The 1st World Congress on CONTROVERSIES IN CASTROENTEROLOGY(CIGI)

Effects of Low-dose Aspirin on Colorectal Tumor Recurrence in Japanese Population (JCAPP study)

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15 June 2013 (13:15–15:25) Plenary Session 35 «**Chemoprevention in high risk populations** »

Introduction

Report of a meta-analysis in 4 randomized adenoma prevention trials

Trials	No. events / No. of examined (%)		Risk ratio (95% CI)
	Aspirin	Placebo	
AFPPS (Aspirin 81 or 325 mg/d)	300 / 721 (41.6)	171 / 363 (47.1)	0.88 (0.77 – 1.02)
APACC (Aspirin 160 or 300 mg/d)	65 / 128 (50.8)	62 / 116 (53.4)	0.95 (0.75 – 1.21)
CALGB (Aspirin 325 mg/d)	43 / 259 (16.6)	70 / 258 (27.1)	0.61 (0.44 – 0.86)
ukCAP (Aspirin 325 mg/d)	99 / 434 (22.8)	121 / 419 (28.9)	0.79 (0.63 – 0.99)
All	507 / 1542 (32.9)	424 / 1156 (36.7)	0.83 (0.72 – 0.96) P=0.012

Aspirin reduces the recurrence of colorectal adenoma (Cole BF, et al., *J Natl Cancer Inst* 2009)

Advantages of aspirin use as a cancer chemopreventive agent

- **Aspirin has been used clinically for a long time and its adverse effects are well known in detail.**
- **The cost-effectiveness of using aspirin to prevent cardiovascular disease has also been demonstrated.**

A huge amount of evidence of the utility of aspirin has been accumulated in Western countries;

however, evidence of aspirin in Asian countries is limited.

Aim

To investigate the effects of 100 mg/day of enteric-coated aspirin tablets for 2 years in a double-blind, randomized, placebo-controlled clinical trial.

Inclusion criteria

- Patients with at least one colorectal tumor (intramucosal cancer and adenoma)
- All colorectal tumors as confirmed by histological diagnosis have been successfully removed endoscopically
- Men or women aged ≥ 40 and ≤ 70 years

Exclusion criteria

- Patients currently taking antithrombotics, such as Bayaspirin, Bufferin, Panaldine, Warfarin and Persantin
- Patients with Lynch syndrome or those who had undergone colorectal resection

Preventive treatment and follow-up

Informed consent
Registration
Randomization

Colonoscopy

Follow-up

2 year

2-3 year

Aspirin (100 mg/day) enteric-coated tablet or Placebo tablet

Adverse event report

Ethical monitoring committee

excise tumor

+ histological examination

(The criteria ; Japanese Classification of Colorectal Carcinoma)

Control of subject's treatment compliance

- The study office sent newsletter to each subject every month.
- The study office received the empty PTPs, unused tablets and "drug use diary" every month.

End points

＜The primary endpoint ＞

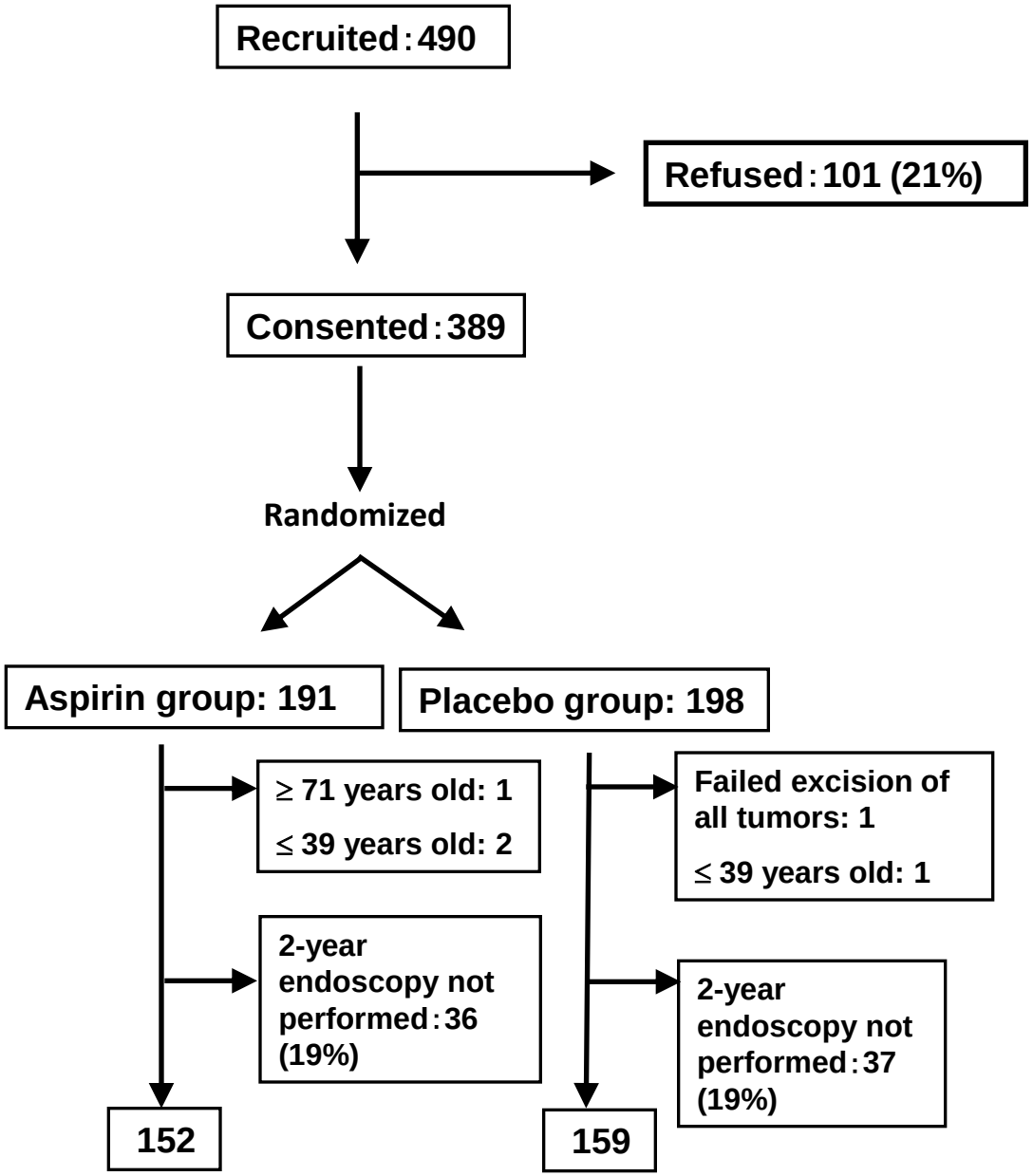
- **The recurrence of a colorectal tumor (adenoma or cancer)**

＜The secondary endpoints＞

- **The number, size and histology of the recurring tumor**
- **Effects of lifestyle such as smoking and alcohol drinking**
- **The frequency of adverse effects**

Results

Flowchart of subject recruitment



Characteristics of the two groups

		Aspirin (n=152)	Placebo (n=159)
Age		60.0 ± 7.3 (SD)	60.5 ± 6.6 (SD)
Sex		Male 79.6%	Male 78.6%
BMI		23.6 ± 2.7 (SD)	23.9 ± 2.8 (SD)
Current smokers		45 (29.6%)	34 (21.4%)
Alcohol Drinker		83 (54.6%)	92 (57.9%)
Number of tumors on entry into the trial		5.3 ± 5.7 (SD)	5.1 ± 7.0 (SD)
Past history of CRC		40 (26.3%)	39 (24.5%)

Alcohol drinker: drinks more than 3 times a week.

BMI, Body mass index = Weight (kg) / height (m) squared

The primary endpoint

Odds ratios of tumor

	No. of subjects with or without colorectal tumor			Adjusted OR (95% CI)
	- (without tumors)	+ (with tumors)	Total	
Placebo group	86	73	159	1
Aspirin group	96	56	152	0.60* (0.36-0.98)

- CI: Confidence interval
- Adjusted OR: Odds ratio is adjusted by sex, age, and number of tumors.
- * p <0.05 vs placebo group, by two-sample t test

The secondary endpoints

	No. of subjects with or without colorectal tumor			Adjusted OR (95% CI)
	-	+	Total	
Current smoker				
Placebo group	26	19	45	1
Aspirin group	14	20	34	3.44* (1.12-10.64)
Non-smoker				
Placebo group	60	54	114	1
Aspirin group	82	36	118	0.37* (0.21-0.68)

- Adjusted OR: Odds ratio is adjusted by sex, age, and number of tumors.
- p <0.05 vs placebo group, by two-sample t test
- Non-smoker: never and former smokers.

The secondary endpoints

	No. of subjects with or without colorectal tumor			Adjusted OR (95% CI)
	-	+	Total	
Alcohol drinker				
Placebo group	51	41	92	1
Aspirin group	47	36	83	0.72 (0.37-1.40)
Social drinker				
Placebo group	35	32	67	1
Aspirin group	49	20	69	0.44* (0.21-0.95)

- Adjusted OR: Odds ratio is adjusted by sex, age, and number of tumors.
- p <0.05 vs placebo group, by two-sample t test
- Alcohol drinker: drinks more than 3 times a week. Social drinker: drinks less than 2 times a week.

Adverse effects

There were no severe adverse effects,

such as GI bleeding, in either group.

Development of colorectal adenocarcinomas

Aspirin group:	**early carcinoma**	**(1)**
	advanced carcinoma	**(1)**
Placebo group:	**early carcinoma**	**(2)**

Cf) All other tumors were tubular adenomas, and villous adenomas were not found.

Summary

- **Low-dose enteric-coated aspirin tablets reduce the recurrence of colorectal tumor development in an Asian population.**

- **This trial is totally in line with the observations of other aspirin adenoma trials.**

- **Smoking and alcohol drinking may decrease the chemopreventive effects of aspirin.**

Discussion

(1) induction of platelet hyperactivity by smoking
(2) chronic inflammation by smoking
(3) effect of alcohol on gut microflora

- **Follow-up for several years after a randomized trial for evaluating the effects of aspirin is ongoing.**

Rationale for determination of the sample size

Incidence of adenoma was 13 to 27% in the placebo group while the incidence of polyp in the aspirin group was decreased to about 60% of that in the placebo group （NEJM 2003).

Incidence in the placebo group	Incidence in the aspirin group	Necessary number of subjects per group
25%	15% (25-25x0.4)	250
40%	24% (40-40X0.4)	152
50%	30% (50-50x0.4)	93

(Present trial: 46%　　37%　　)

We calculated that about 250 randomized patients would give the study 80 % power (with a 5 % type I error) to detect a difference in the recurrence rate of adenoma of 40 %, given a 40 % risk of recurrence in the placebo group.

Five randomized adenoma prevention trials including this trial

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J-CAPP (Aspirin 100 mg/d)	56 / 152 (36.8)	73 / 159 (45.9)	0.80
All	**563 / 1694 (33.2)**	**501 / 1315 (38.1)**	**0.87**