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Randomized Control Trials

Green tea extracts for the prevention of metachronous colorectal polyps among patients who underwent endoscopic removal of colorectal adenomas: A randomized clinical trial

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SUMMARY

Objectives: To determine the preventive effect of green tea extract (GTE) supplements on metachronous colorectal adenoma and cancer in the Korean population.

Materials and methods: One hundred seventy-six subjects (88 per each group) who had undergone complete removal of colorectal adenomas by endoscopic polypectomy were enrolled. They were randomized into 2 groups: supplementation group (0.9 g GTE per day for 12 months) or control group without GTE supplementation. The 72-h recall method was used to collect data on food items consumed by participants at baseline and the 1-year follow-up during the past 48 h. Follow-up colonoscopy was conducted 12 months later in 143 patients (71 in control group and 72 in the GTE group).

Results: Of the 143 patients completed in the study, the incidences of metachronous adenomas at the end-point colonoscopy were 42.3% (30 of 71) in control group and 23.6% (17 of 72) in GTE group (relative risk [RR], 0.56; 95% confidence interval [CI], 0.34–0.92). The number of relapsed adenoma was also decreased in the GTE group than in the control group (0.7 ± 1.1 *vs.* 0.3 ± 0.6, $p = 0.010$). However, there were no significant differences between the 2 groups in terms of body mass index, dietary intakes, serum lipid profiles, fasting serum glucose, and serum C-reactive protein levels (all $p > 0.05$).

Conclusion: This study of GTE supplement suggests a favorable outcome for the chemoprevention of metachronous colorectal adenomas in Korean patients (ClinicalTrials.gov number, NCT02321969).

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1. Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer, and the fourth most common cause of cancer-related death in the world [1,2]. In Korea, colorectal cancer has the second and the third highest incidences among men and women respectively in 2011 [3]. Especially, the incidence showed a rapid increase with an annual change of 5.6% in men and 4.3% in women between 1999 and 2012 [4]. The increase in CRC might be associated with environmental factors including westernized lifestyle and economic development in recent decades.

The world's second most popular beverage is tea. Among them, green tea contains high concentrations of catechins; in contrast, high amounts of theaflavins and thearubigins were found in black tea. A previous metaanalysis of epidemiologic studies on the effect of green tea on CRC including both case–control studies and prospective cohort studies showed a significant reduction in colorectal cancer risk by 20% [5]. However, a recent metaanalysis that

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; EGCG, (−)-epigallocatechin gallate; GTE, green tea extract; HDL-C, high density lipoprotein cholesterol; hsCRP, highly-sensitive C-reactive protein; LDL-C, low density lipoprotein cholesterol; NSAID, non-steroidal anti-inflammatory drug; PCNA, proliferative cell nuclear antigen; RMPI, rectal mucosal proliferation index; RR, relative risk; UNL, upper limit of the normal range.

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included only prospective cohort studies showed an insignificant association [6]. Therefore, the preventive effect of green tea on CRC still remains to be elucidated.

In addition, with respect to the optimal dose of green tea to prevent cancer, at least 10 Japanese cups of green tea (approximately 2000 mL) per day are considered the daily cancer preventive amount, which accounts for approximately 2.5 g of green tea extract (GTE) [7]. At this high dose, however, adverse effects can occur including nausea, heartburn, stomachache, headache, insomnia and palpitation, which are at least partly related to caffeine. To ease green tea polyphenol supplementation and to reduce its side effects, GTE capsules or tablets could be prepared. Previously, a Japanese pilot study showed that the supplementation of 1.5 g of GTE per day for 12 months decreased metachronous colorectal adenoma by half [8]. In Europe, a large multicenter randomized controlled trial is in progress called GTE *versus* placebo for metachronous colon adenoma in an elderly population [9].

Based on this background, we performed a prospective clinical trial on this issue. As far as we know, this is the first Korean study. The purpose of this study was to investigate the preventive effect of GTE supplements on metachronous colorectal adenomas by administrating GTE tablets with each tablet equivalent to 0.9 g/day GTE, 0.6 g/day catechin.

2. Methods

2.1. Subjects

The present study is a single-center prospective randomized open-labelled study. Between 2010 and 2015, patients who had undergone endoscopic polypectomy for the complete removal of colorectal adenomas were enrolled from Seoul National University Bundang Hospital. The inclusion criteria were as follows: 1) subjects were men or women between the ages of 19–85 years; 2) colorectal adenoma(s) were removed by endoscopic polypectomy or endoscopic mucosal resection at the time of enrollment; and 3) adequate bowel preparation (Boston Bowel Preparation Score ≥ 2 in all 3 segments) was performed. The followings were the exclusion criteria: 1) suspicious hereditary CRC (such as familial adenomatous polyposis and hereditary non-polyposis colorectal cancer); 2) personal history of any cancer; 3) presence of inflammatory bowel disease (such as ulcerative colitis and Crohn's disease); 4) previous history of a resection of the small or large intestine; 5) co-administration of aspirin or any NSAIDs; 6) previous history of a major organ transplantation or co-administration of immunosuppressive drugs; and 7) poor bowel preparation in the initial colonoscopy. The subjects were randomized into 2 groups using a blocked randomization method (block size = 4) as follows: a treatment group with GTE supplementation (0.9 g GTE per day for 12 months) and a control group without GTE supplementation. *A priori* power analysis determined that a sample size of 176 patients (88 per each group) was required to give the study 80% power to detect a difference assuming a two-sided significance test at the 0.05 level. Among these subjects, 143 (71 in the control group and 72 in the GTE group) completed the study protocol (Fig. 1).

The study participants were checked every 3 months to evaluate adverse effects and compliance. In addition, co-administration of aspirin or NSAIDs was checked at each follow-up. A follow-up colonoscopy was conducted at 12 months to observe the occurrence of any new colorectal polyps. The endoscopists were not informed on which group the study participants belonged to which excluded any potential bias. In addition, the study subjects underwent laboratory tests, answered a questionnaire which included their habitual tea and coffee consumption (at baseline only), and for the dietary assessment, a structured 3-day recall questionnaire was given at baseline and 1-year follow-up. The Ethics Committee at Seoul National University Bundang Hospital approved the study protocol (B-1006-103-00).

2.2. Green tea extract tablet formulation

The green tea extract tablets (both water and ethanol extracts) were provided by the AmorePacific R&D Center (Gyeonggi-do, Korea). Fresh green tea leaves (*Camellia sinensis*) harvested in 2009 from 3 tea-growing areas in the Jeju island (south Korea) were used to manufacture the tablets. One GTE tablet (500 mg) contained 225 mg of GTE consisting of 51.5 mg (−)-epigallocatechin gallate (EGCG), 11.6 mg (−)-epicatechin, 65.5 mg (−)-epigallocatechin, 5.7 mg (−)-epicatechin gallate, and 10.9 mg caffeine, which is approximately equivalent to 2 Japanese-size cups (approximately 400 mL) of green tea. The GTE supplementation group received two GTE tablets 30 min after a meal twice a day for 12 months, which is equivalent of 0.9, 0.6 and 0.2 g/day GTE, catechin, and EGCG, respectively.

2.3. Blood testing

For all the study participants, blood was drawn by venipuncture at baseline and at the 1-year follow-up. Each time we investigated serum liver enzymes [alanine transaminase (ALT)/aspartate transaminase (AST)], lipids [total cholesterol, triglyceride, low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C)], C-reactive protein (CRP), and fasting glucose levels.

2.4. Evaluation of the rectal mucosal proliferation index

Additionally, to evaluate the rectal mucosal proliferation index (RMPI) using a known proliferation marker (Ki-67), at least two random biopsies of rectal mucosa were taken. Among the study participants, 30 patients (30 pairs at baseline and after 1 year) were analyzed to select well-stained and the tissue sections showing well-oriented, U-shaped crypts that were open from the apical lumen to the base. Formalin-fixed, paraffin-embedded tissue blocks of polyp were cut (3 μm thickness) and mounted on coated glass slides. Immunohistochemistry was done with an automated slide preparation system Benchmark XT (Ventana Medical systems Inc, Tucson, AZ). EZ prep, CC1 (cell conditioning solutions 1), and the BMK ultraVIEW diaminobenzidine (DAB) detection system (Ventana Medical Systems) were used for deparaffinization, epitope retrieval, and staining according to the manufacturer's instructions. Sections were stained with Ki-67 (ab15580, 1:700). Ultra-VIEW copper was used to amplify the positive signals. Hematoxylin and blueing reagent were used to counterstain the sections. Microscopic examinations were performed (OLYMPUS BX53). Images were captured (CellSens, Olympus, ×200) for all slides, and positively stained cells in the crypts were counted with the IMT i-Solution software (version 10.1). All the % values in one patient were averaged to produce an average % of Ki-67 stained cells.

2.5. Statistical analysis

Data on food intake obtained from the 3-day recall questionnaires were analyzed by the Computer Aided Nutritional Analysis version 3.0 (CAN-pro 3.0, Nutritional Assessment Program, 2006, The Korean Nutrition Society, Seoul, Korea) [10]. To evaluate whether any significant difference was present in demographic or clinical features between controls and GTE group, univariate analysis with Student's *t*-test or χ^2-test was performed. The paired *t*-test was used to analyze the paired samples. For the comparison in the changes in body weight, body mass

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