Jpn. J. Cancer Res. 87, 676–679, July 1996

A Pilot Study for a Randomized Controlled Trial to Prevent Gastric Cancer in High-risk Japanese Population: Study Design and Feasibility Evaluation

Shoichiro Tsugane,[1,4] Yoshitaka Tsubono,[1] Shunji Okubo,[2] Masato Hayashi[2] and Tadao Kakizoe[3]

[1]Epidemiology and Biostatistics Division, National Cancer Center Research Institute, East, 6-5-1 Kashiwanoha, Kashiwa 277, [2]Hiraka General Hospital, 1-30 Ekimae-cho, Yokote 013 and [3]National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104

Observational epidemiological studies suggest that some nutrients reduce the risk of gastric cancer and that individuals with atrophic gastritis are at high risk of developing gastric cancer. One possible measure for gastric cancer prevention is therefore nutritional supplementation for the high risk group. Before recommending this strategy for the general public, however, a randomized controlled trial (RCT) is necessary. To evaluate the feasibility of an RCT, the authors conducted a pilot study using recipients of a health check-up program in a general hospital in Japan. The subjects who were asked to participate in the trial had been diagnosed as having atrophic gastritis on the basis of serum pepsinogen I <70 ng/ml and the ratio of pepsinogen I to II <3.0. They were requested to ingest double-blinded capsules containing different levels of vitamin C and β-carotene every day. Out of the 219 subjects (118 males, 101 females) who were eligible for the study and had the required pepsinogen measurement, 90 (41%) met the criteria for atrophic gastritis. Among them, 55 (61%) (35 males, 20 females) gave their informed consent to participate in the RCT. Fifty-four participants completed a 3-month course of supplementation, and all of them agreed to a 5-year supplementation period. The authors concluded that an RCT using double-blinded nutritional supplements and targeting apparently healthy individuals is feasible in an intervention study for cancer prevention in Japan.

Key words: Gastric cancer — Atrophic gastritis — Prevention — Nutrient — Randomized controlled trial

Gastric cancer is the most common cancer in Japan with 47,000 Japanese dying of the disease in 1993 (Ministry of Health and Welfare, Japan. Vital Statistics 1993). The Japanese government has supported a mass gastric cancer screening program since 1983 which screens over 6 million people annually.[1)] This program may be significant in reducing gastric cancer mortality. However, an alternative method of primary prevention should be utilized to reduce the incidence of gastric cancer.

Many observational epidemiological studies have examined the risk of gastric cancer as well as preventative factors. Intake of salty foods or infection with *Helicobacter pylori* increase the risk, while fresh fruits and vegetables decrease it.[2)] Vitamin C in fruits and vegetables is believed to be a preventative substance, inhibiting nitrosamine formation and also acting as a free radical scavenger.[3,4)] Atrophic gastritis is considered to be a precursor of intestinal-type gastric cancer. A recent Japanese study found that subjects with this condition have a six times greater risk of developing gastric cancer.[5)] The combination of a low pepsinogen I (PGI)/pepsinogen II (PGII) ratio and a low PGI level in the sera is indicative of atrophic gastritis among asymptomatic subjects with high sensitivity and specificity.[6)] We have reported that β-carotene may protect against the progression of atrophic gastritis,[7)] and therefore β-carotene is another candidate for gastric cancer prevention.

Based on these findings and biological probabilities, we propose nutritional supplementation with vitamin C and β-carotene as a measure to prevent gastric cancer, particularly in subjects with atrophic gastritis. However, a randomized controlled trial (RCT) is necessary before recommending this strategy for the general public. An RCT is a standard method for testing the efficacy of a specific treatment such as chemotherapy or chemoprevention in Western countries which has recently been adopted in some clinical trials in Japan,[8,9)] although it is considered difficult to conduct a cancer prevention trial using apparently healthy subjects.[10)] However, no reports have indicated difficulty of completing an RCT in an intervention study of cancer chemoprevention.

We therefore conducted a pilot study using the subjects of a health check-up program to evaluate the feasibility of this type of RCT in Japan.

MATERIALS AND METHODS

Subjects The subjects were recipients of a health check-up program in a local general hospital. Their ages ranged from 40 to 69 years. Measurements of PGI and PGII

[4] Author to whom correspondence should be addressed.

were conducted after having obtained informed consent. Subjects whose level of PGI was less than 70 ng/ml and PGI/PGII ratio was less than 3.0 were asked to participate in the study, unless they had a prior history of gastric cancer, gastric operation, liver cancer, liver cirrhosis, any cancer within the past 5 years, a diagnosed gastric cancer in the health check-up or abnormal liver function with aspartate aminotransferase (GOT) >100 IU/liter or alkaline phosphatase (Alp) >800 IU/liter, or used either vitamin C or β-carotene as a nutritional supplement.

Informed consent All subjects satisfying the above eligibility criteria were requested by a doctor or public health nurse to participate in this study. They were informed both orally and in writing of the purpose and procedure of our study, the anticipated efficacy and side effects of vitamin C and β-carotene, and their other rights. Those who gave their written consent were entered in the study.

Randomization The participants were randomly assigned to 1 of 9 possible groups according to a three-by-three factorial design with three levels of vitamin C (0, 50 or 1000 mg/day) and β-carotene (0, 3 or 30 mg/day) and were asked to consume a total of four capsules (three for vitamin C and one for β-carotene) each day for 3 months. This 3-month supplementation was designed to obtain information about the changes of the blood levels of vitamin C and β-carotene in relation to the supplemented dosage. The appearance of the capsules was the same regardless of the content of vitamin C or β-carotene, and neither the participants nor the hospital staff were informed of the content. The capsules were allocated to each participant in a control center located in the Epidemiology and Biostatistics Division, National Cancer Center Research Institute, East and a random permuted block was used for the nine possible allocations. After a 3-month period, the second random allocations were conducted according to a two-by-two factorial design with two levels of vitamin C (50 or 500 mg/day) and β-carotene (0 or 15 mg/day) regardless of the first allocation group. They were scheduled to be supplemented for 5 years, in addition to the participants in the main study. The authors have initiated a double-blinded RCT using a similar protocol for the recipients of a comunity-based health check-up program.

Endpoints and check items The primary endpoint of this pilot study is the number of participants providing informed consent among the eligible subjects. The compliance of the general public in consuming the capsules for 3 months and the possible side effects are other factors in evaluating the study. The changes in plasma level after consumption of vitamin C and β-carotene were also measured. We evaluated the compliance of our subjects by counting the number of capsules not taken during the assigned period. The side effects were monitored both by a questionnaire in which the subjects described their symptoms and by analyzing their blood for GOT, Alp blood count and other items.

Study period The subject recruitment was started on January 6, 1995 and ended on June 27, 1995, after 55 subjects had agreed to participate and at least six participants were allocated to each of the nine groups.

Ethical approval The protocol of this pilot study was submitted to the ethical committees of both the National Cancer Center and Hiraka General Hospital and approved by them.

RESULTS

The following is our report of the participation rate, compliance, and side effects recorded during the first 3-month period.

The participation rate Out of the 231 participants (125 males, 106 females), 40 to 69 years old, in the health check-up program during the study period, 10 subjects were ineligible due to past history of gastric cancer (1), uterine cancer (1), gastrectomy (2), and supplement use (6). Two subjects were excluded due to the diagnosis of gastric cancer based on the examination conducted in the health check-up program (1), and rejection of blood sampling for the study (1). No subject was excluded on

Table I. Summary of the Pilot Study

Study phase	Males	Females	Total
Health check-up recipients ages 40–69 years	125	106	231
Eligible subjects for screening of atrophic gastritis	118	101	219
Subjects diagnosed as having atrophic gastritis through serum levels of pepsinogen I and II	54	36	90
Subjects participating in the randomized controlled trial	35	20	55
Participation rate (%)	65	56	61

the basis of abnormal liver function. Serum pepsinogens were measured for the remaining 219 subjects (118 males, 101 females), and 90 (41%) were diagnosed as having atrophic gastritis based on the criteria of PGI <70 ng/ml and PGI/PGII ratio <3.0. Fifty-five subjects (35 males, 20 females) provided written informed consent and began taking supplements, yielding a 61% response rate (Table I).

Reasons for rejection Reasons for nonparticipation were investigated through a questionnaire mailed to 35 subjects who did not volunteer for the study. The subjects were asked to choose one of the four pre-specified reasons they thought most adequately described their nonparticipation. If the questionnaire was not returned, the subjects were further contacted by telephone. The most common reason for rejection was that the subjects felt no need to take vitamin supplements as they regarded themselves as healthy (13), that they were too busy to participate in the study (7), felt anxious about potential side effects of the supplements (5), felt that they were being treated like an experimental animal (5), felt it was too much trouble to take the supplements every day and schedule follow-up examinations periodically (3), did not want to take any drug (1) and unknown reason (1).

Compliance On average, the subjects took 97% of the vitamin C and β-carotene capsules prescribed (range = 90 to 100%). No difference was observed in these rates among the three treatment groups for either vitamin C or β-carotene.

Side effects During the 3-month course of supplementation, clinically relevant symptoms were observed in two cases: erythema of the body trunk of a subject taking 50 mg/day of vitamin C and 30 mg/day of β-carotene, and yellowing of the palms in a subject taking 1000 mg/day of vitamin C and 30 mg/day of β-carotene. The subject with erythema dropped out of the study; the one with palmar yellowing remained and completed the full course of supplementation, as did the other 53 subjects with no symptoms.

DISCUSSION

RCT is considered to be the most scientific method for evaluating the efficacy of a prevention/treatment program and is a useful way to control the potential bias in human study. Furthermore, we believe that RCT is the most ethically appropriate method if the candidates are informed of the design and procedure of the trial and agree to participate before randomization. However, this type of phase III efficacy trial has rarely been conducted in Japan, even in the field of cancer treatment.[11]

Efficacy evaluation by RCT is essential in the field of cancer chemoprevention, because the expected reduction of cancer incidence is not high enough to detect by a non-randomized trial. Nutritional Intervention Trials in Linxian, China showed a 21% reduction in stomach cancer mortality[12] and the Beta-Carotene and Retinol Efficacy Trial (CARET) estimated that its sample size could expect a 23% reduction in lung cancer incidence.[13] This relatively small reduction, however, can contribute to preventing cancer throughout the world, since the target population is so large.

The use of double-blinded capsules is essential for a long-term prevention study, because of the possible biases. The participants may alter their dietary habits, including supplement use, because of taking the allocated capsules. Physicians may be influenced in their assessment of potential side effects and diagnoses of gastric cancer. We did not utilize complete placebo capsules, which contain neither vitamin C nor β-carotene, in the main study. The use of placebo capsules is useful if the effect of the nutrient itself is to be evaluated. However, people consume vitamin C and β-carotene from fruits and vegetables in daily life, and therefore it is impossible to set up a null consumer of these nutrients. The primary purpose of the trial should be to test which regimen of nutritional supplementation is effective in reducing the incidence of gastric cancer.

In this pilot study, we asked 90 subjects who were diagnosed through serum pepsinogen values as having atrophic gastritis to participate in the trial. We used a written brochure to inform the subjects about the trial and the rationale, purpose, and methods, including the random allocation, potential side effects and the results of the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study.[14] After having been informed, 55 subjects (61%) volunteered to participate in the trial and 54 completed the 3-month supplementation and continued to the 5-year supplementation. They consumed 97% of the supplements for 3 months and only one participant dropped out from the trial due to the clinical symptom of erythema possibly associated with the supplement intake.

We concluded from this pilot study that it is feasible to conduct a double-blinded, randomized controlled chemoprevention trial that targets high-risk individuals in the general population. Therefore, we initiated a full-scale trial for the participants in community-based health check-up programs in the same region where the pilot study was undertaken, and approximately five hundred subjects have been enrolled in the first year. However, we halted the beta-carotene supplementation in the main study on January 25, 1996 in response to a release by the National Cancer Institute (U.S.) on January 18, 1996 which indicated that β-carotene and vitamin A may be causing harm, based on interim study results of CARET. Details of the study will be reported in subsequent communications.

ACKNOWLEDGMENTS

We thank all participants in this study. We also thank Dr. Tadashi Ogiwara, Mr. Takashi Sato, Ms. Shigeko Ishinari, and other staff members at Hiraka General Hospital, and Dr. Yoshimichi Miyajima, former director of Yokote Public Health Center, for their valuable assistance. This study was supported in part by Grants-in-Aid for the Second Term Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health and Welfare of Japan.

(Received March 25, 1996/Accepted April 22, 1996)

REFERENCES

1) Hisamichi, S., Tsubono, Y. and Fukao, A. Screening for gastric cancer: a critical appraisal of the Japanese experience. GI *Cancer,* **1,** 87–93 (1995).
2) Fuchs, C. S. and Mayer, R. J. Gastric carcinoma. *N. Engl. J. Med.,* **333,** 32–41 (1995).
3) Tannenbaum, S. R., Wishnok, J. S. and Leaf, C. D. Inhibition of nitrosamine formation by ascorbic acid. *Am. J. Clin. Nutr.,* **53,** 247S–250S (1991).
4) Block, G. Vitamin C and cancer prevention: the epidemiologic evidence. *Am. J. Clin. Nutr.,* **53,** 270S–282S (1991).
5) Kato, I., Tominaga, S., Ito, Y., Kobayashi, S., Yoshii, Y., Matsuura, A., Kameya, A., Kano, T. and Ikari, A. A prospective study of atrophic gastritis and stomach cancer risk. *Jpn. J. Cancer Res.,* **83,** 1137–1142 (1992).
6) Samloff, M. I., Varis, K., Ihamaki, T., Siurala, M. and Rotter, J. I. Relationships among serum pepsinogen I, serum pepsinogen II, and gastric mucosal histology. *Gastroenterology,* **83,** 204–209 (1982).
7) Tsugane, S., Kabuto, M., Imai, H., Gey, F., Tei, Y., Hanaoka, T., Sugano, K., Watanabe, S. *Helicobacter pylori,* dietary factors, and atrophic gastritis in five Japanese populations with different gastric cancer mortality. *Cancer Causes Control,* **4,** 297–305 (1993).
8) Shimoyama, M., Ota, K., Kikuchi, M., Yunoki, K., Konda, S., Takatsuki, K., Ichimaru, M., Ogawa, M., Kimura, I., Tominaga, S., Tsugane, S., Taguchi, H., Minato, K., Takenaka, T., Tobinai, K., Kurita, S., Oyama, A., Hisana, S., Kozuru, M., Matsumoto, M., Nomura, K., Takiguchi, T., Sugai, S., Yamaguchi, K., Hattori, T., Kinoshita, K., Tajima, K. and Suemasu, K. Chemotherapeutic results and prognostic factors of patients with advanced non-Hodgkin's lymphoma treated with VEPA or VEPA-M. *J. Clin. Oncol.,* **6,** 128–141 (1988).
9) Iizuka, T., Ide, H., Kakegawa, T., Sasaki, K., Takagi, I., Ando, N., Mori, S., Arimori, M. and Tsugane, S. Preoperative radiotherapy for esophageal carcinoma, randomized evaluation trial in 8 institutions. *Chest,* **93,** 1054–1058 (1988).
10) Ishikawa, H., Akedo, I., Suzuki, T., Otani, T. and Soube, T. Interventional trial for colorectal cancer prevention in Osaka: an introduction to the protocol. *Jpn. J. Cancer Res.,* **86,** 707–710 (1995).
11) Fukushima, M. The overdose of drugs in Japan. *Nature,* **342,** 850–851 (1989).
12) Blot, W. J., Li, J. Y., Taylor, P. R., Guo, W., Dawsey, S., Wang, G., Yang, C. S., Zheng, S., Gail, M., Li, G., Yu, Y., Liu, B., Tangrea, J., Sun, Y., Liu, F., Fraumeni, J. F., Zhang, Y. and Li, B. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease specific mortality in the general population. *J. Natl. Cancer Inst.,* **85,** 1483–1492 (1993).
13) Omenn, G. S., Goodman, G., Thornquist, M., Grizzle, J., Rosenstock, L., Barnhart, S., Balmes, J., Cherniack, M. G., Cullen, M. R., Glass, A., Keogh, J., Meykens, F., Valanis, B. and Williams, J. The beta-carotene and retinol efficacy trial (CARET) for chemoprevention of lung cancer in high risk populations: smokers and asbestos-exposed workers. *Cancer Res.,* **54,** 2038s–2043s (1994).
14) The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N. Engl. J. Med.,* **330,** 1029–1035 (1994).