the stage of randomized allocation to an exercise regimen were as follows: anyone already attending a fitness club, anyone whose home or place of work was too far away from the fitness clubs we could recommend, anyone with ischaemic heart disease, serious arrhythmia (fitted with a pacemaker, etc.), cardiac failure, or a history of cardiac disease, anyone with poorly controlled diabetes or thyroid dysfunction, anyone pregnant, anyone presently with a cardiac murmur, systolic blood pressure greater than 200 mm Hg or diastolic greater than 120 mmHG, anyone with a cardiothoracic ratio greater than 55% on chest radiograph, anyone with hypokalaemia or hypomagnesaemia, anyone with joint or other musculoskeletal disorders, and anyone unable to exercise for any other reason.

### Methods

Enrolment in this study was conducted in two stages. Firstly, at the outpatient clinic of one of the collaborators (Hideki Ishikawa), all patients fulfilling the study criteria were invited to participate (Informed Consent A). In a 20 minute interview, using printed materials an explanation was given to each subject concerning the aim and methods of the clinical trial, the possible benefits and risks to the subject, the existence of alternative treatments, the fact that no harm would come to anyone who did not consent to participate in

the trial, that they may drop out of the trial at any time even after giving their consent, and all other matters pertaining to their rights. Written consent was obtained from all subjects who agreed to participate.

After consent is obtained, for all subjects a 3 consecutive days' eating meals survey was conducted, on the basis of which dietary advice was given. Three months later a 3 consecutive days' eating meals survey was again conducted, and where necessary further dietary advice given. At the same time, all subjects who did not fall under the exclusion criteria for an exercise regimen were invited to participate in the exercise part of the study (Informed Consent B). Those subjects who gave their consent were then randomly allocated to either Group A, dietary advice plus exercise regimen at a recommended fitness club; or Group B, dietary advice alone. Subjects allocated to Group B agreed not to attend a fitness club for a period of 2 years.

Allocation was made by asking the subjects to pull an envelope out of a box by themselves. The envelope was opened on the spot, deciding which group the subject would be allocated to. If the subject was allocated to Group A, they were able to use, for 2 years without charge, one of a group of fitness clubs that have agreed to help with our study. The number of subjects required for our study is 100 for both Group A and B, for a total of 200. The number of subjects needed was estimated in the following way. The expected recurrence rate of endoscopically diagnosed colorectal tumors after 2 years is 40% for Group A, and 60% for Group B. To establish a significant difference between the two regimens, to fix the  $\alpha$  error at 5%, and for the  $\beta$  error to be 20%, at least 97 patients are needed for each group, giving a requirement of 100 subjects for each group.

The entry period has been set at 2 years, and the intervention period at 2 years. Approval was obtained for this trial from the Ethics Committee of the Osaka Medical Center for Cancer and Cardiovascular Diseases.

### Dietary advice

With 3 consecutive days' eating meal surveys conducted at the time of entry, 3 months later, and at the end of the 2 year period, a thorough grasp of the subjects' eating habits is possible. On this basis, advice is given to modify the dietary intake of fats and polyunsaturated fatty acids. Subjects are advised to limit the proportion of their calorie intake provided by fats to 18~22%, and maintain a ratio of N6/N3 polyunsaturated fatty acids of less than 2.5.

### Exercise regimen

Subjects in Group A were advised to attend the fitness club at least once weekly, and undertake the prescribed exercise load (50% time at VO<sub>2</sub>Q Max) (Tanaka et al., 1992).

### Measurement of biological parameters

At the end of the 2 year study period, each subject is scheduled to undergo colonoscopy, looking for the

development of new colorectal tumors. This is the main endpoint of the study.

The other biological parameters measured are as follows: six-monthly measurement of weight, body fat ratio (impedance method), blood pressure, and waist/hip ratio, recording by the subject of a 7 day diary of non-work related exercise, at the time of entry, after 3 months and at the end of 2 years measurement of NK cell activity (Kusaki and Morimoto, 1992), NK cell counts, CD4 and CD8 positive cell counts in peripheral blood, at 3 months and 2 years measurement of VO<sub>2</sub> Max, using an ergometer (at loads of 25, 50, 75 and 100 W for 3 minutes each for a total of 12 minutes), at the time of entry and after 2 years measurement of bowel transit time, using a radio-opaque marker (Hinton et al., 1969), at the time of the colonoscopy at the end of the 2 years measurement of colon mucosal cell proliferation (Ki-67) (Paspatis et al., 1998), at the time of entry, at 1 year and at 2 years measurement of fecal volume, using the single stool method (Wilkinson 1971).

## Results

Enrolments were commenced from October 1997. By March 2000 (figure), 211 patients meeting the entry criteria had been invited to join the trial, of whom 165 (78%) consented to participate in the dietary advice part of the study. The reasons for refusal to participate were: pressure of business, 28 cases; hospital too far away, 3 cases; sickness in the family, 5 cases; no need for dietary advice as already taking care with diet, 2 cases; too much trouble, 3 cases; didn't want to think about bowel disease, 1 case; reason unknown, 4 cases.

Of the subjects who were consented to participate in the study, 3 months passed for 165 since receiving dietary advice. Of these, 41 were excluded according to the exclusion criteria for the exercise regimen. The reasons were: cardiac disease, 3 cases; unable to exercise due to advanced diabetes, bone fractures, lung surgery, etc., 11 cases; already attending a fitness club, 19 cases; too far from a fitness club, 8 cases. The remaining 124 subjects were further invited to participate in the exercise regimen part of the study (Informed Consent B). One hundred and three (83%) subjects gave their consent, and they were randomly allocated to Group A, 53 subjects (age, mean  $\pm$  standard deviation; 52.6  $\pm$  4.5) to receive dietary advice and undergo an exercise regimen, and Group B, 50 subjects (52.1  $\pm$  5.0) to receive dietary advice alone. Of the 21 who declined to participate, the reasons were: doing enough exercise at present, 8 cases; too busy to go to a fitness club, 9 cases; will pay for it myself if I want to go, 2 cases; don't like fitness clubs, 2 cases. The product of the agreement rate of Informed Consent A and Informed Consent B is 65%.

Only one subject has been unable to continue with the study, passing away from lung cancer 18 months after enrolment. The study continues satisfactorily at the present.

## Discussion

The conduct of randomized clinical trials can be troublesome. It can be difficult to recruit enough subjects for cancer prevention studies, even in Western countries (Alberts et al., 2000).

If the necessary number of subjects cannot be recruited, a suppressive effect cannot be demonstrated. If the rate of refusal to participate is high, larger numbers of people need to be invited to join. This means not only more time and effort, but also increases the likelihood that those who agree to participate differ in some way from the general population. The results of the study cannot then be applied to the target population. It is therefore important to maximize the participation rate.

Various measures have been used to improve participation rates. Zelen (1979) reported a system where he randomizes the subjects before seeking consent, and then obtains consent only from those subjects allocated to the new treatment. Some researchers feel that there are ethical problems with not seeking informed consent from the control group. Zelen (1990) further proposed a system where the subjects are randomized first, and consent then sought from the control subjects and from those subjects allocated to the new treatment. The problem with this system is that refusal to participate after allocation becomes common, and when intent-to-treat analysis is performed, the ability to detect significant differences is severely reduced.

A number of improvements are possible to improve participation rates, such as offering various benefits to the participants, supplying detailed information. For this study, we made 3 improvements. The first is a two stage invitation to participate in the study. Initially, we invite subjects to participate in the diet modification part of the study, with no randomization involved. A high participation rate was achieved in this part of the study because there was no need for randomization, involving dietary advice only with virtually no possibility of any harmful effects.

While earnestly engaging in the dietary modification exercise, the subjects came to know the setup of the study, and a harmonious relationship developed between the subjects and researchers. This is thought to have led to the high level of acceptance achieved when, at this stage, subjects were further invited to participate in the randomized exercise part of the study.

The second improvement was that the lifestyle modification measures were all free of charge. It may be thought that since this is a research project, it should be free as a matter of course. If one had to pay for 3 separate one on one sessions of dietary advice from a dietitian, and 2 years' membership of a fitness club, this would come to a fairly large sum.

The third improvement was that the subjects drew an envelope from the box by themselves to decide their allocation. Randomization can also be done by computer, but there are advantages if the subjects draw an envelope in that the result can be known immediately, they know in a

direct manner that it is indeed random, they can accept the result more easily. In this study we used a single box, but more complex allocations can be made by the use of multiple boxes.

With these modifications, we were able to achieve a relatively high participation rate (65%). The use of this system should lead to high participation rates in a variety of clinical trials, not just in the field of cancer prevention.

Unfortunately, participants who obtained the approval of the study were 103 subjects, and did not reach 200 subjects target. If the expected recurrence rate of endoscopically diagnosed colorectal tumors after 2 years is 32%, with a risk decrease of 47% for Group A, we can establish a significant difference between the two regimens. In a cohort study (Giovannucci et al., 1995), it has been reported that the exercise decreased by half the incidence of colorectal cancer. Therefore, we plan to complete this study with the present number of participants.

## Conclusion

We were able to plan and conduct a trial of lifestyle modification for cancer prevention, achieving a high participation rate. Obtaining informed consent in two stages, the free provision of lifestyle modification measures, and subjects drawing an envelopes by themselves, were factors that contributed to this favorable participation rate.

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