

Randomized trial of dietary fiber and *Lactobacillus casei* administration for prevention of colorectal tumors

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The epidemiologic evidence that dietary fiber protects against colorectal cancer is equivocal. No large-scale clinical study of the administration of *Lactobacillus casei* has been reported. We examined whether dietary fiber and *L. casei* prevented the occurrence of colorectal tumors. Subjects were 398 men and women presently free from tumor who had had at least 2 colorectal tumors removed. Subjects were randomly assigned to 4 groups administered wheat bran, *L. casei*, both or neither. The primary end point was the presence or absence of new colorectal tumor(s) diagnosed by colonoscopy after 2 and 4 years. Among 380 subjects who completed the study, 95, 96, 96 and 93 were assigned to the wheat bran, *L. casei*, both and no treatment groups, respectively. Multivariate adjusted ORs for occurrence of tumors were 1.31 (95% CI 0.87–1.98) in the wheat bran group and 0.76 (0.50–1.15) in the *L. casei* group compared to the control group. There was a significantly higher number of large tumors after 4 years in the wheat bran group. The occurrence rate of tumors with a grade of moderate atypia or higher was significantly lower in the group administered *L. casei*. No significant difference in the development of new colorectal tumors was observed with administration of either wheat bran or *L. casei*. However, our results suggest that *L. casei* prevented atypia of colorectal tumors.

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The incidence of colon cancer is rapidly increasing in Japan.¹ It has been suggested that this trend is caused by the high-fat, low-dietary fiber diet resulting from Westernization of the lifestyle among Japanese. Indeed, intake of dietary fiber by the Japanese has decreased significantly over the past 10 years.²

Since Burkitt³ proposed that a diet high in dietary fiber prevented colorectal cancer, basic studies have suggested the possibility of prevention of colorectal cancer by dietary fiber, through actions including absorption of carcinogens by insoluble dietary fiber⁴ and dilution of bile acids and decrease of mutagenicity due to the increase in stool volume.^{5,6}

A large number of case-control studies have suggested that dietary fiber may prevent the development of colorectal cancers.⁷ However, reports of large-scale cohort studies have failed to show a preventive effect of dietary fiber against colorectal cancer, causing controversy.^{8–11}

Randomized clinical trials have been conducted in Western countries^{12–16} to evaluate the effectiveness of dietary fiber, using the development of colorectal adenoma as an end point. Many of these studies failed to prove that dietary fiber prevented the development of colorectal adenoma. No intervention study on dietary fiber has been reported in Asians.

It has been shown that *Lactobacillus casei* strain Shirota reduces DNA damage induced by chemical carcinogens in laboratory studies¹⁷ and prevents carcinogenesis in animal experiments.^{18,19} In addition, it has been reported, in humans, that lacto-

bacilli reduce the level of mutagens in stool.²⁰ Furthermore, oral administration of *L. casei* strain Shirota preparation decreased the recurrence of superficial bladder cancer after transurethral resection,^{21,22} and habitual intake of a fermented product with *L. casei* strain Shirota reduced the risk of bladder cancer in an epidemiologic study.²³ Thus, we decided to use a *L. casei* strain Shirota preparation in the present study. It has been suggested that high intake of yogurt and fermented milk is responsible for the low incidence of colon cancer in Finland, where consumption of fat is higher than in other countries.²⁴ Two case-control studies have shown that yogurt²⁵ and fermented milk²⁶ prevent colon cancer. In the Netherlands Cohort Study, it was reported that fermented milk intake showed an inverse relationship with the development of colon cancer, although there was no statistical significance.²⁷

In 1993, we initiated a randomized clinical trial to determine whether dietary fiber from wheat bran and *L. casei* prevented the occurrence of colorectal tumors.

Material and methods

Study design and subjects

Part of the study design and methods have been previously described in detail.²⁸ Subjects were recruited at the Osaka Medical Center for Cancer and Cardiovascular Diseases between June 1993 and September 1997. The study protocol was approved by the Ethics Committee of the Osaka Medical Center for Cancer and Cardiovascular Diseases. Written informed consent was obtained from all subjects.

Inclusion criteria were men and women aged 40–65 years who had had at least 2 colorectal tumors (adenomas and/or early cancers) removed endoscopically within 3 months before recruitment. Endoscopic examination had been conducted twice, to detect and resect polyps, respectively. It must have been performed on the entire large intestine, and the subjects must have had an adequate nutritional status. Excluded were subjects with other malignant tumors, a history of intestinal or gastric resection (except appendectomy), familial adenomatous polyposis and severe illness.

Four regimens were incorporated for prevention of colorectal cancer: A, dietary instruction and regular intake of wheat bran biscuits; B, dietary instruction and regular intake of *L. casei* preparation; C, dietary instruction and regular intake of wheat bran biscuits and *L. casei* preparation; and D, dietary instruction alone.

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One of the 4 regimens was assigned randomly in advance each week. Physicians recruited subjects according to the regimen decided at the beginning of the week. Patients received consultation, including histologic diagnosis of the resected polyp, from group physicians as soon as possible from 1 week following endoscopic treatment. Since the regimen assignment could not be changed by the physicians or participants or arbitrarily manipulated by the authors, it was regarded as random. Trial physicians recruited all outpatients who met the inclusion criteria.

The amount of wheat bran biscuits and *L. casei* preparation to be consumed in 1 month was given to the participant at the start of the trial, and thereafter the amount for 3 months was given. The trial was started after confirming that the subject understood the procedure of the regimen. During the trial, consultation was performed every 3 months to check the participant's physical condition and to confirm the intake of wheat bran biscuits and the *L. casei* preparation. The regimen was continued for 4 years. Participants' compliance with taking wheat bran biscuits and/or the *L. casei* preparation was assessed at the consultations performed every 3 months. At each consultation, the numbers of unconsumed biscuit packages and silver packages of *L. casei* preparation were estimated by verbal inquiry of the patients, and the amounts of wheat bran biscuits and *L. casei* preparation taken in the past 3 months were calculated as the percentage of the target intake. Consultations were performed 16 times, every 3 months for 4 years, and the average at those 16 consultations was taken as the compliance over 4 years.

The target number of subjects was 100 in each group, for a total of 400 subjects. As the incidence of tumors in the control group can be estimated to be about 60%, a significant difference would be obtained if the occurrence rate of tumors could be reduced to 50% (suppression rate 17%) by administration of wheat bran or *L. casei* preparation. No midpoint analysis was performed.

Tumors discovered by colonoscopy performed at the end of the 2nd and 4th years were included in the analysis. The analysis included subjects with poor compliance with the regimen for intake of wheat bran biscuits and *L. casei* preparation on an intention-to-treat basis. For patients with early colorectal cancers resected during colonoscopy before entry in the trial, colonoscopy was performed 6 months after entry (35, 29, 25 and 24 subjects of groups A, B, C and D, respectively). Tumors discovered by colonoscopy performed at 6 months were excluded from analysis. Subjects who refused participation and dropouts were excluded from analysis.

Dietary instruction

The core purpose of the dietary instruction was to restrict fat intake so that the energy from fat constituted 18–22% of total energy intake. Subjects were asked to record, on a diet record form, the contents of their meals for the 3 days before consultation; and nutritionists calculated, from these records, the total energy intake and intake of fat and oil. Compliance with the dietary instructions on the restriction of fat intake was evaluated at dietary checkups 3 months and 4 years after beginning the regimen, and, when necessary, instruction was given again.

Wheat bran biscuits

Biscuits containing wheat bran at 30% of dry weight were prepared.²⁹ Patients were instructed to eat 25 g/day wheat bran biscuits (7.5 g as wheat bran) before each meal. Biscuits were developed by Ezaki Glico (Osaka, Japan) and Horii Pharmaceutical Industry (Osaka, Japan). The components and contents of the wheat bran biscuits were as follows: energy, 454 kcal/day; protein, 2.9 g/day; lipid, 3.3 g/day; and nonfibrous carbohydrate, 17.5 g/day.

L. casei preparation

The *L. casei* strain Shirota preparation was a powder containing approximately 10^{10} viable cells/g. It was stored in a refrigerator, and 1 g was taken after every meal. The *L. casei* preparation was provided by Yakult Honsha (Tokyo, Japan). The viable cell count

of *L. casei* and absence of bacterial contamination were confirmed for all lots every 6 months during the 2-year storage period. To confirm the viable cell count of *L. casei*, MRS agar medium for detection of *L. casei* was used. It has been confirmed in previous studies that the number of bacteria per 1 g of *L. casei* preparation remained in the range of 1.5×10^9 to 2.1×10^{10} during 24 months when stored in a cool place (15°C). In addition, the average number of bacteria is 8.0×10^9 after 24 months.

Colonoscopy

The main end point of the trial was the presence or absence of new colorectal tumor(s). Colonoscopy was performed 2 and 4 years after the start of the regimen. The entire large intestine, from the anus to the cecum, was examined. Examinations for detection of new lesions were performed by 2 physicians. All lesions, except hyperplastic polyps clearly evaluated by colonoscopy, were examined histologically on the basis of the guidelines of the Japanese Society for Cancer of the Colon and Rectum.³⁰ All histologic diagnoses (inflammatory polyp; hyperplastic polyp; adenoma with mild atypia, with moderate atypia, with severe atypia; early cancer) were performed blindly without identification of the participant's dietary regimen.

In patients with early colorectal cancer, which was diagnosed from tumor tissue resected by colonoscopy before entry in the trial, colonoscopy was performed to detect local recurrence after 6 months of participation. All colorectal tumors discovered with this procedure were resected.

Statistical analysis

All colorectal tumors discovered at the end of the 2nd and 4th years were defined as "new". Analyses at years 2 and 4 were performed separately, and 2×2 contingency table analysis was performed. Comparison of baseline characteristics of subjects with or without wheat bran biscuits or *L. casei* intake was performed by appropriate tests such as *t*-test and the χ^2 test. Logistic regression models were used to estimate the odds ratio (OR) adjusted for covariates such as age and sex. Confidence intervals (CIs) based on Wald statistics were used to assess significance.

Results

Enrollment and randomization

The number of patients who met the inclusion criteria during the screening period was 470 (Fig. 1). All were invited to participate in the trial, but 60 patients (13%) declined. Of 410 patients who agreed to participate, 12 were excluded because of incompatibility with the protocol, including detection of cholangiocarcinoma and gastric cancer in 4, history of gastrectomy in 3, colectomy in one, familial adenomatous polyposis in one, advanced age in one, young age in one and more than 3 months after endoscopic treatment in one. Thus, 398 patients were assigned to the 4 groups.

Baseline characteristics of subjects

Table I shows the baseline characteristics of the 398 patients randomly assigned and the number of dropouts. There was no difference in baseline characteristics of subjects such as dietary content among the 4 groups. A total of 18 patients (4.5%) did not complete endoscopic examinations. The reasons for not receiving endoscopic examinations were death in 2 patients (from lung cancer and cerebral hemorrhage), serious illness in 5 patients and trial discontinuation in 11 patients. There was no difference in the rate of dropouts among all groups. Excluding 18 dropouts, 380 patients were included in the analysis.

Colonoscopy

Colonoscopic examination was possible throughout the length of the large intestine, up to the cecum, in all cases. There was no difference in the intervention period among groups (Table II).

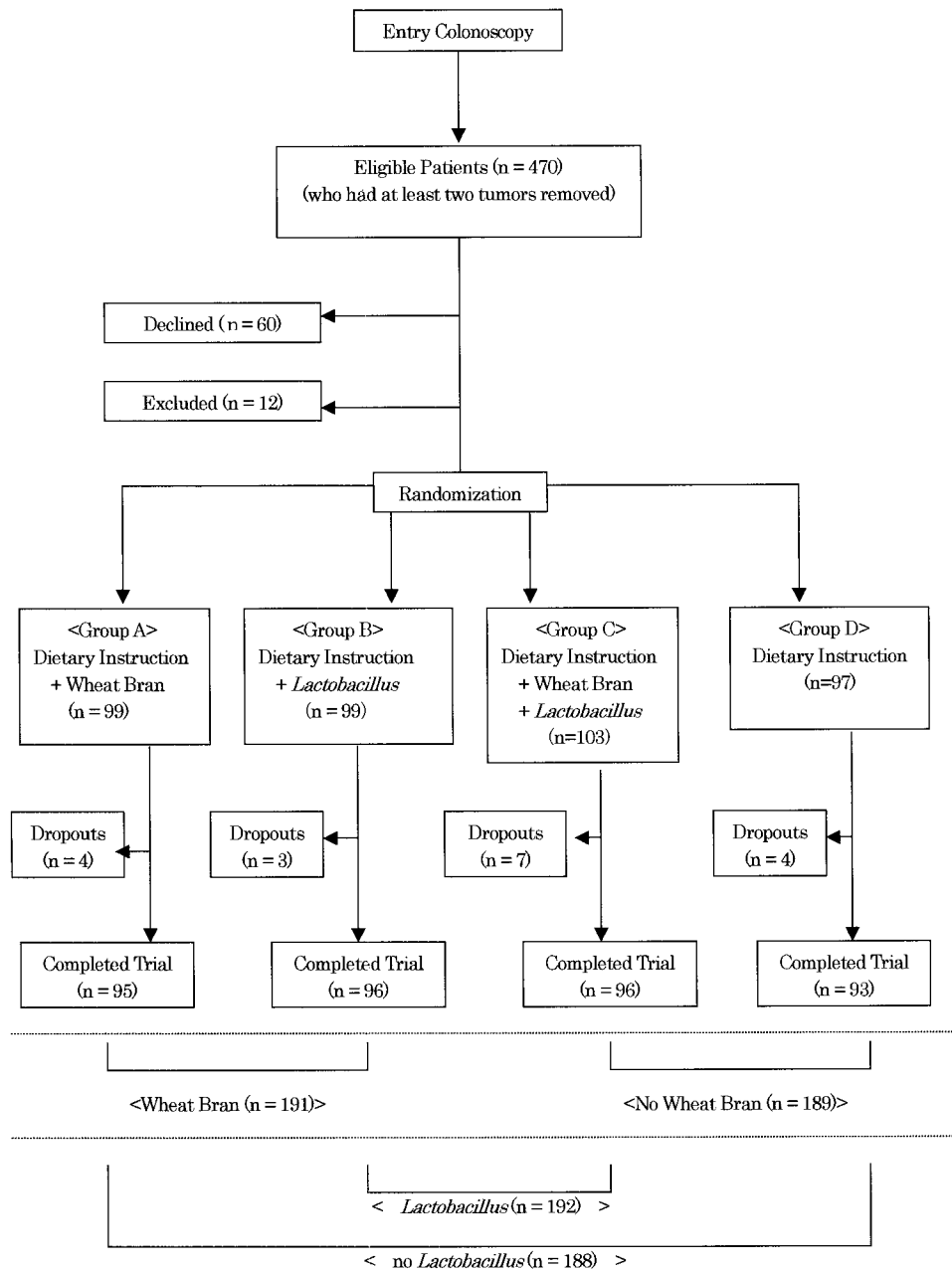


FIGURE 1 – Study participant data.

There was no difference in the time required for insertion into and removal from the cecum in all groups. No difference was found in the proportion of nonneoplastic lesions (inflammatory polyps and hyperplastic polyps).

Compliance

Compliance with intake of wheat bran biscuits was over 90% in 77 persons (40%) and over 70% in 135 persons (71%) for the entire 4 years. Compliance with intake of the *L. casei* preparation was over 90% in 130 persons (68%) and over 70% in 168 persons (88%).

Occurrence of tumors

The results after intake of wheat bran biscuits are shown in Table III. The wheat bran biscuit administration group included 191 persons, while the nonadministration group included 189 persons. The adjusted OR of developing at least one tumor

was 1.31 (95% CI 0.87–1.98) after 2 years in the administration group compared to the nonadministration group. It was 1.31 (95% CI 0.87–1.97) after 4 years, showing some increase in adjusted OR, although not statistically significant. The adjusted OR for developing tumors larger than 3 mm was 1.14 (95% CI 0.76–1.72) in the administration group compared to the nonadministration group after 2 years and 1.57 (95% CI 1.04–2.37) after 4 years, showing a significant increase. In particular, the occurrence of tumors larger than 10 mm after 2 years showed no difference between the wheat bran administration and nonadministration groups. However, after 4 years, these tumors did not occur in the nonadministration group while they occurred in 7 patients (3.7%) in the administration group, showing a significant increase. There was no difference in the occurrence of more than one or more than 3 tumors with moderate or severe atypia.

Table IV shows the results after *L. casei* administration. The *L. casei* administration group included 192 persons and the nonad-

TABLE I – BASELINE CHARACTERISTICS OF SUBJECTS¹

	Group A: wheat bran (n = 99)	Group B: <i>Lactobacillus</i> (n = 99)	Group C: wheat bran + <i>Lactobacillus</i> (n = 103)	Group D: no treatment (n = 97)
Age (years)	54.7±6.1	54.8±6.5	54.9±6.2	55.5±6.2
Male sex, number (%)	83 (83.8)	79 (79.8)	80 (77.7)	83 (85.6)
Height (cm)	164.6±8.4	164.6±7.3	163.0±7.1	164.1±7.6
Weight (kg)	66.1±10.5	64.6±10.5	62.7±8.7	63.2±9.4
Dietary intake				
Energy (kcal/day)	2,075±368	2,066±411	2,058±402	2,163±404
Total fat (g/day)	54.6±15.2	53.0±13.5	52.8±16.7	56.6±14.9
Dietary fiber (g/day)	15.1±3.9	14.5±3.9	15.4±4.7	15.5±4.0
Calcium (mg/day)	635.4±237.1	638.7±218.4	636.6±246.7	661.4±247.7
Alcohol drinking every day, number (%)	50 (50.5)	37 (37.4)	49 (47.6)	48 (49.5)
Current smoker, number (%)	47 (47.5)	41 (41.4)	43 (41.7)	44 (45.4)
Tumors before recruitment				
Total tumors	5.9±4.3	5.8±5.6	5.2±3.6	5.0±3.4
Adenomas with mild atypia	2.8±2.9	2.7±3.9	2.5±2.6	2.0±2.7
Adenomas with moderate atypia	2.1±2.2	2.4±2.1	1.9±1.8	2.0±1.9
Adenomas with severe atypia	0.6±0.8	0.4±0.7	0.5±1.1	2.0±1.9
Early cancers, number (%)	37 (37.4)	31 (31.3)	29 (28.2)	28 (28.9)
History of colorectal cancer in one parent or sibling, number (%)	15 (15.2)	8 (8.1)	15 (14.6)	11 (11.3)
Dropped out, number (%)	4 (4.0)	3 (3.0)	7 (6.8)	4 (4.1)

¹Values are means ± SD.

TABLE II – INTERVENTION PERIOD OF COLONOSCOPY

Intervention period	Group A: wheat bran (n = 95)	Group B: <i>Lactobacillus</i> (n = 96)	Group C: wheat bran + <i>Lactobacillus</i> (n = 96)	Group D: no treatment (n = 93)
Period of 2nd year from entry (days)				
Mean ± SD	679.4±60.8	674.2±31.0	672.1±27.6	680.3±56.9
Maximum	1,009	827	778	925
Minimum	568	617	600	617
Period of 4th year from entry (days)				
Mean ± SD	1,339.6±46.9	1,339.7±51.1	1,338.1±40.5	1,367.4±120.4
Maximum	1,611	1,660	1,617	2,129
Minimum	1,275	1,275	1,233	1,201

ministration group, 188 persons. The adjusted OR of developing at least one tumor was 0.76 (95% CI 0.50–1.15) in the administration group compared to the nonadministration group after 2 years. After 4 years, it was 0.85 (95% CI 0.56–1.27), showing a decrease after both 2 and 4 years, although not statistically significant. For the occurrence of tumors with moderate or severe atypia, the adjusted OR was 0.80 (95% CI 0.52–1.22) in the administration group compared to the nonadministration group after 2 years and 0.65 (95% CI 0.43–0.98) after 4 years, showing a significant decrease after 4 years. There was no difference in the size and number of new tumors that developed.

When the results were examined separately for the different levels of compliance, they were similar to those described above.

Synergistic effects

Tumor occurrence in the group administered both wheat bran and *L. casei* was higher than that in the groups administered wheat bran or *L. casei* and lower than that in the nonadministered group (data not shown). No notable synergistic effects between the treatments were observed.

Adverse events

During the study period, colorectal cancers were discovered in 4 persons by endoscopy, including one person each in groups B, C and D after 2 years and one person in group B after 4 years. There was no bias in their occurrence among the groups. All were cancer invasion of mucosa and were completely resected endoscopically, not requiring colectomy. During the study period, 2 patients died, one of lung cancer in group A and one of cerebral hemorrhage in group C. One person each in groups A and C underwent surgery for peritonitis resulting from acute appendicitis. There was no other serious adverse event.

Discussion

It was found that *L. casei* intake appeared to suppress the development of colorectal tumors; in particular, it prevented, with statistical significance, the development of tumors with moderate and severe atypia. This large-scale randomized clinical study shows that an *L. casei* preparation prevented the development of colorectal tumors.

Since our study was performed at one hospital, the evaluations of endoscopic findings were thought to be consistent. All patients who satisfied the conditions for participation were asked to participate, and the rate of consent to participation was extremely high at 88%, supporting the high validity of the results. The reasons for the high rate of consent could be that a special organization was instituted in this hospital for this trial and that all participants were offered dietary instruction. In addition, the dropout rate was low at 4.5% and compliance was high, indicating that the results were highly reliable. Endoscopic examination was conducted twice before entry so that we could minimize oversights.

In our previous prevention studies, subjects were patients with at least one tumor, whereas the present study included patients with at least 2 tumors. It is known that patients with at least 2 tumors in the large intestine have a higher risk of colon cancer than those with only one tumor. It is difficult to apply the results of our clinical study to the general population. Many of the patients participating in this trial, different from other reports in the past, had a larger number of colorectal tumors together with a history of cancer. This difference appears to have resulted from the background of the population, who had a higher risk of colorectal cancer than those participating in previous clinical trials. Accordingly, our results should be discussed not on the basis of the general population but on the basis of a population with a high risk of colorectal cancer. Nonetheless, our study included patients

TABLE III – RISK OF TUMOR OCCURRENCE WITH WHEAT BRAN BISCUITS

Year	Wheat bran (groups A + C) (n = 191)	No treatment (groups B + D) (n = 189)	Crude		Adjusted		
			relative risk	(95% CI)	OR	(95% CI) ¹	
Number of tumors							
At least one	2	119 (62.3%)	106 (56.1%)	1.11	(0.94–1.31)	1.31	(0.87–1.98)
	4	106 (55.5%)	93 (49.2%)	1.13	(0.93–1.37)	1.31	(0.87–1.97)
≥ 2	2	57 (29.8%)	60 (31.7%)	0.94	(0.70–1.27)	0.92	(0.60–1.43)
	4	51 (26.7%)	53 (28.0%)	0.95	(0.69–1.32)	0.95	(0.60–1.50)
≥ 4	2	11 (5.8%)	14 (7.4%)	0.78	(0.36–1.67)	0.78	(0.34–1.76)
	4	11 (5.8%)	12 (6.3%)	0.91	(0.41–2.00)	0.91	(0.39–2.13)
Size of largest tumor (mm)							
≥ 3	2	95 (49.7%)	88 (46.6%)	1.07	(0.87–1.32)	1.14	(0.76–1.72)
	4	97 (50.8%)	76 (40.2%)	1.26	(1.01–1.58)	1.57	(1.04–2.37)
≥ 4	2	51 (26.7%)	52 (27.5%)	0.97	(0.70–1.35)	0.97	(0.61–1.54)
	4	52 (27.2%)	51 (27.0%)	1.01	(0.73–1.40)	1.02	(0.65–1.60)
≥ 10	2	4 (2.1%)	4 (2.1%)	0.99	(0.25–3.90)	1.00	(0.25–4.06)
	4	7 (3.7%)	0 (0.0%)	—	<i>p</i> < 0.01 ²		
Atypia of tumors							
≥ With moderate	2	64 (33.5%)	66 (34.9%)	0.96	(0.73–1.27)	0.94	(0.61–1.44)
	4	77 (40.3%)	74 (39.2%)	1.03	(0.80–1.32)	1.06	(0.70–1.60)

¹OR of recurrent tumors in the wheat bran biscuits group compared to the no treatment group, adjusted for age, sex and *Lactobacillus* group.—² χ^2 test.

TABLE IV – RISK OF TUMOR OCCURRENCE WITH LACTOBACILLUS PREPARATION

Year	<i>Lactobacillus</i> (groups B + C) (n = 192)	No treatment (groups A + D) (n = 188)	Crude		Adjusted ¹		
			relative risk	(95% CI)	OR	(95% CI)	
Number of tumors							
At least one	2	107 (55.7%)	118 (62.8%)	0.89	(0.75–1.05)	0.76	(0.50–1.15)
	4	96 (50.0%)	103 (54.8%)	0.91	(0.75–1.11)	0.85	(0.56–1.27)
≥ 2	2	56 (29.2%)	61 (32.4%)	0.90	(0.66–1.22)	0.88	(0.57–1.36)
	4	53 (27.6%)	51 (27.1%)	1.02	(0.73–1.41)	1.08	(0.68–1.71)
≥ 4	2	10 (5.2%)	15 (8.0%)	0.65	(0.30–1.42)	0.67	(0.29–1.53)
	4	15 (7.8%)	8 (4.3%)	1.84	(0.79–4.23)	1.98	(0.81–4.83)
Size of largest tumor (mm)							
≥ 3	2	86 (44.8%)	97 (51.6%)	0.87	(0.70–1.07)	0.77	(0.51–1.15)
	4	83 (43.2%)	90 (47.9%)	0.90	(0.72–1.13)	0.85	(0.56–1.28)
≥ 4	2	41 (21.4%)	62 (33.0%)	0.65	(0.46–0.91)	0.56	(0.35–0.89)
	4	58 (30.2%)	45 (23.9%)	1.26	(0.90–1.76)	1.38	(0.87–2.19)
≥ 10	2	4 (2.1%)	4 (2.1%)	0.98	(0.45–3.86)	1.01	(0.25–4.12)
	4	4 (2.1%)	3 (1.6%)	1.31	(0.30–5.75)	1.29	(0.28–6.00)
Atypia of tumors							
≥ With moderate	2	61 (31.8%)	69 (36.7%)	0.87	(0.65–1.14)	0.80	(0.52–1.22)
	4	66 (34.4%)	85 (45.2%)	0.76	(0.59–0.98)	0.65	(0.43–0.98)

¹OR of recurrent tumors in the *Lactobacillus* group compared to the no treatment group, adjusted for age, sex and wheat bran biscuit group.

with at least 2 tumors for the following reasons: (i) it is more efficient for the analysis of preventive methods against colon cancer to use subjects in higher-risk groups and (ii) since the occurrence rates of colon tumors after 2 and 4 years were higher in patients in the high-risk group, a preventive effect would be more prominent in this group.

The weak point of this trial is that it was not a double-blind study. Therefore, there could be bias from the fact that the participants and medical professionals did know the group to which each participant belonged. However, since it is widely believed in Japan that dietary fiber prevents colorectal cancer and nobody would think that dietary fiber would cause tumors to enlarge, it is highly unlikely that the unexpected results obtained in this study were biased. Histologic evaluations were performed blindly, without group identification, by pathologists. Therefore, there is unlikely to be a bias resulting from this not being a double-blind study in the result that administration of *L. casei* prevented the development of tumors with moderate or severe atypia.

The occurrence of tumors larger than 4 mm was significantly suppressed by *L. casei* administration after 2 years but not after 4 years. This might have resulted from a suppressive effect of *L. casei* administration against enlargement of colon tumors lasting for only a limited period. At the present time, it is not clear

how *L. casei* influences the early stages of tumor development. We are planning to examine the effect of *L. casei* administration on cellular proliferation histopathologically, to find the best administration method that will clearly show a suppressive effect on tumor development.

Although clinical studies on the administration of *L. casei* for the prevention of colorectal tumors have not been reported, there are a few reports of clinical studies aimed at changing the intestinal flora. Roncucci *et al.*³¹ reported that lactulose appeared to slightly suppress the development of colorectal tumors, although without statistical significance.

The *L. casei* preparation used in our study was a quality-controlled homogeneous live preparation. *L. casei* survives well in gastric acid³² and is used as an intestinal conditioning agent in Japan. It is known to augment immunity³³ and inhibit enzyme activity involved in carcinogenesis.¹⁷ It has been reported to suppress the development of colorectal tumors in rats.³⁴

The mechanism of the suppression by *L. casei* of the development of colorectal tumors with moderate or severe atypia is not clear. Further analyses are in progress examining stools, colonic mucous membrane and serum collected from patients who participated in this study.

Several similar studies from Western countries have reported that dietary fiber supplementation did not prevent or promote the

development of colorectal tumors. In the clinical study by Bonithon-Kopp *et al.*,¹⁶ dietary fiber-rich psyllium significantly increased the development of adenomas after 3 years as analyzed by endoscopy (OR = 1.67), consistent with our results. Alberts *et al.*¹⁵ reported, from a clinical study with large and small quantities of wheat bran cereal, that there was no difference in the development of adenomas but that the number of patients who developed at least 3 adenomas was significantly higher in the high-dietary fiber group. Since it was found in a previous study²⁹ that the diets of participants were changed by administration of a large quantity of dietary fiber, the quantity

of dietary fiber was lower in the present study than that used in other studies. To target the high-risk group for colorectal cancer, patients with multiple colorectal tumors were included as subjects. In spite of these differences from previous studies, the development of colorectal tumors was not prevented by dietary fiber also in this study.

Thus, there has been no consensus on the efficacy of dietary fiber against colorectal cancer. From the results of our study as well as the previous results of supplementation studies, it is not recommended to take supplements containing a high concentration of dietary fiber for the prevention of colorectal cancer.

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