The preventive effects of low-dose enteric-coated aspirin tablets on the development of colorectal tumours in Asian patients: a randomised trial


ABSTRACT
Objective To evaluate the influence of low-dose, enteric-coated aspirin tablets (100 mg/day for 2 years) on colorectal tumour recurrence in Asian patients with single/multiple colorectal tumours excised by endoscopy.
Design A double-blinded, randomised, placebo-controlled multicentre clinical trial was conducted.
Participants 311 subjects with single/multiple colorectal adenomas and adenocarcinomas excised by endoscopy were enrolled in the study (152 patients in the aspirin group and 159 patients in the placebo group). Enrolment began at the hospitals (n=19) in 2007 and was completed in 2009.
Results The subjects treated with aspirin displayed reduced colorectal tumourigenesis and primary endpoints with an adjusted OR of 0.60 (95% CI 0.36 to 0.98) compared with the subjects in the placebo group. Subgroup analysis revealed that subjects who were non-smokers, defined as those who had smoked in the past or who had never smoked, had a marked reduction in the number of recurrent tumours in the aspirin-treated group. The adjusted OR for aspirin treatment in non-smokers was 0.37 (CI 0.21 to 0.68, p<0.05). Interestingly, the use of aspirin in smokers resulted in an increased risk, with an OR of 3.44. In addition, no severe adverse effects were observed in either group.
Conclusions Low-dose, enteric-coated aspirin tablets reduced colorectal tumour recurrence in an Asian population. The results are consistent with those obtained from other randomised controlled trials in Western countries.
The clinical trial registry website and the clinical trial number http://www.umin.ac.jp (number UMIN00000697).

INTRODUCTION
Among chemopreventive interventions, aspirin (acetylsalicylic acid) has been examined in numerous trials that support its suppressive effect on colorectal cancer (CRC) development. Aspirin is a synthetic medicine based on the structure of salicylates, which are commonly found in fruits and vegetables. Aspirin’s antineoplastic effects have been mechanistically explained by its cyclooxygenase (COX) inhibitory activity. The use of aspirin as a cancer chemopreventive agent is advantageous because it has a long history of clinical use.
and its adverse effects are well known. Moreover, the cost-effectiveness of aspirin administration to prevent other diseases, such as cardiovascular disease, has also been demonstrated.1

An early prospective cohort study of 662,424 adults (the Cancer Prevention Study II cohort) demonstrated that the CRC death rate decreased with frequent aspirin use. The decreased relative risk (RR) of CRC among frequent aspirin users (≥16 times/month for at least 1 year with doses greater than 160 mg) was 0.60 (95% CI 0.4 to 0.89) in men and 0.58 (95% CI 0.37 to 0.9) in women.2 An updated analysis of this cohort (the Cancer Prevention Study II Nutrition cohort) demonstrated that long-term daily aspirin use (≥325 mg/day for ≥5 years) is associated with reduced incidence of CRC compared with non-users (RR=0.68, 95% CI 0.52 to 0.90 among men and women collectively).3 4 The factors that may affect the impact of aspirin include the population, dose of aspirin and duration of intervention.4 In the general population, trials of 75–325 mg/day aspirin for 3 years reduced the risk of recurrent colorectal adenoma by 17%.5 Moreover, the use of aspirin for 3 years or longer reduced the incidence and mortality of CRC by 30%–40% after 20-year follow-up.6

A considerable amount of evidence on the utility of aspirin has been generated in Western populations; however, the evidence for aspirin as a cancer chemopreventive agent in Asian populations is limited. Thus, it is important to present evidence that aspirin is also effective as a cancer chemopreventive agent in Asian populations.

We recently reported a double-blinded, randomised, placebo-controlled clinical trial of a high-risk CRC group, familial adenomatous polyposis, to evaluate the effect of low-dose, enteric-coated aspirin tablets. Secondary endpoint data from the trial revealed that subjects with a mean baseline polyp diameter of <2 mm administered aspirin displayed a significant reduction in mean polyp size.7

We investigated the effects of low-dose, enteric-coated aspirin tablets administered for 2 years in a double-blinded, randomised, placebo-controlled clinical trial in patients with a single/multiple colorectal adenomas and/or adenocarcinomas with invasions confined to the mucosa and excision by endoscopy. This population was considered to be a high-risk colorectal tumour group. Low-dose, enteric-coated aspirin tablets (100 mg/day) were chosen for the study because low-dose aspirin may circumvent the risk of upper GI toxicity.8 In addition, the enteric coating may decrease gastric mucosal damage, as demonstrated in the MAJIC study targeting high-risk cardiovascular Japanese patients9 as well as other short-term endoscopic studies.10

Here, we report the efficacy and safety of low-dose, enteric-coated aspirin tablets in the suppression of colorectal tumour recurrence in Asian patients with colorectal adenomas and/or adenocarcinomas with confined mucosal invasions that were excised by endoscopy.

METHODS

**Trial methodology**

In this double-blinded (both subjects and investigators), randomised, placebo-controlled trial using low-dose, enteric-coated aspirin tablets, the subjects received either 100 mg/day aspirin or placebo for 2 years. Each case was randomised by investigators using a computer-aided system from the Medical Research Support website. Using a minimisation algorithm, the primary examination selection was balanced with respect to three stratification variables: institution, age (≤60 and >60 years) and sex (male or female). The website was only available to the trial investigators. Subject enrollment and intervention assignment began at each hospital in January 2007, and the trial ended in July 2009. To further evaluate the effects of aspirin, follow-up for more than 2 years after the randomised trial was also planned. An Ethics Monitoring Committee was established for this multicentre trial (n=19) that was primarily based at Osaka Central Hospital. A system to ensure continuous follow-up of adverse events was also established. All hospitals participating in this trial obtained approval from their own ethics committees. This trial is registered and details are available at http://www.umin.ac.jp (number UMIN000000697), where the full trial protocol can be accessed.

**Trial population**

The trial population (n=389) consisted of patients with single/multiple colorectal adenomas and/or adenocarcinomas with invasions confined to the mucosa. The colorectal tumours of all subjects participating in the trial were excised by endoscopy before the trial start. An endoscopic examination was performed twice before the start of the trial; the examinations occurred at an average of 488.4 ±472 (mean±SD) days apart to confirm that all colorectal tumours were excised. All of the subjects were Asian men or women 40–70 years-old living in Japan. The following are exclusion criteria for the trial: (1) patients with familial adenomatous polyposis, Lynch syndrome or colorectal resection; (2) patients currently taking an antithrombotic or anticoagulant, including aspirin; (3) individuals with a history of stroke or gastric/duodenal ulcers (with the exception of patients with confirmed scars resulting from the successful eradication of Helicobacter pylori); (4) patients with IBD, haemorrhagic diverticulitis or haemorrhagic tendency; (5) patients with a platelet count of ≤100 000/mm3 or abnormal prothrombin time; (6) patients with a known aspirin allergy; (7) patients currently taking an anticancer drug; (8) pregnant patients or those who planned to become pregnant during the trial period; and (9) patients taking non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief more than thrice weekly. We calculated that 266 randomised patients would achieve an 80% power (with a 5% type I error) to detect a 40% difference in the recurrence rate of adenoma given a 40% risk of recurrence in the placebo group.11 However, data were unavailable to calculate an appropriate number of individuals to recruit from the Asian population; therefore, we set our recruitment goal in the initial aspirin protocol to 700 randomised patients.

Consent interviews were performed individually, and written informed consent was obtained from all patients.

**Investigational drug**

Low-dose, enteric-coated aspirin tablets (100 mg per tablet) and the placebo tablets were kindly provided by Bayer Pharma AG (Leverkusen, Germany) and imported into Japan. The trial was financed by research funding from the Ministry of Health, Labor and Welfare, not by Bayer Pharma AG. We signed an agreement to certify that no conflicts of interest with Bayer Pharma AG existed. The investigational drugs were placed in blister packages (calendar sheets of 31 tablets), and both sides of the package were aluminium-laminated.

**Trial questionnaire**

At the time of trial enrolment, the height, body weight, medical history, smoking history, alcohol ingestion and use of NSAIDs were investigated for each patient using a questionnaire. In addition, data regarding everyday meals were collected using a self-administered food-frequency questionnaire developed by the Department of Health Promotion and Preventive Medicine,
Nagoya-City University Graduate School of Medical Science, Aichi, Japan. Non-smokers were defined as people who had smoked in the past or never smoked. Occasional drinkers were defined as people who drank less than twice a week.

To ensure the accurate characterisation of adverse effects and evaluation of tolerability, the subjects were asked to keep a treatment diary that documented their conditions during treatment, such as drug compliance and medical conditions, and a blister sheet was sent to the data centre every month.

**Trial endpoints**
Colonoscopy was performed at least three times, twice before the start of the trial and once at the end of the trial. All the patients were given an oral lavage solution for colonoscopy at the time of the colonoscopy for clear imaging, and a medical colonoscopy specialist carefully examined the patients from the rectum to the cecum. The final endoscopy examination was performed 2 years after the start of the trial. Recurrent tumours were further diagnosed by histology after tumour excision. The primary endpoint was the incidence of adenoma or adenocarcinoma recurrence. The data were analysed using logistic regression and ORs, and general factors, such as sex, age and the tumour number before the trial, were used to adjust occasional deviation during the randomised allocation. Each tumour was removed and examined histologically by a pathologist. Tumours were classified as adenomas or adenocarcinomas according to the ‘Japanese Classification of Colorectal Carcinoma’ criteria. The secondary endpoints included recurring tumour number, size and histology as well as the effects of lifestyle, such as smoking and alcohol drinking, and the frequency of adverse effects.

**Statistical analysis**
The baseline characteristics of the two arms were compared using the \( \chi^2 \) test or the \( t \) test. The adverse effect rates of both arms were compared using the \( \chi^2 \) test. If needed, Fisher’s exact probability was applied due to sparse data in a table. To adjust for potential confounding effects at baseline, logistic regression was performed.

We also examined the effect modification (interaction) of several factors, such as (1) sex, (2) age, (3) smoking and (4) alcohol drinking, on the main effect of aspirin by adding an interaction term to the logistic regression. In this analysis, we determined the ORs of the subgroups of the above factors and the difference in the ORs of the subgroups.

All statistical analyses were based on the intention-to-treat and performed using PC-SAS (V9.3; SAS Inc., Cary, North Carolina, USA), with \( p<0.05 \) considered statistically significant.

### RESULTS

**Characteristics of the trial subjects**
A total of 490 patients were screened, and 389 patients provided informed consent. Subject enrolment began in January 2007, and the trial ended in July 2009. Subject recruitment ended according to the planned time schedule. After randomisation, the aspirin and placebo group consisted of 191 and 198 subjects, respectively. At the end of the trial, 152 subjects from the aspirin group and 159 subjects from the placebo group underwent a 2-year follow-up endoscopy examination (figure 1). The characteristics of the subjects in the aspirin and placebo groups after randomisation are displayed in table 1. No significant differences between the two groups were observed with regard to the following characteristics: age, sex, smoking status, alcohol drinking status, height, body mass index, tumour number upon entry into the trial, past history of CRC with invasion confined to the mucosa, treatment period, compliance (ie, whether patients correctly take medicine and follow the doctors’ instructions (data not shown)), surgical history (data not shown) and family history of CRC (data not shown). The serum concentrations of alanine transaminase, aspartate amino transferase, γ-glutamyl transpeptidase and triglycerides were almost identical between the groups (data not shown).

**Colonrectal tumour recurrence as the primary endpoint**
In total, 96 patients did not experience colorectal tumour recurrence in the aspirin group (total 152), and 86 patients in the placebo group (total 159) did not recur. In crude analyses, the subjects in the aspirin group tended to demonstrate a reduced number of colorectal tumours, which was the primary endpoint, compared with subjects in the placebo group. The OR was 0.69 (95% CI

### Table 1 Characteristics of the trial subjects

<table>
<thead>
<tr>
<th></th>
<th>Aspirin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>152</td>
<td>159</td>
</tr>
<tr>
<td>Age, y</td>
<td>60.0 ± 7.3*</td>
<td>60.5 ± 6.6</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>121 (79.6%)</td>
<td>125 (78.6%)</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>45 (29.6%)</td>
<td>34 (21.4%)</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drinker†</td>
<td>83 (54.6%)</td>
<td>92 (57.9%)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>164.7 ± 6.8</td>
<td>165.5 ± 7.3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>64.3 ± 9.7</td>
<td>65.6 ± 10.1</td>
</tr>
<tr>
<td>BMI‡</td>
<td>23.6 ± 2.7</td>
<td>23.9 ± 2.8</td>
</tr>
<tr>
<td>Number of tumours upon trial entry</td>
<td>5.3 ± 5.7</td>
<td>5.1 ± 7.0</td>
</tr>
<tr>
<td>Past CRC history</td>
<td>40 (26.3%)</td>
<td>39 (24.5%)</td>
</tr>
<tr>
<td>Treatment period</td>
<td>751 ± 67 days</td>
<td>764 ± 90 days</td>
</tr>
</tbody>
</table>

*SD.
†Alcohol drinker: drinks more than three times a week.
‡Body mass index (BMI)=Weight (kg)/height (m) squared.
CRC, colorectal cancer.
0.44 to 1.08); despite a marginal difference, the value was not statistically significant. To adjust for potential confounders, such as sex, age and the number of recurrent tumours, we performed logistic regression and obtained a significant OR value of 0.60 (95% CI 0.36 to 0.98). The OR for the number of recurrent tumours <4 in the aspirin group was 0.34 (0.09 to 1.26), and the OR for a tumour >3 mm in longitudinal diameter was 0.86 (0.63 to 1.16), but the value was not statistically significant.

The effects of smoking and drinking on colorectal tumour recurrence

Using a logistic regression with smoking as the interaction term and aspirin as the effect, we observed that smoking displays strong effect modification on the main effect of aspirin (p for interaction=0.004). Namely, the OR for non-smokers was 0.37 (95% CI 0.21 to 0.68), and this value was significantly different from the OR for smokers (OR 3.44, 95% CI 1.12 to 10.64) after adjustment for age, sex and the number of tumours (table 2). In contrast, no significant effect modification for sex (p=0.68), age (p=0.53) or alcohol consumption (p=0.32) was observed. With regard to sex, the OR was 0.48 (95% CI 0.15 to 1.53) and 0.63 (95% CI 0.36 to 1.08) among men and women, respectively. For age, the OR was 0.68 (95% CI 0.36 to 1.28) and 0.49 (95% CI 0.22 to 1.08) for subjects aged <60 and ≥60 years, respectively. For alcohol consumption, the OR was 0.72 (95% CI 0.37 to 1.40) and 0.44 (95% CI 0.21 to 0.95; p<0.05) for drinkers and occasional drinkers, respectively.

In addition, no severe adverse effects, such as cardiovascular events, were reported in either group. GI bleeding was not observed. Of note, colorectal adenocarcinomas were observed in four subjects: two cases from the aspirin group (one adenocarcinoma with invasion confined to the mucosa, and one adenocarcinoma with muscularis propria invasion) and two in the placebo group (two adenocarcinomas with invasion confined to the mucosa). The remaining tumours were tubular adenomas; villous adenomas were not identified. In addition, three high-grade dysplasias were detected; one case was observed in the aspirin group, and two cases were noted in the placebo group. The adenocarcinomas were 10–20 mm in diameter. The lesions were localised to the transverse colon (n=2), the descending colon (n=1) and the sigmoid colon (n=1).

**DISCUSSION**

In the present trial, we enrolled subjects with single/multiple colorectal adenomas and/or adenocarcinomas with invasions confined to the mucosa that were excised by endoscopy. Patients treated with low-dose, enteric-coated aspirin tablets for 2 years were shown to have a low risk of incidental colorectal tumour development, and this appeared to be reduced after adjustment for sex, age and the number of baseline tumours. Moreover, smoking significantly modified the preventive effect of aspirin.

In a meta-analysis of subjects with a history of colorectal adenoma or cancer in four randomised adenoma prevention trials (nearly 3000 patients), aspirin reduced the occurrence of advanced lesions (ie, tubulovillous adenomas, villous adenomas, adenomas ≥1 cm in diameter, adenomas with high-grade dysplasia or invasive cancer) by 28% (adenoma 17%; RR=0.83; 95% CI 0.72 to 0.96). Our trial also demonstrated reduced adenoma occurrence (OR=0.69), and similar effects were obtained compared with the meta-analysis by Cole et al. However, the ORs we used have a predictable effect on the comparison of the two sets of analyses. Regarding the limitations of our trial, the number of subjects enrolled is rather small, but the tumour recurrence results are consistent with previous studies. Thus, our data demonstrate that aspirin is also useful as a CRC chemopreventive agent in an Asian population. Of note, the first Asian adjuvant study (ASCOLT, NCT00565708) is ongoing, wherein patients with Dukes C or high risk Dukes B CRC are treated with aspirin (200 mg/day for 3 years).

Although the daily aspirin doses administered for vascular disease prevention are as effective as high-dose (1200 mg/day) aspirin,11 analyses comparing moderate (300–325 mg/day) and lower (81–160 mg/day) aspirin doses trials (AFPPS11 and APACC13) revealed that the reduced risk of all adenoma recurrence was only observed with lower doses.7 Our trial using low-dose, enterico-coated aspirin tablets (100 mg/day) was designed in light of these trials, thereby confirming that low-dose, enterico-coated aspirin tablets effectively reduce recurrence. In addition, low-dose regimens may have an advantage that the lower doses potentially reduce adverse effects. Aspirin has been reported to induce GI bleeding at a rate of 1–2 GI bleeds per 1000 person-years.14 In our trial, no severe adverse effects due to aspirin treatment were observed.

Aspirin’s antineoplastic effects are explained by COX-dependent and -independent mechanisms. In humans, aspirin inhibits COX-1 and COX-2 at high doses15 and appears to effectively inhibit prostaglandin synthesis in the colon.16 COX-independent mechanisms underlying aspirin’s antineoplastic effects are attributed to the modulation of nuclear factor κB: the induction of spermidine/spermine N1-acetyltransferase, caspase-8 and -9; and the activation of S5’ adenosine monophosphate-activated protein kinase, Erk and β-catenin.17–23

Despite copious information regarding aspirin’s functions, the mechanism by which smoking negates aspirin’s CRC chemopreventive effects remains unclear. A strong association between antiplatelet therapy resistance (aspirin resistance) and smoking has been reported. Specifically, a statistically significant interaction exists based on the multivariate analysis (risk ratio 11.47, CI 6.69 to 18.63, p<0.0001), which is likely due to smoking-induced platelet hyperactivity and chronic inflammation.25 In addition, smoking-induced decreased basal GI blood flow may also be involved. Thus, it is suggested that smoking negated aspirin’s chemopreventive effects in CRC. However, the evidence is limited. It is important to review and generate additional aspirin trial data to examine the association between NSAIDs use and smoking history and to determine whether the benefits of aspirin are limited to non-smokers.

In conclusion, although the size of this trial is small, the results are consistent with the observations of other aspirin adenoma trials; thus, aspirin may be useful for chemoprevention in Asian

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**Table 2** The effects of aspirin on colorectal tumour development in smokers

<table>
<thead>
<tr>
<th>Subanalysis</th>
<th>No. of subjects with (+) or without (−) colorectal tumour</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo group</td>
<td>26 19 45</td>
<td>1</td>
</tr>
<tr>
<td>Aspirin group</td>
<td>14 20 34</td>
<td>3.45 (1.12 to 10.64), p=0.03</td>
</tr>
<tr>
<td>Non-smoker*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo group</td>
<td>60 54 114</td>
<td>1</td>
</tr>
<tr>
<td>Aspirin group</td>
<td>82 36 118</td>
<td>0.37 (0.21 to 0.68), p=0.01</td>
</tr>
</tbody>
</table>

Adjusted OR, OR is adjusted by sex, age and the number of tumours prior to the trial.

*Non-smoker: never smoked and former smokers.
patients with single/multiple colorectal tumours and no ante-
ccedent risk of GI bleeding. Several years of follow-up after a ran-
domised trial are necessary to evaluate the effects of aspirin as 
proposed by the CAP2 randomised trial. Moreover, it would 
be informative to test aspirin in combination with other chem-
preventive agents that have demonstrated effectiveness and 
agents that prevent GI bleeding (eg, proton-pump inhibitors).

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Contributors HI, MM, SS, ST and KW were involved in the literature search, trial design and development, data analysis, data interpretation and writing of the manuscript. TH, YS, TA, SO, MT, TJ, ST, SK, TM, MI, TY, TT, YS, KL, SK, MM, YS, NG, KS, MK and NM were responsible for the data collection. SS, CG, and TS were responsible for the data analysis and data interpretation. All authors have contributed to, read and approved the final draft.

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Competing interests None.

Patient consent Obtained.

Ethics approval All hospitals participating in this trial obtained approval from their own ethics committees to conduct the trial.

Provenance and peer review Not commissioned; externally peer reviewed.

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