RAPID COMMUNICATION Jpn. J. Cancer Res. 86, 707–710, August 1995

Interventional Trial for Colorectal Cancer Prevention in Osaka: An Introduction to the Protocol

Hideki Ishikawa,[1,4] Ikuko Akedo,[1] Takaichiro Suzuki,[1] Toru Otani[2] and Tomotaka Sobue[3]

[1]Department of Cancer Epidemiology, Research Institute, and [2]Department of Gastroenterology, The Center for Adult Diseases, Osaka, 3-3 Nakamichi 1-chome, Higashinari-ku, Osaka 537 and [3]Cancer Information and Epidemiology Division, National Cancer Center Research Institute, 1-1 Tsukiji 5-chome, Chuo-ku, Tokyo 104

We established a protocol for an interventional randomized controlled trial for prevention of colorectal cancer by attaching special importance to feasibility. The subjects were patients with multiple colorectal tumors. Two regimens were formulated for prevention of colorectal cancer. One was dietary guidance alone (Regimen I), and the other was dietary guidance plus eating wheat bran biscuits (Regimen II). The main end points of the trial were examinations for recurrence of colorectal tumors after 2 and 4 years. The target number of patients was 200 in total, i.e. 100 for each group. During the 18 months from the beginning of recruiting of subjects (up to November 1994), 28 (97%) of the 29 patients recruited for Regimen I and 32 (97%) of the 33 patients recruited for Regimen II agreed to participate in the trial. The trial is progressing well.

Key words: Colorectal cancer — Prevention — Randomized controlled trial

The development of a preventive regimen against cancer requires a number of steps from laboratory investigations to clinical application. Before its clinical application, the effectiveness of the regimen in humans must be accurately evaluated. This evaluation can best be made by a randomized controlled trial (RCT), which is used for drug efficacy studies.[1)] However in RCT, assignment of regimens by lot gives a strong impression of experimenting on living humans, and there is no financial advantage to the participants because all persons are covered by the Japanese Medical Insurance system. It use of placebo-treated controls seems especially questionable. Therefore, RCT to evaluate a preventive measure has not been considered feasible in Japan. In fact, there has been no report of a completed typical RCT concerning prevention of cancer.

We planned an RCT in a high risk group for colorectal cancer in order to study preventive methods against cancer and formulated a feasible protocol. This plan was approved by the Ethics Committee, The Center for Adult Diseases, Osaka in March, 1993, and entry of subjects was started in June, 1993. The protocol has been in progress approximately as scheduled for a year and a half. Herein, the protocol that we formulated is explained, and its characteristics are described. We also report the results obtained to date.

The subjects were patients with multiple colorectal tumors, who are a high risk group for colorectal cancer. They were limited to those in whom two or more colorectal lesions have been diagnosed histologically after endoscopic examination to be carcinoma or adenoma. All the tumors have been resected radically by endoscopic procedures. The subjects must also be aged 45–65 years, have no history of intestinal resection except appendectomy, be presently free of malignant diseases, and have no serious complications.

Two regimens were established for prevention of colorectal cancer. The first regimen (Regimen I) is dietary guidance alone, and the second regimen (Regimen II) consists of dietary guidance and regular intake of wheat bran (WB) biscuits. A regimen is assigned at random for each week in advance, and doctors who recruit subjects are informed of the regimen of the week at the beginning of the week. However, when the difference in the number of subjects who have been recruited by the end of the previous week was 5 or more between the two regimens, subjects are recruited in the next week for the regimen with fewer recruits. The day of endoscopic treatment for the patients treated by the doctors in our group is decided automatically by the ward director, and endoscopic treatment is performed immediately after admission. The patient is scheduled to receive consultation on the day nearest the day after a week has elapsed, when a doctor in our group is on duty, and is advised of the histological diagnosis of the resected polyp. All patients who have received endoscopic treatment, who have been seen by a doctor in our group, and who fulfilled the entry criteria were recruited. If the day of consultation had to be

[4] To whom correspondence should be addressed.

changed at a patient's request, the patient was recruited according to the original recruiting schedule to exclude arbitrariness of the patients or doctors in the assignment of the regimens.

According to the "Patients' Guide," we explained the purpose and the method of the clinical trial, the expected effects, the risks, and other aspects of the study. Informed consent of patients to participate in the trial was recorded on a "Consent Form."

At the entry of the subjects in the trial, information is obtained concerning their height, body weight, endoscopic findings, presence or absence of complications, familial history, previous treatments, and regular medications.

The core of the dietary guidance is to restrict the energy intake from oil and fat to 18–22% of the total energy intake.[2] The contents of meals on 3 consecutive days before the consultation are recorded in "Diet Record Forms," a nutritionist interviews the patient on the basis of this record, and the total energy intake and the intake of fat and oil are estimated. For nutritional guidance, the patient is requested to visit the hospital with the family, and instructions about the intake of oil and fat are given individually over about 1 h by a nutritionist assigned exclusively to this project, using a "Pamphlet for Guidance of Oil and Fat Intake" prepared especially for this trial. On a later day, the mean daily intake of each nutrient is calculated using a computer from the date of the dietary investigation, and the results are returned by mail to the patients with comments by the nutritionist. Follow-up dietary investigations are made after 3 months and 1 year to examine the effects of the dietary guidance, and, if necessary, guidance is given again.

The WB biscuits that we developed have a wheat bran content of about 30 weight percent.[3] The patients are instructed to eat 25 g of WB biscuits (7.5 g as wheat bran) daily before each meal. How to eat WB biscuits and adverse effects that may occur after eating WB biscuits are explained at the examination, using a pamphlet, "How to Eat WB Biscuits," which is distributed to each patient. The biscuits are given for 1 month, and the test regimen is begun after confirmation that the patient can regularly eat the biscuits. The regimen is continued for 4 years.

If severe adverse effects that may be due to the biscuits occur, the regimen may be interrupted at the judgment of the attending physician, and resumed on confirmation of alleviation of the symptoms. The regimen may be discontinued if the adverse effects reappear on resumption of the regimen.

The main end point of the trial is examination of the presence or absence of recurrence of colorectal tumors. Colorectal endoscopy is performed 2 and 4 years after the beginning of the regimen to search for recurrence of colorectal tumors. A videocolonoscope system (Olympus EIVS 200), is used for the examination. Examination is always done by two or more doctors to detect new lesions. All lesions observed are biopsied and examined histologically without knowledge of the group to which the patient belongs. Cell proliferation in the biopsy specimens from ascending and sigmoid colons is also studied by an immunohistochemical technique,[4] and this examination is also done without knowledge of the group to which the patient belongs.

The tolerability of the biscuits is assessed by examining compliance through a questionnaire. The compliance with the dietary guidance is evaluated according to the percentage of oil and fat in the total energy intake at follow-up dietary investigations 3 months and 1 year after the beginning of the regimen.

The registration period of subjects is from June, 1993 to March, 1996, and the trial will be completed in March, 2000, when the 4-year follow-up of the last patient will be over. Determination of the necessary number of subjects for each group was performed as follows. We estimated that the recurrence rate of colorectal tumors diagnosed by endoscopic examination after 2 years in Regimen I (dietary guidance alone) would be 60%, and that of colorectal tumors in Regimen II (dietary guidance plus eating WB biscuits) would be 40%. To identify a significant difference in the number of recurrences between the two regimens, the α error should be 5%, and β error should be 80%, so that 97 patients are needed for each group. We therefore set the number of subjects for each group as 100. If the number might not be filled, it should be considered to prolong the registration period.

From June 1993 to November 1994, 28 (97%) of the 29 patients recruited for Regimen I and 32 (97%) of the 33 patients recruited in Regimen II consented to participate in the trial. There were no significant differences in the number of consentees, sex or the mean values of age, height and body weight between the two groups. There was also no significant difference in the number of colon tumors resected. Therefore, a good randomization was considered to have been obtained (Table I). None of the patients requested a change in the group at entry, and there have been no dropouts after entry to date. The proportion of registered patients who consumed more than 80% of the WB biscuits given was 94, 89, 75, 79, 66, 66, and 71%, respectively at 1, 3, 6, 9, 12, 15, and 18 months after entry. This was considered to be acceptable.

In a standard RCT as described in textbooks, the study is explained, and consent to entry is obtained first, and then the subjects are assigned by lot to different regimens. A standard and best available treatment is performed in the control group, and the regimen to which a particular subject has been assigned must be concealed from both

Table I. Patients' Characteristics

	Regimen I	Regimen II	P
Number of patients recruited	29	33	
Consentees	28	32	NS[a]
Non-consentees	1	1	
Dropouts	0	0	
Male:Female	26:3	31:2	NS[b]
Age[d]	56.0±6.6	54.2±5.5	NS[c]
Height (cm)[d]	162.4±7.3	165.1±5.8	NS[c]
Body weight (kg)[d]	63.2±8.4	65.7±8.0	NS[c]
Number of neoplasms			
2–3	11	12	NS[a]
4–5	8	6	
6–10	6	11	
11–	3	4	

Abbreviation: NS, not significant ($P \geqq 0.05$).
a) The statistical significance of differences between groups was analyzed by use of the χ^2 test.
b) The statistical significance of differences between groups was analyzed by using Fisher's exact probability test.
c) The statistical significance of differences between groups was analyzed by use of Student's *t* test.
d) Mean±standard deviation.

the subject and the investigator (double blind).[1,5] On the other hand, in our protocol, (1) regimens are assigned week by week, (2) the regimen is decided first for the week, and subjects are recruited for that regimen, (3) one treatment is given to both groups, and another treatment is added in one of the groups, (4) no placebo is used, and therefore, (5) the study is not blind.

1) As mentioned above, the days of consultation of the subjects are determined independently of the doctors' or patients' wishes, and regimens are assigned randomly on a weekly basis, so that the outcome of this assignment is considered to be comparable to the results of random individual assignment.

2) The regimen was determined first for the following reasons. In actual treatment, the doctor usually chooses prospective therapy first and then asks if the patient is willing to try it. Therefore, we expected that our approach would allay the uneasiness of the patients, and a higher percentage of patients would agree to participate. Actually, 97% of the patients who have been recruited to date (a year and a half after the beginning of registration) have entered the trial for both Regimens I and II. This high entry rate may be explained partly by the facts that all patients had tumors of the large intestine and were not healthy subjects, and that individual dietary guidance by a nutritionist, which is usually not available in Japan, is provided free of charge. Also, no subject in either group has requested a change in the regimen. If this situation is maintained, the results of assignment of regimens by this method are expected to be similar to the results of a typical textbook assignment.

3) If two preventive regimens are compared separately, the results of individual regimens are difficult to evaluate, because both regimens are involved in the results. In our protocol, dietary guidance is given to both groups, and another treatment is added in one group. If any difference is observed in the results between the two groups, the difference is considered to be ascribable to the additional treatment given in one group.

For prevention of colorectal cancer, we considered that the conventional approach of doing nothing would not be the best policy. We therefore selected dietary guidance as the basic treatment.

Additional treatment must be provided when: it is considered to be effective from the results of epidemiological and laboratory investigations; it is theoretically reasonable; and it has been shown to be safe by animal experiments. Also its safety, effect on the body, tolerability, and appropriate doses must have been sufficiently clarified in humans. The WB biscuits used in our protocol are a food, so that animal experiments were not necessary. Instead, we administered the biscuits to 12 healthy adult males for 3 months to evaluate their effects and showed that they are safe and tolerable at twice the amount given in this study but that the fecal-weight-increasing effect is optimal at the amount used in this study.[3]

4) In a textbook RCT, administration of a placebo might be considered as a control of WB biscuits given as an additional regimen. The following two advantages are expected in the use of a placebo. First, the placebo effect can be controlled when a parameter liable to show a placebo effect (for example, when a subjective symptom is used as the endpoint). Secondly, placebo administration may prevent patients in the untreated group from personally obtaining the drug assigned to the treated group. We used the pathological parameter of new growth of colorectal tumors as the endpoint of our protocol, and this is expected to be essentially unaffected by the placebo effect. Moreover, the WB biscuits that we developed are not available elsewhere, and other biscuits with high fiber contents are not widely available in Japan at present. Therefore, the likelihood that patients in the dietary guidance group would regularly take similar biscuits is considered to be minimal. For these reasons, we consider the disadvantages of not using a placebo to be negligible in the present study.

5) In our protocol, doctors know which regimen each patient is receiving so that care is needed to eliminate subjective judgment from evaluation of the effects of the regimens. Therefore, examination of the large intestine was always done by two or more doctors by the use of a

videocolonoscope system to ensure more objective evaluation. Also, histological examination was done in a blind design to prevent bias in the results.

An intervention trial in human subjects for investigation of preventive measures against cancer could be successfully conducted in Japan based on a protocol formulated in this way. The concepts on which this study is based are considered to be applicable not only to prevention of cancer but also to clinical investigations in various fields.

This work was supported by a Grant-in-Aid for the Second Term Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health and Welfare, Japan.

(Received March 13, 1995/Accepted May 17, 1995)

REFERENCES

1) Fletcher, R. H., Fletcher, S. W. and Wagner, E. H. "Clinical Epidemiology — The Essentials," pp. 127–152 (1982). Williams & Wilkins, Baltimore/London.
2) Shike, M., Winawer, S. J., Greenwald, P. H., Hill, M. J., Swaroop, S. V. and the WHO Collaborating Center for the Prevention of Colorectal Cancer. Primary prevention of colorectal cancer. *WHO Bull. OMS*, **68**, 377–385 (1990).
3) Ishikawa, H. Interventional trial for colorectal cancer prevention in Osaka — Preliminary report. *J. Jpn. Soc. Cancer Ther.*, **30**, 161 (1995).
4) Alberts, D. S., Einspahr, J., Rees-McGee, S., Ramanujam, P., Buller, M. K., Clark, L., Ritenbaugh, C., Atwood, J., Pethigal, P., Earnest, D., Villar, H., Phelps, J., Lipkin, M., Wargovich, M. and Meyskens, F. L., Jr. Effects of dietary wheat bran fiber on rectal epithelial cell proliferation in patients with resection for colorectal cancers. *J. Natl. Cancer Inst.*, **82**, 1280–1285 (1990).
5) Hamajima, N. "Randomized Clinical Trials," pp. 84–95 (1993). Cancer and Chemotherapy Publishers Inc., Tokyo.