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Effects of Aged Garlic Extract (AGE) on Colorectal Adenomas: a double-blinded study

Shinji TANAKA[1], Ken HARUMA[2], Masaki KUNIHIRO[1], Shinji NAGATA[1], Yasuhiko KITADAI[3], Noriaki MANABE[3], Masaharu SUMII[3], Masaharu YOSHIHARA[4], Goro KAJIYAMA[5] and Kazuaki CHAYAMA[3]

1) *Department of Endoscopy, Hiroshima University Hospital, 1–2–3 Kasumi, Minami-ku, Hiroshima, 734–8551, Japan*
2) *Division of Gastroenterology, Department of Internal Medicine, Kawasaki Medical School, Matsushima 577, Kurashiki, 701–0192, Japan*
3) *Department of Medicine and Molecular Science, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Sciences, Hiroshima University, 1–2–3 Kasumi, Minami-ku, Hiroshima, 734–8551, Japan*
4) *Health Service Center, Hiroshima University, 1–7–1 Kagamiyama, Higashihiroshima, 739–8521, Japan*
5) *Onomichi General Hospital, 7–19 Kohama-cho, Onomichi, 722–8508, Japan*

ABSTRACT

Aged garlic extract (AGE) is a material that has the possibility of a cancer-preventive effect according to epidemiologic and animal studies. In order to confirm the effects of AGE on colorectal adenomas, we conducted a double-blinded randomized study using high-AGE (AGE 2.4 ml/day) and low-AGE (AGE 0.16 ml/day) doses 1 groups. Fifty-one patients who were diagnosed as having colorectal adenomas by colonoscopy were randomly assigned to the high-AGE and low-AGE groups. The number and size of adenomas before intake (0 month) and 6 and 12 months after intake were measured using colonoscopy. In 37 patients chosen as efficacy evaluated subjects, 47.4% (9/19) in the high-AGE and 66.7% (12/18) in the low-AGE group had at least one new adenoma for the first and second interval (0 to 12 months after intake), and its relative risk was 0.71. The decrease rate of at least one adenoma was 50.0% (7/14) in the high-AGE group for the second interval (6 to 12 months after intake), whereas there was no decrease in subjects in the low-AGE group (p=0.02). The difference from the base-line for total size of adenomas increased in the low-AGE group, whereas an increase in the high-AGE group was suppressed for the second interval (p=0.04). The difference from the base-line for the total size of adenomas in subjects who had adenomas on the base-line increased in the low-AGE group and decreased in the high-AGE group for the second interval (p=0.03). The results of this study suggest the possibility of preventive and therapeutic effects of AGE on colorectal adenomas, though it is necessary to investigate these in larger-scale and longer-term trials.

Key words: *Aged garlic extract, Colorectal adenoma, Cancer prevention*

Cancer and lifestyle relate closely, and it is suggested that the prevention of cancer is possible through an improved lifestyle. Foods that have the possibility of preventing cancer are listed in many epidemiologic and animal studies, and garlic is given as one of them[4]. In many case-control and cohort studies, garlic consumption suppresses cancer risk, and Fleischauer et al[6] suggest the preventive effect of garlic in stomach and colorectal cancers from these epidemiologic literatures.

Raw garlic is processed by various methods to avoid a toxicity of gastrointestinal disorders[13], and aged garlic extract (AGE) is one of the processed products. AGE and its related organosulfur constituents suppress the incidence of colorectal[24], stomach[26], skin[19], mammary[17] and liver[7] tumors induced by various carcinogens according to animal studies. Moreover, the immune function[16], antioxidant activity[14] and glutathione S-transferase activity[24] are stimulated, and research

Correspondence to: Shinji Tanaka, Department of Endoscopy, Hiroshima University Hospital, 1–2–3 Kasumi, Minami-ku, Hiroshima 734–8551, Japan
Tel: +81–82–257–5538, Fax: +81–82–257–5538, E-mail: colon@hiroshima-u.ac.jp

The place where the work was conducted with the exact postal address:
Hiroshima University Hospital, 1–2–3 Kasumi, Minami-ku, Hiroshima 734–8551, Japan

regarding their cancer preventive mechanisms has been reported[2,5,7,12,17]. Therefore, AGE may be considered to have a cancer-preventive effect.

On the other hand, as a method that evaluates the prevention of colorectal cancer or the treatment of colorectal adenomas, there is an intervention study which investigates the recurrence or decrease of colorectal adenomas (precancerous lesions), using colonoscopy. This study has been conducted with dietary fiber[1,21], calcium[3], antioxidant vitamins[10], nonsteroidal anti-inflammatory drugs (NSAIDs)[9,20,22], and hormone replacement therapy[27].

Thus, it is meaningful to investigate whether AGE affects the incidence and decrease of colorectal adenomas using this method, and to evaluate the colorectal cancer-preventive effect of AGE. As a preliminary study to confirm this, we investigated the effects of high-AGE and low-AGE on patients diagnosed as having colorectal adenomas, using a double-blinded randomized method.

MATERIALS AND METHODS

Subjects

Patients who were diagnosed as having colorectal adenomas (patients who had adenomas of more than 5 mm removed by polypectomy were included), and who were aged 40 to 79, were selected as subjects. Exclusion criteria were as follows: patients who had severe complications; who had a history of gastrointestinal operations other than appendectomy; who had received cancer chemotherapy treatment, herbal medicine or nonsteroidal anti-inflammatory drugs (NSAIDs); who had a dislike of garlic; who had a history of drug hypersensitivity, and who were judged to be unsuitable by investigators.

Ethics

Following approval by the Institutional Review Board of this hospital, and with due protection for the human rights of the subjects in accordance with the Declaration of Helsinki, this study was conducted at the Hiroshima University Hospital from October 2000 through October 2002.

Before the beginning of the test supplement intake, the patients were fully informed by documents that the examination involved research. The purpose of the examination and the methods employed were explained and they were informed about the expected benefits and adverse reactions. They were told that they might refuse to participate or withdraw from the examination at any time, and advised of the instructions that they would be required to observe, and other relevant matters. The written consent of the patients for their participation in the examination was then obtained.

Test supplements

Six capsules of high-AGE, as a test supplement, contained 2.4 ml of aged garlic extract, and six capsules of low-AGE, as a control supplement, contained 0.16 ml of aged garlic extract. Aged garlic extract (AGE) is produced by long term extraction from garlic in aqueous ethanol, and the AGE capsules contain AGE powder prepared by mixing AGE with crystalline cellulose as an excipient. Although AGE reduces the smell of garlic by aging, the powder has a characteristic smell and taste. In order to provide an indistinguishable state for the subjects, low-AGE with some garlic smell and taste was chosen as a control. Both supplements were supplied by Wakunaga Pharmaceutical Co., Ltd. (Osaka, Japan), and were confirmed to be indistinguishable in appearance (capsule and packaging) by the controller. Each subject took high- or low-AGE at a dose of 3 capsules twice a day after breakfast and dinner for 12 months.

Test methods

Allocation. The controller allocated a food number to the test supplement (high- or low-AGE) for one subject using a table of random numbers for the two groups before the trial was started, and each subject who was judged eligible by the investigators was given the allocated test supplement in order of enrollment. The key table was sealed and retained by the controller until blind-breaking. Blind-breaking was conducted by the controller after data and evaluated subjects were fixed.

Colonoscopy. The evaluations of colorectal adenomas were performed before intake of high- or low-AGE (0 month) and 6 and 12 months after intake with a magnifying high-resolution videocolonoscope manufactured by Fujinon (EC-410CM, EC-410ZM, Fujinon Corp., Omiya, Japan) or Olympus (CF-200Z, CF-240Z, Olympus Corp., Tokyo, Japan). The endoscopists recorded the location and size of all colorectal adenomas, and each adenoma was histologically examined using the standard technique when it was removed by polypectomy.

Adverse events

When any subjective or objective symptoms occurred following intake of the test supplements, the following were investigated and recorded: the nature of the symptom, its degree of seriousness (mild, moderate, severe, or serious), the day of its appearance and disappearance, any action taken for it, the outcome, and the causal relation between the test supplements and the symptom (i.e., Yes, Probably, Indeterminate, Probably not, and No). A symptom was treated as an adverse reaction if a causal relation between the test supplement and the symptom could not be denied.

Statistical analysis

For comparison of the two groups (the high-AGE

group versus the low-AGE group), we used Fisher's exact probability test for proportional data and the Mann-Whitney U test for the number or total size of adenomas. For the comparisons of each group with the base-line, we used the Wilcoxon rank sum test for the number or total size of adenomas. Statistical analyses were performed with two-tailed tests, using STATISTICA (StatSoft JAPAN Inc., Tokyo, Japan).

In the comparison for the incidence of at least one adenoma between the two groups, the relative risk and 95% confidence interval were adjusted for age and calculated by the methods used by Mantel-Haenszel[18] and Greenland et al[11].

RESULTS

Subjects

A flow diagram of subjects is shown in Fig. 1. A total of 51 patients were enrolled and randomized in this study (25 in the high-AGE group, 26 in the low-AGE group). Twelve patients (6 in the high-AGE, 6 in the low-AGE group) withdrew from the study within 6 months and were lost to follow-up colonoscopies for the following reasons: 8 (3 in the high-AGE, 5 in the low-AGE group) for participant's reasons, 2 (in the high-AGE) did not come to the hospital, 1 (in the high-AGE) for poor compliance, 1 (in the low-AGE) for an adverse reaction. One patient (in the low-AGE group) was unavailable for follow-up colonoscopies because pre-treatments had been poor at 6 and 12 months. One patient (in the high-AGE group) who withdrew at 7 months for his own reason was included in the efficacy evaluation, because a follow-up colonoscopy at 6 months was available. One patient (in the low-AGE) was excluded from the efficacy evaluation, because he regularly took an aspirin preparation that was a forbidden concomitant drug. Therefore, the efficacy evaluated subjects included 37 patients (19 in the high-AGE, 18 in the low-AGE group). The rate of compliance, investigated in an interview, was 80% or more in all efficacy evaluated subjects. The base-line characteristics of all randomized and efficacy evaluated subjects are shown in Table 1. Though the number of adenomas before polypectomy in the high-AGE group was higher than in the low-AGE group in the efficacy evaluated subjects (p=0.01), there were no significant differences between the two groups in other characteristics.

Efficacy on colorectal adenomas

The incidence and decrease of colorectal adenomas are shown in Table 2. The subjects with at least one new adenoma included 9 (47.4%) in the high-AGE group and 12 (66.7%) in the low-AGE group for the first and second interval (0 to 12 months after intake). The relative risk in the high-AGE as compared with the low-AGE group was 0.71 (95 percent confidence interval, 0.40 to 1.25).

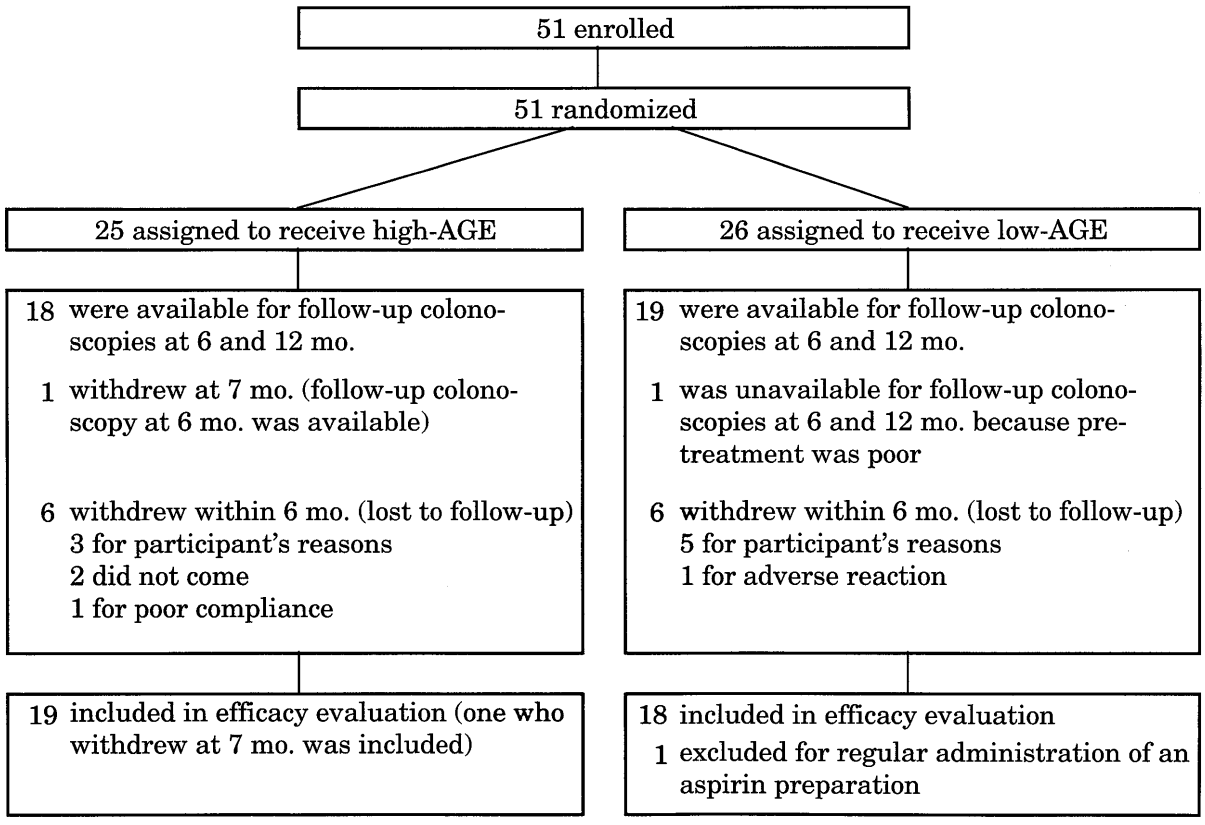


Fig. 1. Flow diagram of subjects

Table 1. Base-line characteristics of the subjects

Characteristic	All randomized subjects			Efficacy evaluated subjects		
	High-AGE (n=25)	Low-AGE (n=26)	p value	High-AGE (n=19)	Low-AGE (n=18)	p value
Sex—no. (%)						
Male	20 (80.0)	17 (65.4)	0.35[a]	15 (78.9)	12 (66.7)	0.48[a]
Age—yr.	58.8 ± 1.5	61.1 ± 1.7	0.39[b]	57.6 ± 1.3	61.3 ± 2.0	0.28[b]
Range	49–78	49–76		49–69	51–76	
Subjects who had adenomas—no.						
Before polypectomy	24 (96.0)	25 (96.2)	1.00[a]	18 (94.7)	17 (94.4)	1.00[a]
Remaining adenomas	9 (36.0)	7 (26.9)	0.56[a]	8 (42.1)	4 (22.2)	0.30[a]
No. of adenomas[c]						
Before polypectomy	2.60 ± 0.34	2.00 ± 0.27	0.17[b]	2.89 ± 0.43	1.56 ± 0.23	0.01[b]
Remaining adenomas	0.80 ± 0.25	0.35 ± 0.12	0.35[b]	0.95 ± 0.31	0.22 ± 0.10	0.15[b]
Total size of adenomas[c,d]—mm						
Before polypectomy	21.6 ± 3.7	17.0 ± 3.2	0.26[b]	22.3 ± 4.7	13.9 ± 3.19	0.16[b]
Remaining adenomas	2.56 ± 0.83	0.81 ± 0.32	0.33[b]	2.84 ± 0.97	0.39 ± 0.20	0.14[b]

Plus-minus values are means ± SE.
[a] Fisher's exact probability test. [b] Mann-Whitney U test.
[c] It was calculated as 0 when there was no adenoma.
[d] The total size of adenomas was calculated as the sum of the adenoma diameters.

Table 2. Incidence and decrease of colorectal adenomas

	High-AGE (n=19)	Low-AGE (n=18)	p value	RR (95%CI)[a]
	no./ total no. (%)	no./ total no. (%)		
Incidence of adenomas				
First interval (0–6 mo.)	10/19 (52.6)	8/18 (44.4)	0.89[c]	1.17 (0.61–2.27)
Second interval (6–12 mo.)	6/18 (33.3)	8/18 (44.4)	0.74[c]	0.75 (0.32–1.76)
First and second interval (0–12 mo.)[b]	9/19 (47.4)	12/18 (66.7)	0.39[c]	0.71 (0.40–1.25)
Decrease of adenomas (in subjects who had adenomas on the base-line)				
First interval (0–6 mo.)	3/ 8 (37.5)	1/ 4 (25.0)	1.00[d]	
Second interval (6–12 mo.)	7/14 (50.0)	0/ 9 (0.0)	0.02[d]	
First and second interval (0–12 mo.)	5/ 8 (62.5)	0/ 4 (0.0)	0.08[d]	

[a] RR and CI denote relative risk and confidence interval. Both estimates were adjusted for age.
[b] One subject (in the high-AGE group) withdrew on 7 months after intake was included.
[c] Mantel-Haenszel method. [d] Fisher's exact probability test.

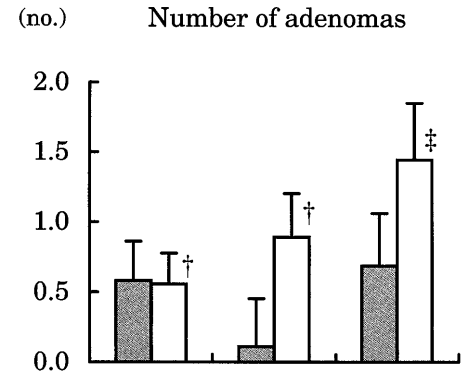
The decrease rates of at least one adenoma in the subjects who had adenomas on the base-line were 50.0% (7/14) in the high-AGE and 0% (0/9) in the low-AGE group for the second interval (6 to 12 months after intake, p=0.02), and 62.5% (5/8) and 0% (0/4) for the first and second interval, respectively.

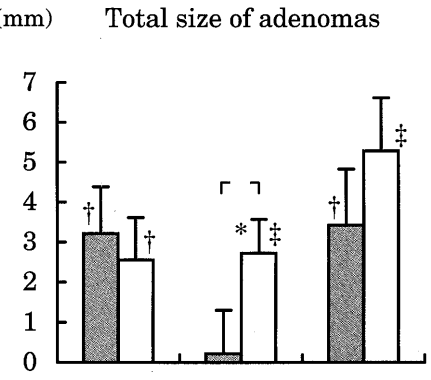
The subjects who underwent polypectomy at 6 or 12 months were 4 subjects in the high-AGE and 3 subjects in the low-AGE group. One subject in the low-AGE group had a histologically detected mucosal carcinoma, and all the other polyps were adenomas.

The results of the difference from the base-line for the number and total size of adenomas in the efficacy evaluated subjects are shown in Fig. 2A. The difference for the number of adenomas for the second interval increased to 0.89 ± 0.31 (means ± SE, $p<0.05$ vs. the base-line) in the low-AGE group, whereas in the high-AGE the increase was restrained to 0.11 ± 0.34. The difference for the total size of adenomas for the second interval showed a similar pattern, it was 2.72 ± 0.84 mm ($p<0.01$ vs. the base-line) in the low-AGE, 0.22 ± 1.08 mm in the high-AGE group, and there was a significant difference between the two groups (p=0.04).

The difference from the base-line for the number and total size of adenomas in subjects who had adenomas on the base-line are shown in Fig. 2B. The number of adenomas in the low-AGE group increased to 0.78 ± 0.46 for the second interval, whereas in the high-AGE group it decreased to –0.21 ± 0.35. The total size of adenomas for the second interval were 2.56 ± 1.04 mm ($p<0.05$ vs. the base-line) in the low-AGE, –0.86 ± 1.08 mm in the high-AGE group, and there was a significant difference between the two groups (p=0.03).

A



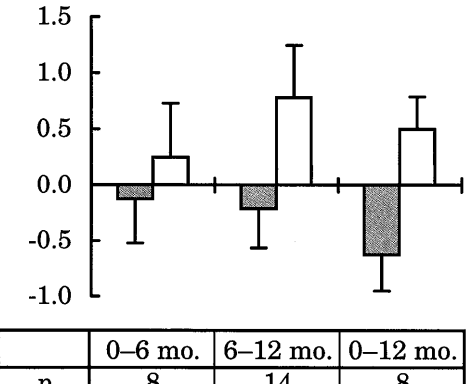


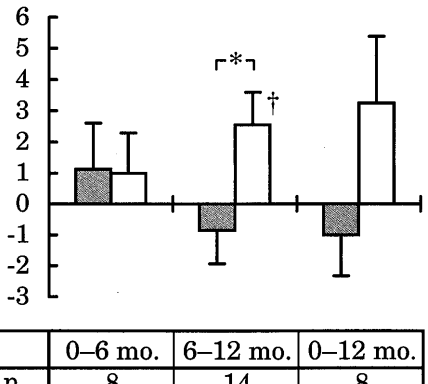
Group		0–6 mo.	6–12 mo.	0–12 mo.[a)]
High AGE	n	19	18	19
	Mean	0.58	0.11	0.68
	SE	0.28	0.34	0.38
Low AGE	n	18	18	18
	Mean	0.56	0.89	1.44
	SE	0.22	0.31	0.41
p value[b)]		0.82	0.10	0.21

Group		0–6 mo.	6–12 mo.	0–12 mo.[a)]
High AGE	n	19	18	19
	Mean	3.21	0.22	3.42
	SE	1.17	1.08	1.41
Low AGE	n	18	18	18
	Mean	2.56	2.72	5.28
	SE	1.05	0.84	1.34
p value[b)]		0.66	0.04	0.28

■ High-AGE □ Low-AGE

B





Group		0–6 mo.	6–12 mo.	0–12 mo.
High AGE	n	8	14	8
	Mean	−0.13	−0.21	−0.63
	SE	0.40	0.35	0.32
Low AGE	n	4	9	4
	Mean	0.25	0.78	0.50
	SE	0.48	0.46	0.29
p value[b)]		0.68	0.11	0.07

Group		0–6 mo.	6–12 mo.	0–12 mo.
High AGE	n	8	14	8
	Mean	1.13	−0.86	−1.00
	SE	1.48	1.08	1.32
Low AGE	n	4	9	4
	Mean	1.00	2.56	3.25
	SE	1.29	1.04	2.14
p value[b)]		0.93	0.03	0.11

Fig. 2. Differences from the base-line for the number and total size of adenomas in the efficacy evaluated subjects (Panel A), and differences from the base-line for the number and total size of adenomas in subjects who had adenomas on the base-line (Panel B).
The values are expressed as means ± SE.
[a)] One subject (in the high-AGE group) who withdrew 7 months after intake is included.
[b)] The p value of Mann-Whitney U test for comparison between the two groups. *$p<0.05$ (Mann-Whitney U test for comparison between the two groups). †$p<0.05$, ‡$p<0.01$ (Wilcoxon sign rank test for comparison with the base-line)

Safety

The adverse reactions that occurred in this study were seen in 1 subject in the high-AGE and 3 subjects in the low-AGE group. One in the high-AGE had an itchy back, and 3 in the low-AGE group had eczema on the upper limbs, epigastric pain and glossitis. These adverse reactions were mild. The intake of test supplements was able to be continued except for one subject with epigastric pain in the low-AGE group.

DISCUSSION

In this double-blinded randomized exploratory study, we confirmed the possibility that AGE had a preventive and therapeutic effect on colorectal adenomas. The intervention studies which evaluate the number or size of colorectal adenomas include a preventive study which evaluates the recurrence of adenomas after removing all adenomas before intervention[1,3,10,20,21], and a therapeutic study which evaluates the decrease in the remaining adenomas[9,22]. According to the usual surveillance technique, we also evaluated the decrease at the same time as the incidence of adenomas including subjects who had remaining small adenomas of 5 mm or less.

The incidence of colorectal adenomas was 66.7% in the low-AGE group and 47.4% in the high-AGE group for the first and second interval. There was about a 20% difference between the high-AGE and low-AGE group, and the relative risk (RR) was 0.71 (95% confidence interval, 0.40 to 1.25), though it was not a significant difference. However, it is estimated that it will be possible to detect a significance level of 5% if there are more than 60 subjects in one group. This RR was lower than the 0.81 RR in the Calcium Polyp Prevention Study[3], and nearer to the 0.68 RR for colon cancer by garlic consumption in the Iowa Women's Health Study[23] as a cohort study.

The decreasing effect of colorectal adenoma was admitted in the latter half of one year. The decrease rates of adenoma were 50.0% in the high-AGE and 0% in the low-AGE group for the second interval ($p=0.02$). If AGE is taken for one year or more, this effect might become clearer.

The total size of adenomas increased in the low-AGE for the second interval, whereas the high-AGE prevented an increase in size of adenomas ($p=0.04$). The difference from the base-line for the total size of adenomas in subjects who had adenomas on the base-line for the second interval decreased to –0.86 mm the high-AGE group, in the low-AGE group it increased to 2.56 mm, and there was a significant difference between the two groups ($p=0.03$). It is reported that sulindac[9] and celecoxib[22], which are cyclooxygenase inhibitors, reduce the number and size of colorectal polyps in patients with familial adenomous polyposis. The adenoma-decreasing effect of AGE is notable, though it cannot indiscriminately compare with these drugs because the subjects are different.

Thus, the results of this study suggest the possibility of a preventive and therapeutic effect of AGE on colorectal adenomas. However, it is necessary to execute larger-scale and longer-term trials to confirm this.

In the safety evaluation, though mild adverse reactions were seen in 1 subject in the high-AGE and 3 subjects in the low-AGE group, the intake of test supplements was able to be completed excluding 1 subject in the low-AGE group. There was no other remarkable incidence.

The various foods or nutrients that are considered to have a cancer-preventive effect in epidemiologic and animal studies are evaluated by various intervention trials of which the end point is the incidence of cancers or precancerous legions. The polyp prevention trial (PPT) which evaluates the recurrence of colorectal adenomas using colonoscopy is consistent with these trials. It is reported that the PPTs of dietary fiber[1,21] and antioxidant vitamins[10] show that they do not influence the risk of recurrent colorectal adenomas, while the effect of calcium[3] is significant though moderate. Currently, a PPT of n-3 unsaturated fatty acid[25], and intervention trials of AGE on stomach cancer[8] and hereditary non-polyposis colorectal cancer[15] are under way. It seems likely that cancer-preventive food or nutrients will be evaluated by various randomized controlled intervention trials in the future.

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