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REVIEW

Chemoprevention of colorectal cancer -experimental and clinical aspects-

Tetsuji Takayama, Takahiro Goji, Tatsuya Taniguchi, and Atsushi Inoue

Department of Gastroenterology and Oncology, Institutes of Health Bioscience, the University of Tokushima Graduate School, Tokushima, Japan

Abstract : Colorectal cancer is a leading cause of cancer-related mortality worldwide. Therefore, an appropriate prevention strategy should be urgently established. Chemoprevention involves the use of oral agents to suppress the development of cancer. Recent progress in the molecular analysis of colorectal cancer has revealed many candidate molecules for chemoprevention. Many new agents targeting these molecules have also been developed. These agents are largely classified into three categories : 1) Signal transduction modulators including epidermal growth factor (EGF) receptor inhibitors, anti-vascular endothelial growth factor (VEGF) antibodies, and inhibitors of oncogene products. 2) Epigenetic modulators including peroxisome proliferative activated receptor (PPAR)-γ agonists, estrogen receptor (ER)-β, and histone deacetylase inhibitors. 3) Anti-inflammatory modulators including cyclooxygenase (COX)-2, EP 1-4, and NF-kB. Of these agents, some actually proceeded to human clinical trials, and have been shown to be active chemopreventive agents. J. Med. Invest. 56 : 1-5, February, 2009

Keywords **:** *colorectal cancer, chemoprevention, aberrant crypt foci*

INTRODUCTION

Colorectal cancer is a disease with a high incidence and mortality rate, and has been increasing in prevalence worldwide (1). Therefore, various prevention strategies have been investigated. Primary prevention attempts to prevent the occurrence of colorectal cancer by lifestyle modification, and secondary prevention aims to arrest the progression of colorectal cancer through early diagnosis and treatment. In addition to these, recently, chemoprevention, the use of oral drugs to prevent cancer, has attracted much attention. Many compounds have been tested to assess their inhibition of colorectal carcinogenesis in animal models, and some of them have been proceeded to clinical trials for chemoprevention.

Recent progress in the molecular analysis of colorectal carcinogenesis has revealed many candidate molecules for chemopreventive agents. In this review, we summarize new findings regarding experimental data and clinical trials for the chemoprevention of colorectal cancer.

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Address correspondence and reprint requests to Tetsuji Takayama, M.D., Ph.D., Department of Gastroenterology and Oncology, Institutes of Health Bioscience, the University of Tokushima Graduate School, Kuramoto-cho, Tokushima, 770-8503, Japan and Fax : +81-88-633-9235.

ANIMAL MODEL OF COLORECTAL CANCER

It is very important to use an animal model for the evaluation of chemopreventive agents against colorectal carcinogenesis. There are two kinds of rodent model for colorectal cancer. One is the model of chemical carcinogenesis employing carcinogens such as azoxymethane, 1, 2-dimethylhydrazine (DMH), N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG), etc. Of these, the azoxymethane model is

the most widely used as a model of sporadic colorectal carcinogenesis, and is reportedly very similar to human colorectal cancer in terms of the clinical symptoms, clinical course, and pathological findings (2). The other one is the genetic model harboring gene mutations such as APC, p53, etc. The Min mouse and Apc delta716 knockout mouse, both of which have APC mutations, are also used worldwide (3, 4).

In 1987, Bird reported a tiny lesion consisting of large, thick crypts in a methylene blue-stained specimen of the colon from mice treated with azoxymethane, and suggested to be a precursor lesion of colorectal cancer in the animal model (5). Then, abundant evidence was reported to support that aberrant crypt foci (ACF) are a precursor lesion of colorectal cancer. Thus, ACF are often used as a target lesion to test chemopreventive effects in animal models of colorectal carcinogenesis.

CHEMOPREVENTIVE AGENTS AND TARGET MOLECULES

Recent progress in the molecular analysis of colorectal cancer has made it possible to target a specific molecule for chemoprevention (6). Many promising target molecules have been reported so far (Table 1). These can be mainly classified into 3 categories based on the mechanism : 1) signal transduction modulation, 2) epigenetic modulation, and 3) anti-inflammatory modulation.

1) Signal transduction modulator

The signal transduction pathway has been searched for a long time as a target of chemotherapy and chemoprevention. EGF receptor inhibitors (Erlotinib, etc.), anti-EGF receptor antibody (Cetuximab), and anti-VEGF antibody (Bevacizumab) are well-known as therapeutic agents for cancer and commonly used worldwide (7). Although these agents have not yet been applied to chemoprevention, they themselves or their analogues may be put to practical use as chemopreventive agents of colorectal cancer in the future. Since mutations of K-ras and p53 are frequently observed in colorectal cancer, their oncogenic pathway is a possible target. Anti-ras agents such as Tipifarnib and perilyl alcohol, and anti-p53 agents such as CP31398 have been reported to inhibit colorectal carcinogenesis in animal models (8). Other signal transduction modulators targeting Bcl-2, ODC, GST-pi, etc., have also been examined for their chemopreventive effect on colorectal cancer.

2) Epigenetic modulation

It is well known that peroxisome proliferator-activated receptor (PPAR)-γ and -δ play a role in the

Table 1 Candidate of chemopreventive agents and target molecules for colorectal cancer

Mechanism	Target	Agents
Signal transduction modulation	EGF receptor	Cetuximab, Erlotinib
	Bcl-2	ABT-737
	Ras	Tipifarnib, Perillyl alcohol
	p53	CP31398
	Matrixmetalloproteinases	Marimistat, Prinomastat
	ODC	DFMO, NSAIDs, Retinoids
	VEGF/VEGF receptor	Bevacizumab
	GST-pi	HGBP, TLK119
Epigenetic modulation	Peroxisome proliferator activated receptor(PPAR)	Rosiglitazone, Pioglitazone
	Vitamin D	Vitamin D3 analogue
	ER-β	Resveratorol, TAS-108
	Histone deacetylase	SAHA
	Retinoic acid receptor	Retinoids
Anti-inflammation	COX-2	NSAIDs, Celecoxib, Etodorac
	EP1-4	ONO-8711
	NF-κB	Bortezomib, Curcumin, Tea polyphenols, Statins, NSAIDs

process of colorectal carcinogensis. Of these, PPAR-γ agonists such as rosiglitazone and pioglitazone reportedly inhibit the formation of colorectal cancer in animal models (9). Currently, they are being tested in human trials. There are some studies in which vitamin D inhibited the development of colorectal adenoma and cancer. Other epigenetic modulators including ER-β, histone deacetylase, and retinoic acid receptor have been reported to be potential chemopreventive agents in animal models.

3) Anti-inflammatory modulation

Cyclooxygenase-2 (COX-2) is reportedly overexpressed in colorectal adenoma and cancer of rodents and humans. It is also reported that COX-2 promotes the cell growth and inhibits apoptosis of colorectal epithelia. When an Apc delta716 knockout mouse, a model of human familial adenomatous polyposis, was crossed with a COX-2 knockout mouse, the number and size of intestinal polyps were markedly reduced (10). Moreover, there are many studies showing that selective COX-2 inhibitors suppressed colorectal adenoma and cancer. Thus, the efficacy of targeting the COX-2 molecule for chemoprevention was theoretically confirmed in animal models. There are also many other anti-inflammatory agents including EP1-4 and NF-κB currently under investigation.

CLINICAL TRIAL FOR CHEMOPREVENTION

Representative human chemopreventive trials are shown in Table 2. They are mainly classified into 3 categories according to the target lesion. The first one is a trial that targets a pre-existing polyp. Giardiello, *et al.* reported that sulindac significantly suppressed the number and size of polyps in familial adenomatous polyposis patients in 1993 (11). This study prompted investigators to conduct a trial to examine whether or not sulindac suppresses sporadic polyps. However, it did not significantly suppress the number or size of the polyps (12). This trial revealed that a pre-existing polyp is not necessarily an appropriate target for chemoprevention; a large polyp close to a cancer may not be able to respond to chemopreventive agents. Thus, chemoprevention targeting the development of a new polyp in polypectomized patients was conducted thereafter. Several randomized trials showed that aspirin inhibited the development of polyps. Since COX-2 was shown to be a good target molecule for chemoprevention in animal experiments, as noted above, two large-scale randomized clinical trials using a selective COX-2 selective inhibitor (celecoxib) were performed. Arber, *et al.* reported that celecoxib (400 and 800 mg/day) significantly reduced the new development of

Table 2 Representative chemopreventive studies for colorectal cancer

	Sporadic/FAP	Agents	Period	Results	Author
Pre-existing polyp					
	FAP	Sulindac	4 yr	No change	Giardiello, *et al.* (2002)
	FAP	Celecoxib	6 mo	30% reduction	Steinbach, *et al.* (2000)
	Sporadic	Sulindac	4 mo	No change	Ladenheim, *et al.* (1995)
	FAP	Sulindac	9 mo	65% reduction	Giardiello, *et al.* (1993)
Development of new polyp					
	Sporadic	Celecoxib	3 yr	38% reduction	Bertagnolli, *et al.* (2006)
	Sporadic	Celecoxib	3 yr	35% reduction	Arber, *et al.* (2006)
	Sporadic	Aspirin	1 yr	37% reduction	Sandler, *et al.* (2003)
	Sporadic	Aspirin	1~3 yr	17% reduction	Baron, *et al.* (2003)
	Sporadic	Calcium	4 yr	15% reduction	Baron, *et al.* (1999)
Development of cancer					
	Sporadic	Vitamin D Calcium	6 yr	32% reduction No change	Martinez, *et al.* (1996)
	Sporadic	Vitamin D Calcium	4 yr	26% reduction No change	Bostick, *et al.* (1993)
	Sporadic	Folic acid	6 yr	31% reduction	Giovannucci, *et al.* (1993)

adenoma compared to a placebo group (13). Bertagnolli, *et al.* also reported that celecoxib (400 and 800 mg/day) significantly reduced the development of adenoma in a different large-scale trial (14). However, in these trials, severe cardiovascular events including myocardial infarction and stroke occurred in about 20% of cases. Therefore, it is considered that the COX-2 inhibitor is an effective agent for the prevention of colorectal cancer, but it cannot be recommended for chemoprevention because of potential cardiovascular events.

The third one is a trial that targets the development of cancer. This kind of trial is theoretically ideal because it examines if each agent indeed suppresses the development of cancer itself. However, it takes more than 4 years, and prolongation of the trial sometimes causes severe side effects and poor compliance.

CHEMOPREVENTION TARGETING ACF

Since ACF are the earliest precursor lesions of colorectal cancer (15, 16), they would be an appropriate target for chemoprevention (Fig. 1). The advantages of using ACF as targets over a polyp and cancer are as follows : (1) short-term treatment for evaluation, (2) fewer complications caused by drugs, and (3) good compliance. Thus, we performed an open trial in which sulindac was administered for various periods to subjects positive for ACF. The results showed that the majority of ACF were eradicated after only a few months. Based on this, we next performed a randomized double-blind trial targeting ACF consisting of groups receiving sulindac, etodolac (a selective COX-2 inhibitor), or a placebo. The detailed results of this study will be clarified in the near future.

EPILOGUE

Many candidate agents for chemoprevention are currently being tested, and some of them have actually shown potential chemopreventive activity in human trials. Although the COX-2 inhibitor failed to be a major chemopreventive agent, other effective new agents will be identified in the near future.

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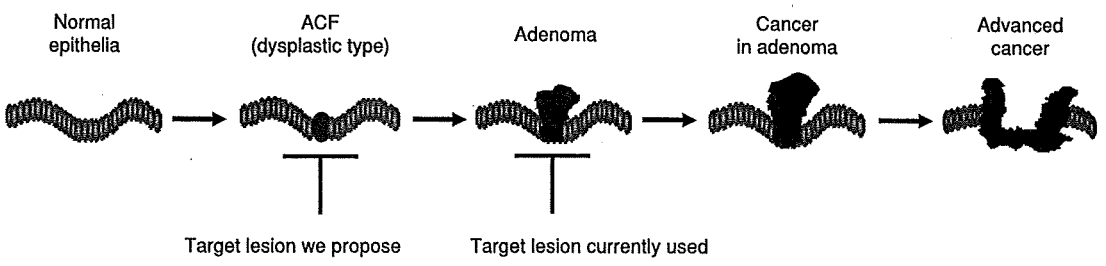

Figure 1 Colorectal carcinogenesis and target lesions for chemoprevention. In the majority of chemopreventive studies performed so far, adenoma has been used as a target lesion for evaluation. We propose the use of aberrant crypt foci (ACF), an earlier lesion, as a target. This makes it possible to evaluate the effect of a chemoprevenitve agent within a shorter period.

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Journal of Gastroenterology

Chemoprevention of colorectal cancer in Japan: a brief introduction to current clinical trials

HIDEKI ISHIKAWA[1], TOMIYO NAKAMURA[1], ATSUKO KAWANO[2], NOBUHISA GONDO[3], and TOSHIYUKI SAKAI[1]

[1]Department of Molecular-Targeting Cancer Prevention, Kyoto Prefectural University of Medicine, 3-2-17 Imahashi, Chuo-ku, Osaka 541-0042, Japan
[2]Division of Preventive and Social Medicine, Department of Hygiene and Public Health, Osaka Medical College, Osaka, Japan
[3]Department of Surgery, Clinical Genetics, Hyogo College of Medicine, Hyogo, Japan

The rapidly increasing incidence of colorectal cancer in Japan poses a great challenge to researchers to develop preventive strategies against this disease. Thus far, several clinical trials for this purpose have been planned in Japanese subjects; some have been completed and documented while others are still ongoing. Also, the Ministry of Health, Labour and Welfare of Japan recognizes the significance of cancer prevention studies, especially against colorectal cancer, including it as one of the pillars in the "Third Research Project on General Strategies against Cancer" and funding several large-scale projects. Among them are two chemoprevention studies currently being performed: in patients with previous sporadic colorectal tumors (J-CAPP study) and in patients with familial adenomatous polyposis (J-FAPP study II). Both are double-blind randomized controlled trials with low-dose aspirin (100 mg/day), which is generally considered to be safe for long-term use. This article outlines relevant past clinical data and gives a brief introduction to these two studies.

Key words: colorectal cancer, chemoprevention, aspirin, clinical trial

Introduction

Gastric cancer used to be the most common type of cancer in Japanese. Its position is, however, rapidly being replaced by colorectal cancer. According to the 2003 statistics, colorectal cancer has become the leading cause of death in overall cancer mortality in Japanese women. With this background, studies on colorectal cancer prevention are now being performed actively in Japan. Among other strategies, cancer prevention by drugs, i.e., chemoprevention, is expected to have great potential for clinical application.

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Reprint requests to: H. Ishikawa

Candidate substances and target populations

Candidate substances expected to prevent colorectal cancer are shown in Table 1.

Based on recent genetic and epigenetic analyses of colorectal cancer,[1,2] many substances are expected to be effective and have been examined. In particular, nonsteroidal antiinflammatory drugs (NSAIDs) have attracted attention and have been studied worldwide. However, none of the NSAIDs has yet been sufficiently proven to be effective for clinical application.

As for target populations, most clinical studies on chemoprevention have been conducted in high-risk groups for colorectal cancer, including patients with a previous sporadic colorectal tumor (adenoma or cancer) after endoscopic resection, familial adenomatous polyposis (FAP), and hereditary nonpolyposis colorectal cancer (HNPCC).

On the other hand, research efforts for cancer prevention in an average-risk group have focused on lifestyle modification including diet, physical exercise, smoking, and drinking.

Chemoprevention for patients with previous sporadic colorectal tumor

Background and past studies

In 2003, Baron et al.[3] reported a 3-year intervention trial in 1121 subjects with a history of colorectal adenoma. The subjects were given placebo or aspirin (81 or 325 mg/day). Although there was no difference in the development of adenoma between the groups, a significant decrease in relative risk (0.59) of advanced lesions

Table 1. Candidate substances for chemoprevention of colorectal cancer

I. NSAIDs	IV. *Dietary fiber*	VII. *Other food components*
Aspirin	Hemicellulose	S-Allylcysteine
Sulindac	Pectin	Fucoidan
Sulindac sulfone	Resistant starch	Curcumin
Indomethacin	Oligosaccharide	Epigallocatechin
Piroxicam	V. *Metals and related substances*	Lactoferrin
Celecoxib	Selenium	Chitin/chitosan
II. Vitamins	Calcium	IX. *Drugs for other diseases*
Folic acid	Phytic acid	Pioglitazone
Vitamin C	VI. *Polyunsaturated fatty acids*	Glivec
Vitamin D	Docosahexanoic acid	Statins
Vitamin E	α-Linolenic acid	α-Glucosidase inhibitor
III. 5-Aminosalycylic acid	VII. *Carotenoid*	5-Fluorouracil
Salazosulfapyridine	α-Carotene /β-Carotene	Lactic acid bacteria
5-Aminosalicylic acid	Lycopene	Ursodeoxicholic acid
		Estrogen

NSAIDs, nonsteroidal antiinflammatory drugs

was observed in the group receiving 81 mg/day aspirin. This finding was, however, not dose dependent, as the relative risk in the group receiving 325 mg/day was not considerably decreased.

At the same time, the results of another clinical trial by the same group of researchers were reported.[4] The subjects, patients with previous colorectal cancer resected surgically, received placebo or aspirin at a dose of 325 mg/day. After 12.8 months, the median intervention period, newly developed adenomas were detected in 27% of the placebo group and in 17% of the aspirin group, which rate was significantly lower in the latter group. With regard to the cumulative incidence, there was an increasing difference between the two groups during the first year, and then the two increasing curves became parallel. Therefore, the effect of long-term aspirin administration remained unclear.

Several large-scale clinical studies including the aforementioned trials have been conducted but failed to provide convincing evidence of the efficacy of aspirin. Based on these results, preventive use of aspirin or other NSAIDs against colorectal cancer in clinical settings is currently not recommended in the United States.[5]

In Japan, Takayama et al.[6] studied the effect of sulindac, another NSAID, in patients with a sporadic colorectal tumor, and reported a decrease in the number of aberrant crypt foci (ACF) in the group receiving sulindac. As for aspirin, however, no large-scale clinical trial has ever been performed in Japan.

Asians, with their generally smaller physique, may differ from Western people in their metabolism of aspirin. Therefore, clinical trials of aspirin in Japanese persons might provide different outcomes than past clinical data obtained from Americans. Based on such an expectation, planning of a multicenter research project in Japan has been initiated.

J-CAPP study

We have designed a clinical trial called the "Japan Colorectal Aspirin Polyps Prevention (J-CAPP) Study" under study director Prof. Shinkan Tokutome of Nagoya City University Medical School. The Ministry of Health, Labour and Welfare of Japan has funded this project within the framework of the Third Research Project on General Strategy against Cancer, Basic and Clinical Research on the Development of Chemopreventive Drugs (Team Leader: Dr. Wakabayashi, National Cancer Center).

The study is a double-blind trial using aspirin enteric-coated tablets (100 mg, one tablet daily) and placebo imported from Bayer HealthCare, Germany. Thirty-one tablets of the investigational drug, dosage for 1 month, were packed in one PTP sheet with a calendar printed on it (Fig. 1). This PTP sheet was coated on both sides with a waterproof aluminum layer. One box containing 30 sheets, for 30 months, was prepared for each subject.

Our study statistician Dr Suzuki was responsible for coding and sealing of boxes containing either placebo or aspirin by using a table of random digits. Then, a specially designed website for this study was set up to enable real-time random allocation by the minimization method.

Our research organization consists of specialists in colonoscopy across the country, and a study statistician as the controller. An ethics monitoring committee was also established. The functions of the data center were commissioned to Medical Research Support. Experts in colonic diseases from 23 institutions participated in this project (Table 2).

The subjects are men and women aged between 40 and 70 years, with a previous colorectal tumor, including early cancer and adenoma. All tumors should have

Table 2. Collaborators and number of cases allocated

Name	Affiliation	No. of cases
Hideki Ishikawa	Osaka Central Hospital	200
Tetsuji Takayama	Sapporo Medical Univ. School of Medicine	60
Takashi Abe	Osaka Police Hospital	36
Motowo Mizuno	Hiroshima City Hospital	30
Shozo Okamura	Toyohashi Municipal Hospital	40
Konishi Naomi	Mie Prefectural General Medical Center	5
Masato Kusunoki	Mie Univ. Graduate School of Medicine	5
Yoshihisa Saida	Toho Univ. School of Medicine	40
Masahiro Tajika	Aichi Cancer Center Hospital	40
Shin-ein Kudo	Northern Yokohama Hospital Showa Univ.	30
Keiji Hirata	Univ. of Occupational and Environmental Health	18
Shinji Tanaka	Hiroshika Univ. Hospital	30
Gondo Nobuhisa	Kimura Hospital	40
Makoto Yamamura	Kobe Ekisaikai Hospital	10
Masaki Iimuro	Higashisumiyoshi Morimoto Hospital	40
Kyowon Lee	Moriguchi Keijinkai Hospital	10
Heita Ozawa	Kitasato Univ. School of Medicine	10
Takashi Joh	Nagoya City Univ. Hospital	20
Shinji Kitamura	Sakai Municipal Hospital	30
Masahiko Tsujii	Osaka Univ. Graduate School of Medicine	10
Kenji Sugimoto	Sugimoto Kenji Clinic	20
Yasushi Sano	Sano Hospital	40
Takahisa Matsuda	National Cancer Center Hospital	40

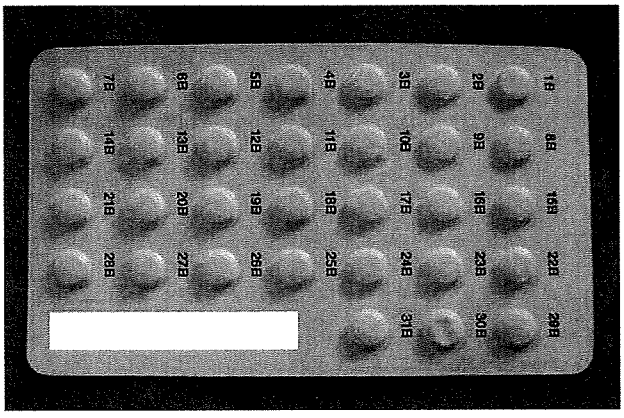

Fig. 1. Thirty-one tablets of investigational drug, for 1 month, were packed in one PTP sheet with a calendar printed on it. This PTP is coated on both sides with an aluminum layer, so it is highly waterproof. One box containing 30 sheets, for 30 months, is prepared for each subject

been resected endoscopically. The target sample size is 700, and the number of cases to be analyzed is 500. Current users of antithrombotic agents such as Bayaspirin and patients who have undergone colectomy and those with FAP or HNPCC are excluded. The duration of intervention is 2 years, followed by another 2 to 3 years of follow-up. The primary endpoint is the presence or absence of new colorectal tumors. The secondary endpoints include the number, size, and dysplasia of newly developed tumors, and frequency of adverse events.

We started registering participants in January 2007. By March 28, 2008, the 13th month of registration, 351 patients had been approached and 283 of them (81%) had consented to participate. The project is now proceeding smoothly.

Chemoprevention for patients with familial adenomatous polyposis

Background and past studies

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited disease characterized by the development of numerous colorectal adenomas. As a causal gene, the *APC* gene has been identified. There are estimated to be 5000–7000 patients in Japan. Persons with this constitution are at high risk of developing colorectal cancer, which may even start in their twenties. By the age of 40, 50% of them are considered to be affected; most patients will be affected. Colectomy is generally indicated in patients diagnosed with FAP to prevent colorectal cancer. However, this procedure is associated with frequent diarrhea, resulting in a significant decrease in patients' quality of life. There is thus a strong need for alternative measures to preventive colectomy, and three options are currently being

studied: lifestyle modification, endoscopic resection, and chemoprevention.

Substances developed for cancer prevention in FAP, as listed in a review article by Ishikawa,[7] include NSAIDs such as sulindac, aspirin, and celecoxib, as well as other substances such as green tea extract, vitamin C, folic acid, and imatinib. Most of the trials tested NSAIDs, especially sulindac.

The first report on sulindac, which was administered in patients with FAP, was published in 1983.[8] Later, a double-blind crossover randomized clinical trial also demonstrated the efficacy of sulindac.[9] Furthermore, a relatively large-scale clinical trial also confirmed the efficacy of sulindac. In all clinical trials testing sulindac, regression of colorectal polyps was documented.[10] Encouraged by these results, we also have tested sulindac in FAP patients.[11] Having had little doubt of the efficacy of sulindac, we designed a randomized study to compare sulindac with docosahexanoic acid (DHA), an n-3 polyunsaturated fatty acid. Our study revealed regression of colorectal polyps by sulindac as expected. At the same time, unfortunately, we observed a high frequency of severe adverse effects including multiple ulcers of the small intestine and perforation of gastric ulcer.[12] This event made us realize the serious problem of long-term administration of sulindac for colorectal cancer prevention. Furthermore, in the group receiving DHA, three of five subjects developed lung cancer, endometrial cancer, or colon cancer by the second year of administration. This result implied that administration of a large amount of DHA might have promoted carcinogenesis.[13]

J-FAPP study II

Despite its efficacy in reducing colorectal polyps, it became clear that sulindac is not suitable for long-term administration because of safety problems. Considering a safe and promising alternative for our next prevention study, we have selected low-dose aspirin because its safety with long-term administration has been demonstrated in patients with heart disease. A clinical study of aspirin, the "Japan Familial Adenomatous Polyposis Prevention Study (J-FAPP Study II)," funded by the Ministry of Health, Labour and Welfare of Japan, has been planned.

The same investigational drug (aspirin 100 mg/day) as in the J-CAPP study is used. This study is a multicenter double-blind randomized controlled trial. The subjects are patients with FAP aged 16 years and over not having had colectomy, or with a history of colectomy but at least 2 cm of rectal mucosa left intact. The target sample size is 100, and the number of cases to be analyzed is 70. The intervention period is 6–10 months. The primary endpoint is changes in rectal polyps. The secondary endpoints are frequency of adverse events and expression of colorectal cancer-related proteins encoded by mRNA from sigmoid mucosa.

Thus far, 45 patients have been approached, and 29 of them have consented to participate. We expect the study outcomes in 2 years.

Conclusions

Among other NSAIDs as candidate drugs for chemoprevention of colorectal cancer, low-dose aspirin is generally considered to be safe for long-term administration based on clinical experience, such as in heart disease. Currently, two double-blind randomized controlled clinical trials of low-dose aspirin (100 mg/day), the first of its kind in Japan, including sporadic colorectal tumors (J-CAPP Study) and FAP (J-FAPP Study II) are being performed. Both studies are funded by the Ministry of Health, Labour and Welfare of Japan. Study outcomes are expected within several years.

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Five-year Incidence of Advanced Neoplasia after Initial Colonoscopy in Japan: A Multicenter Retrospective Cohort Study

Takahisa Matsuda[1], Takahiro Fujii[1], Yasushi Sano[2], Shin-ei Kudo[3], Yasushi Oda[4], Masahiro Igarashi[5], Hiroyasu Iishi[6], Yoshitaka Murakami[7], Hideki Ishikawa[8], Tadakazu Shimoda[9], Kazuhiro Kaneko[2] and Shigeaki Yoshida[2]

[1]Endoscopy Division, National Cancer Center Hospital, Tokyo, [2]Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, [3]Digestive Disease Center, Showa University, Northern Yokohama Hospital, Yokohama, [4]Hattori GI Endoscopy and Oncology Clinic, Kumamoto, [5]Division of Digestive Endoscopy, Cancer Institute Ariake Hospital, Tokyo, [6]Division of Digestive Endoscopy and Gastrointestinal Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, [7]Department of Health Science, Shiga University of Medical Science, Shiga, [8]Department of Molecular-Targeting Cancer Prevention and Epidemiology for Community Health and Medicine, Kyoto Prefectural University of Medicine, Kyoto and [9]Clinical Laboratory Division, National Cancer Center Hospital, Tokyo

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Objective: The National Polyp Study is used as the basis of recommendations for colonoscopic surveillance after polypectomy, establishing an interval of 3 years after removal of newly diagnosed adenomas. The aim of this retrospective cohort study was to estimate the incidence of advanced neoplasia after initial colonoscopy and compare the differences among risk groups.

Methods: Patients over 40 years who were referred for initial colonoscopy at six institutes were selected. They were classified into four groups based on the initial colonoscopy: A, patients without any adenoma; B, with adenomas of <6 mm only; C, with adenomas of ≥ 6 mm; D, with any intramucosal cancer. The index lesion (IL) at follow-up colonoscopy was defined as large adenoma ≥ 10 mm, intramucosal/invasive cancer.

Results: A total of 5309 patients were enrolled in this study. Overall, median follow-up period was 5.1 years. The numbers of eligible patients in the various subgroups were A, 2006; B, 1655; C, 1123; D, 525. A total of 379 ILs were newly diagnosed during follow-up colonoscopy. The cumulative incidence of ILs in each group was A, 2.6%; B, 6.7%; C, 13.4%; and D, 12.6%.

Conclusions: Patients with any adenomas >6 mm or intramucosal cancer at the initial colonoscopy have a higher risk of advanced neoplasia during follow-up colonoscopy.

Key words: colonoscopy – polyp – colorectal cancer – screening – surveillance

INTRODUCTION

Colorectal cancer (CRC) is the third most common cause of cancer mortality in Japan (1). The identification and removal of adenomatous polyps and post-polypectomy surveillance are considered to be crucial for the control of CRC (2,3). However, recommendations for post-polypectomy surveillance in Japan have not been established. In current practice, the intervals between colonoscopies after polypectomy are variable, often annual, and not based on data from randomized clinical trials.

The evolution of CRC from a precursor lesion, the adenoma, was first reported in studies by Morson (4) as the adenoma–carcinoma sequence. The introduction of colonoscopy provided an opportunity for clarifying this sequence because of its ability to examine the entire colon and remove polyps for pathological examination. The epidemiology and natural history of adenomas are not only important for choosing the optimal follow-up policy after polypectomy,

For reprints and all correspondence: Takahisa Matsuda, Endoscopy Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: tamatsud@ncc.go.jp

but also for evaluating endoscopic screening for colorectal adenomas and cancer. The existence of flat and depressed lesions, including some with advanced histology, has been demonstrated in multiple recent series from several countries in the West and Japan (5–8). However, the clinical significance of flat and depressed (non-polypoid) lesions and whether they actually constitute alternative pathways to CRC is still controversial (9).

In the USA, the National Polyp Study (NPS) carried out since 1980 recommended an interval of at least 3 years between the colonoscopic removal of newly diagnosed adenomatous polyps and follow-up examination (2,3,10). However, the NPS was conducted prior to recent epidemiologic studies documenting the prevalence of non-polypoid lesions in the colorectum as well as other recent studies suggesting improvements in yield at colonoscopy with slower withdrawal times (11). Thus, the Japanese style colonoscopy, which consists of a bowel preparation using polyethylene glycol (PEG) solution given in the morning on the day of colonoscopy, and techniques such as chromoendoscopy required for the diagnosis of non-polypoid neoplasia (6,12,13) were not used and may at least in part explain the discrepancy between the results of NPS and those of the recent epidemiologic studies (14,15). The aim of this multicenter retrospective cohort study was to estimate the incidence of advanced neoplasia including the prevalence of non-polypoid lesions after initial colonoscopy using the Japanese style colonoscopy and to compare the differences among risk groups of such incidences.

PATIENTS AND METHODS

Subjects and Study Design

This multicenter retrospective cohort study was coordinated by the Japan Polyp Study Workgroup (JPSWG), which was set up in 2000 in Japan. Cases of screening patients over 40 years who were referred for initial total colonoscopy at the six institutes (National Cancer Center Hospital, National Cancer Center Hospital East, Akita Red Cross Hospital, Kitasato University East Hospital, Osaka Medical Center for Cancer and Cardiovascular Diseases, Hattori GI Endoscopy and Oncology Clinic) in Japan were followed up for >3 years from 1990 to 1995. Patients who did not have a familial or personal history of familial adenomatous polyposis, hereditary non-polyposis CRC, inflammatory bowel disease, a personal history of polypectomy or invasive CRC or a sessile adenoma with a base >30 mm where a piecemeal resection or closer follow-up would have been needed were selected for this retrospective cohort study. Written informed consent for examination and treatment were obtained from all of the studied patients prior to the procedures. We retrospectively reviewed colonoscopy reports and medical records for all patients.

They were classified into four groups according to the most advanced lesion found at initial colonoscopy: Group A, patients without any adenomatous polyp; Group B, patients with adenomas of <6 mm only; Group C, patients with adenomas of ≥6 mm; Group D, patients with any intramucosal (M) cancer. All adenomatous polyps of >6 mm and M cancers were removed at the initial colonoscopy. The index lesion (IL) diagnosed during follow-up colonoscopy was defined as follows: large adenomatous polyp ≥10 mm, M cancer and invasive cancer. In this study, we analyzed the cumulative incidence of ILs at follow-up colonoscopy for each patient based on the four groups.

Endoscopic Procedures

All patients were prepared for colonoscopy by administering 2–3 l of PEG on the examination day morning. Scopolamine butylbromide (10 mg) or glucagon (0.5 mg) was administered intravenously to patients with no contraindication prior to examination to avoid bowel movements. Medium-length colonoscopes were used, and one man method colonoscopy was performed. During colonoscopy, the location and the size of all detected lesions were documented and evaluated in real time and categorized as non-neoplastic or neoplastic using chromoendoscopy or magnifying chromoendoscopy. The size of the lesions was estimated using open biopsy forceps. Those diagnosed as non-neoplastic lesions were left untreated. If lesions were identified as neoplastic, hot biopsy, snare polypectomy or EMR was performed. Basically, polyps <6 mm were removed by coagulation biopsy (hot biopsy), and flat lesions or those ≥6 mm were treated with loop snare polypectomy or EMR. However, diminutive adenomatous polyps <6 mm were occasionally permitted to be left untreated. Finally, all neoplastic lesions with >6 mm and M cancers were completely removed at the initial colonoscopy. If lesions were diagnosed as invasive cancer, biopsy specimen was taken and patients were referred for surgery.

Histopathological Evaluation

Resected specimens were immediately fixed in 10% buffered formalin solution and subsequently stained with hematoxylin–eosin. Experienced gastrointestinal pathologists evaluated all pathological specimens. Histopathological diagnoses were determined according to the Japanese Research Society for Cancer of the Colon and Rectum (JRSCCR) and the World Health Organization (WHO) criteria (16,17).

Statistical Analysis

The cumulative incidence of ILs during the follow-up period was described by the Kaplan–Meier method. The Kaplan–Meier curves were compared in the four groups, and the cumulative incidence at 1-year, 3-year and the maximum follow-up period was estimated, respectively. For comparison, we re-categorized the above-mentioned four groups (A, B, C, D) into two (A + B, C + D), and the

cumulative incidences for the maximum follow-up period between the two groups were compared by a log-rank test. A two-sided P value of <0.05 was considered statistically significant. When the differences of the baseline characteristics between ILs were examined, the chi-squared test was used for the proportion and t-test for continuous variables. All statistical analyses were performed with SPSS statistical software (SPSS, version 16.0J, for Windows, Tokyo, Japan).

RESULTS

Subjects and Outlines of Follow-up Colonoscopy

A total of 5309 patients, including 3328 (63%) male patients, were enrolled in this study as shown in Table 1. Eligible patients were classified into four groups as follows: Group A, 2006 (38%); Group B, 1655 (31%); Group C, 1123 (21%); and Group D, 525 (10%). The mean age was 60.2, 63.2, 63.7 and 65.1 in Groups A, B, C and D, respectively. Overall, the median follow-up period and the frequency of colonoscopy were 5.1 years and 4.1 times, respectively. There were no significant differences in the follow-up period and the number of times in each group. Moreover, the average interval of colonoscopy was 21.3, 17.2, 16.8 and 13.9 months in Groups A, B, C and D, respectively.

Incidence of IL According to Initial Colonoscopy

A total of 379 ILs were newly diagnosed during follow-up colonoscopy. In Table 2, the incidence of ILs (%) and total cases (in parenthesis) in each group were as follows: Group A, 2.6% (52); Group B, 6.7% (111); Group C, 13.4% (150); and Group D, 12.6% (66). In Groups A, B, C and D, the cumulative incidence of ILs at 1 and 3 years was 0.1/0.8%, 1.0/2.9%, 2.5/5.4% and 2.9/5.7%, respectively. When we re-categorized four groups into two, the cumulative incidence of ILs at 1 and 3 years was 0.5/1.9% and 2.7/5.6% in Group A + B (low-risk group) and Group C + D (high-risk group), respectively. A significant difference was found between the low- and high-risk groups ($P < 0.0001$) (Fig. 1).

Clinicopathological Characteristics of ILs

There were 189 (50%), 125 (33%) and 65 (17%) right-sided, left-sided and rectal ILs, respectively, as shown in Table 3. Group A revealed right-sided ILs in 24 (46%), left-sided in 15 (29%) and rectal in 13 (25%). Similarly, Groups B, C and D exhibited right-sided ILs in 59 (53%), 74 (49%) and 32 (48%), left-sided in 32 (29%), 55 (37%) and 23 (35%) and rectal in 20 (18%), 21 (14%) and 11 (17%), respectively.

Of these ILs, 197 (52%) were large adenoma $\geq$10 mm, 143 (38%) were M cancer, 20 (5%) were submucosal (SM) invasive cancer and 19 (5%) were advanced (ADV) cancer. Group A revealed a large adenoma in 28 (54%), M cancer in 13 (25%), SM cancer in 4 (8%) and ADV cancer in 7 (13%). Similarly, Groups B, C and D exhibited large adenoma in 56 (50%), 80 (54%) and 33 (50%), M cancer in 46 (41%), 59 (39%) and 25 (38%), SM cancer in 3 (3%), 6 (4%) and 7 (11%) and ADV cancer in 6 (6%), 5 (3%) and 1 (1%), respectively.

Morphologically, the macroscopic types of ILs apart from ADV cancer were 220 (58%) polypoid, 122 (32%) flat and 18 (5%) depressed lesions (Table 4). Furthermore, concerning the occurrence time of IL, there were 69 (18%), 74 (20%), 50 (13%), 89 (23%) and 97 (26%) within 1, 1–2, 2–3, 3–5 and >5 years, respectively. Group A + B revealed within 1 year occurrence in 21 (13%), 1–2 years in 23 (14%), 2–3 years in 21 (13%), 3–5 years in 44 (27%) and >5 years in 54 (33%). Group C + D exhibited within 1 year occurrence in 48 (22%), 1–2 years in 51 (24%), 2–3 years in 29 (13%), 3–5 years in 45 (21%) and >5 years in 43 (20%).

Association of Baseline Characteristics with ILs

The 379 patients diagnosed with ILs were older than those without such findings (mean age, 65.4 vs. 62.2 years; $P = 0.02$). Patients who were classified into Group C + D seemed more likely to be diagnosed with an IL than those who were classified into Group A + B (4.5% vs. 13.1%; $P = 0.04$) and men seemed more likely than women to have an IL (8.5% vs. 4.8%; $P < 0.0001$) as shown in Table 5.

Table 1. Patient characteristics and outlines of follow-up colonoscopy

	Group A	Group B	Group C	Group D	Total
Patients [no. (%)]	2006 (38)	1655 (31)	1123 (21)	525 (10)	5309
Male sex [no. (%)]	934 (47)	1145 (69)	849 (76)	400 (76)	3328 (63)
Age[a] (years)	60.2 ± 9.8	63.2 ± 9.8	63.7 ± 9.1	65.1 ± 9.2	62.4 ± 9.8
Follow-up period[b] (years)	5.2 (3.0–12.3)	5.3 (3.0–10.7)	5.0 (3.0–11.0)	4.8 (3.0–10.2)	5.1 (3.0–12.3)
Number of exam times of TCS[a]	3.8 ± 1.7	4.3 ± 1.9	4.1 ± 1.8	4.5 ± 1.7	4.1 ± 1.8
Interval of TCS[a] (months)	21.3 ± 11.5	17.2 ± 8.4	16.8 ± 9.2	13.9 ± 6.7	18.3 ± 10.0

[a]Plus-minus values are mean ± SD.
[b]Median (range).

Table 2. Cumulative incidence of index lesions after initial colonoscopy

	Cumulative incidence (%)			*n*	Total number of incidence cases
	1-year	3-year	Maximum follow-up period		
Group A	0.1	0.8	2.6	2006	52
Group B	1.0	2.9	6.7	1655	111
Group C	2.5	5.4	13.4	1123	150
Group D	2.9	5.7	12.6	525	66
Group A + B (low risk)	0.5	1.9	4.5	3661	163
Group C + D (high risk)	2.7	5.6	13.1	1648	216

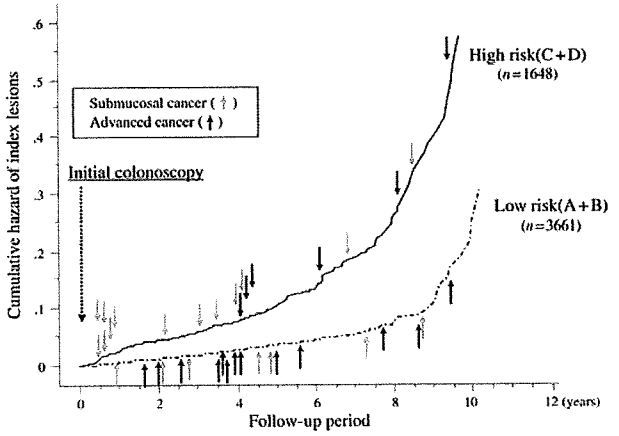

Figure 1. Comparison of cumulative incidence of index lesion and invasive colorectal cancer between risk groups.

Table 3. Clinicopathological characteristics of index lesions in each group

	Group A ($n = 52$)	Group B ($n = 111$)	Group C ($n = 150$)	Group D ($n = 66$)	Total ($n = 379$)
Location [no. (%)]					
Right colon[a]	24 (46)	59 (53)	74 (49)	32 (48)	189 (50)
Left colon[b]	15 (29)	32 (29)	55 (37)	23 (35)	125 (33)
Rectum	13 (25)	20 (18)	21 (14)	11 (17)	65 (17)
Histopathology [no. (%)]					
Adenoma (≥10 mm)	28 (54)	56 (50)	80 (54)	33 (50)	197 (52)
Intramucosal cancer	13 (25)	46 (41)	59 (39)	25 (38)	143 (38)
Submucosal cancer	4 (8)	3 (3)	6 (4)	7 (11)	20 (5)
Advanced cancer	7 (13)	6 (6)	5 (3)	1 (1)	19 (5)

[a]Cecum–transverse colon.
[b]Descending–sigmoid colon.

Table 4. Clinicopathological characteristics of index lesions in each group

	Group A ($n = 52$)	Group B ($n = 111$)	Group C ($n = 1\,50$)	Group D ($n = 66$)	Total ($n = 379$)
Macroscopic type [no. (%)]					
Adenoma/early cancer					
Polypoid	26 (50)	52 (47)	94 (63)	48 (73)	220 (58)
Flat	18 (35)	46 (42)	44 (29)	14 (21)	122 (32)
Depressed	1 (2)	7 (6)	7 (5)	3 (5)	18 (5)
Advanced cancer	7 (13)	6 (5)	5 (3)	1 (1)	19 (5)
Occurrence time [no. (%)]					
<1 (year)	2 (4)	19 (17)	29 (19)	19 (29)	69 (18)
1–2	6 (12)	17 (15)	36 (24)	15 (23)	74 (20)
2–3	6 (12)	15 (14)	24 (16)	5 (7)	50 (13)
3–5	19 (36)	25 (23)	29 (19)	16 (24)	89 (23)
>5	19 (36)	35 (31)	32 (22)	11 (17)	97 (26)

Table 5. Association of baseline characteristics with index lesions

Baseline characteristics	Number (%)	Index lesion		*P* value
		No ($n = 4930$)	Yes ($n = 379$)	
Mean age[a] (year)		62.1 ± 9.7	65.4 ± 9.7	0.02
Age (year)				
40–49	487 (9.2)	463 (95.1)	24 (4.9)	
50–59	1640 (30.9)	1557 (94.9)	83 (5.1)	
60–69	1882 (35.4)	1737 (92.3)	145 (7.7)	
>70	1300 (24.5)	1173 (90.2)	127 (9.8)	
Sex				
Male	3328 (62.7)	3045 (91.5)	283 (8.5)	<0.0001
Female	1981 (37.3)	1885 (95.2)	96 (4.8)	
Category				
Group A	2006 (37.8)	1954 (97.4)	52 (2.6)	0.04
Group B	1655 (31.2)	1544 (93.3)	111 (6.7)	
Group C	1123 (21.1)	973 (86.6)	150 (13.4)	
Group D	525 (9.9)	459 (87.4)	66 (12.6)	

[a]Plus-minus values are mean ± SD.

Description of Patients Diagnosed with Invasive Cancer Within 3 Years

A total of 13 invasive cancers including three ADV cancers were newly diagnosed during the follow-up period within 3 years as shown in Table 6. The cancers were located in different sites; 8 out of the 13 were located at the sigmoid colon or rectum. The mean size was 14.1 ± 5.6 mm (range: 6–20 mm). Macroscopically, of these invasive cancers, six

(46%) were sessile/semi-pedunculated, five (39%) were depressed and two (15%) were flat lesions.

DISCUSSION

This is the first large multicenter retrospective cohort study to analyze the incidence of advanced neoplasia after initial colonoscopy in Japan. From our data, it is thought that patients with any adenomatous polyps of >6 mm or M cancer at the baseline colonoscopy have a higher risk of ILs rather than the other groups. Some authors have reported that patients categorized into a high-risk group, from the findings of initial colonoscopy, had high recurrence rates of colorectal adenomas. Recurrence rates dependent on adenoma characteristics have been reported as 15–60% within 3–4 years after previous endoscopic removal (3,18–21). In Japan, Yamaji et al. reported that recurrence rates of colorectal neoplasia were estimated to be 7.2% per year in those with no initial neoplasia, 19.3% per year in those with small adenomas and 22.9% per year in those with advanced lesions. However, this study was carried out in an asymptomatic patient cohort, unlike our current study, which includes both symptomatic and asymptomatic cases. For advanced colorectal lesions, the incidence rate was 0.21% per year, whereas recurrence rates in those with small adenomas and advanced lesions were 0.64% and 1.88% per year, respectively. From their study, the recurrence rates after polypectomy were elevated; however, the incidence rates in subjects with no neoplastic lesions initially were quite high (22). In contrast, Lieberman et al. (23) reported from the USA that the cumulative result represents the most advanced lesion found on any colonoscopy performed during the 5.5-year study period. Among 298 patients with no neoplasia at baseline who had follow-up evaluation, 67 (22.5%) had small tubular adenomas (<10 mm), and 2.4% had advanced neoplasia, including 1 (0.3%) patient with cancer. Basically, our results were in agreement with this report. The 5-year incidence of ILs in those with no initial neoplasia (Group A) was 2.6%, in those with small adenomas (Group B), large adenomas (Group C) and M cancers (Group D) were 6.7%, 13.4% and 12.6%, respectively. Moreover, the cumulative incidence of ILs at 1 and 3 years was 0.5/1.9% and 2.7/5.6% in Group A + B (low-risk group) and Group C + D (high-risk group), respectively. These results suggested that a surveillance colonoscopy after initial total colonoscopy should be performed at 3-year for patients without any polyps or with polyps <6 mm (low-risk group). In contrast, it should be performed at 1 year for patients with any large polyp (≥6 mm) or intramucosal cancer (high-risk group).

According to the latest guidelines from the USA, the recommendations for the surveillance interval for patients with one or two small (<10 mm) tubular adenomas with no high-grade dysplasia ranged from 5 to 10 years after baseline colonoscopy. On the other hand, patients with three or more adenomas, high-grade dysplasia, villous features or an adenoma ≥10 mm in size should have a 3-year follow-up colonoscopy (24). Lieberman et al. (23) reported that many of the interval cancers and large adenomas were discovered in the first 36 months after initial colonoscopy, raising issues about the quality of the colonoscopy. Among the 379 ILs, a total of 193 (51%) lesions, including 13 invasive cancers, were newly diagnosed within 3 years in our study, especially 7 SM cancers were detected in the first 12 months. A

Table 6. Description of 13 patients diagnosed with invasive cancer during the follow-up period within 3 years

Baseline characteristics		Months since initial colonoscopy	Location	Size/macroscopic type	Depth of lesion (T-stage)
Age (year)/sex	Category (group)				
41/M	C	4	Rectum	8 mm/Is (sessile)	SM (T1)
50/M	D	4	Sigmoid	10 mm/Is (sessile)	SM (T1)
61/M	C	6	Sigmoid	13 mm/Isp (semi-pedunculated)	SM (T1)
68/M	D	6	Sigmoid	15 mm/Isp (semi-pedunculated)	SM (T1)
68/F	C	8	Cecum	20 mm/IIa + IIc (depressed)	SM (T1)
69/F	D	9	Transverse	15 mm/IIa (LST-NG) (flat)	SM (T1)
71/M	B	11	Transverse	20 mm/IIa + IIc (depressed)	SM (T1)
67/F	A	19	Rectum	20 mm/Is (sessile)	MP (T2)
72/F	B	24	Rectum	10 mm/IIa + IIc (depressed)	MP (T2)
58/M	B	25	Ascending	6 mm/IIa + IIc (depressed)	SM (T1)
66/F	D	26	Transverse	6 mm/Is (sessile)	SM (T1)
47/M	A	30	Sigmoid	20 mm/IIa + IIc (depressed)	SS (T3)
75/M	B	32	Sigmoid	20 mm/IIa (LST-NG) (flat)	SM (T1)

SM, submucosa; LST-NG, laterally spreading tumor, non-granular; MP, muscularis propria; SS, subserosa.

diagnosis of ILs soon after complete colonoscopy shows that the procedure is not 100% sensitive in identifying prevalent neoplasia. It strongly suggests the possibility that prevalent neoplasia were missed at baseline colonoscopy. Significant miss rates of single colonoscopy, especially for small adenomas, have been estimated on the basis of back-to-back tandem colonoscopy. Rex et al. (25) reported that the miss rate for adenomas $\geq$10 mm was 6%, for adenomas 6–9 mm was 13% and for adenomas $\leq$5 mm was 27%. Similarly, in a recent study of virtual colonoscopy, conventional colonoscopy failed to detect 12% of lesions $\geq$10 mm (26).

From our data, among all ILs except ADV cancer, there were 122 (32%) flat and 18 (5%) depressed lesions. Non-polypoid colorectal neoplasms (NP-CRNs) are considered to have a high malignant potential and a high miss rate compared with polypoid ones of similar size (27–30). Soetikno et al. reported that the overall prevalence of NP-CRNs and NP-CRNs with *in situ* or SM invasive carcinoma was 9.35% and 0.82%, respectively. They also concluded that NP-CRNs were more likely to contain carcinoma (odds ratio: 9.78) than polypoid lesions, regardless of the size (30). In our study, among all 13 invasive cancers diagnosed during the 3-year follow-up period, there were seven (54%) NP-CRNs (five depressed and two flat lesions). Moreover, the mean size of these lesions was $<$15 mm in diameter. It is quite difficult to recognize such lesions compared with the polypoid ones; therefore, special attention must be paid to NP-CRNs during colonoscopy. Future advances in image-enhanced endoscopy (31), e.g. narrow band imaging (32–35), autofluorescence imaging (36,37) and chromoendoscopy (38,39), may improve the ability to detect flat and depressed lesions during colonoscopy, whereas the effect of such lesions on clinical outcomes still remains to be established.

The incidence of ILs during follow-up colonoscopy was associated with sex and age in our study. The association of advanced lesions with sex and age was not significant in previous studies (22,40,41); however, it can be concluded that ILs are more likely to develop in males and in older patients. Furthermore, we find that patients with polyps of $\geq$6 mm or with any M cancer at initial colonoscopy have a very high risk of interval advanced neoplasia during surveillance. Few studies have performed systematic follow-up of patients after curative resection of CRC (42,43). Nava and Pagana followed 240 patients for 4 years after curative resection of CRC. They detected 28 (11.7%) patients with cancer during the follow-up (43). In our high-risk group (Group C+D), 216 (13.1%) patients had ILs including 19 (1.2%) invasive cancers during the follow-up period. The chronology of this makes it more likely that these were missed lesions or followed the '*de novo* pathway' (44,45) rather than progression of the adenoma–carcinoma sequence.

There are several limitations in this study. First, this present study was a multicenter retrospective cohort study. The number of subjects was probably enough, however, a prospective study would help to overcome some of these limitations. Another point worth mentioning is that we could not investigate the main indication for colonoscopy at the time of initial examination. Therefore, subjects were not limited strictly to asymptomatic patients in this study. Actually, the prevalence of Group A, patients without any adenomatous polyp, was lower than the other study subjects (38% vs. 66%, 63%) (22,23). In addition, we could not evaluate the number of adenomas and adenomas with villous histology at initial colonoscopy. Several studies have found that individuals with either 3 or more adenomas, tubular adenoma $\geq$10 mm, villous adenoma or adenoma with high-grade dysplasia at a baseline screening colonoscopy have a similarly higher risk of advanced neoplasia within 5 years compared with patients with no polyps or 1 or 2 small ($<$10 mm) tubular adenomas. On the basis of the results of our current study, a prospective evaluation of these factors would seem logical in order to validate other international guidelines in the Japanese context. Regarding the JPS, we started to recruit the eligible patients since 2003 (46). The JPS is a multicenter randomized controlled trial designed to evaluate CRC surveillance strategies in patients who have undergone complete colonoscopies on two occasions, with the removal of all detected neoplasia by high-resolution colonoscope, including the removal of flat and depressed lesions. The JPS is intended to continue until 2011, and the last step of the randomization process and complete histopathological assessment are ongoing.

In conclusion, there is a strong relationship between the results of baseline colonoscopy and the rate of serious incident lesions during 5 years of surveillance. Patients with any adenomatous polyps of $\geq$6 mm or M cancer at the initial colonoscopy have a higher risk of advanced lesions compared with the lower risk group. Another issue is that important lesions were missed at the initial colonoscopy and detected during follow-up colonoscopy, although all examinations were performed by experts.

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Conflict of interest statement

None declared.

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Appendix

In addition to the authors listed in the author field, following are the authors who contributed equally to this study.

Kinichi Hotta: Department of Gastroenterology, Saku Central Hospital, Nagano.

Nozomu Kobayashi: Endoscopy Division, National Cancer Center Hospital, Tokyo.

Yutaka Saito: Endoscopy Division, National Cancer Center Hospital, Tokyo.

Kuang-I Fu: Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa.

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ORIGINAL REPORT

Early Detection of Superficial Squamous Cell Carcinoma in the Head and Neck Region and Esophagus by Narrow Band Imaging: A Multicenter Randomized Controlled Trial

Manabu Muto, Keiko Minashi, Tomonori Yano, Yutaka Saito, Ichiro Oda, Satoru Nonaka, Tai Omori, Hitoshi Sugiura, Kenichi Goda, Mitsuru Kaise, Haruhiro Inoue, Hideki Ishikawa, Atsushi Ochiai, Tadakazu Shimoda, Hidenobu Watanabe, Hisao Tajiri, and Daizo Saito

From the Department of Gastroenterology and Hepatology, Kyoto University, Kyoto; Divisions of Gastrointestinal Oncology/Endoscopy and Pathology, National Cancer Center Hospital East, Kashiwa; Divisions of Endoscopy and Pathology, National Cancer Center Hospital; Department of Gastroenterology and Hepatology, Tokyo Jikei University, Tokyo; Department of Surgery, Kawasaki City Municipal Hospital, Kawasaki; Department of Surgery, Showa University Yokohama Northern Hospital, Yokohama; Department of Hygiene and Public Health, Kyoto Prefectural Medical University, Kyoto; and Department of Pathology, Niigata University, Niigata, Japan.

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Corresponding author: Manabu Muto, MD, PhD, Department of Gastroenterology and Hepatology, Kyoto University, 54 Kawaharacho, Shogoin, Sakyo-ku, Kyoto 606-8507 Japan; e-mail: mmuto@kuhp.kyoto-u.ac.jp.

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ABSTRACT

Purpose
Most of the esophageal squamous cell carcinomas (ESCCs) and cancers of the head and neck (H&N) region are diagnosed at later stages. To achieve better survival, early detection is necessary. We compared the real-time diagnostic yield of superficial cancer in these regions between conventional white light imaging (WLI) and narrow band imaging (NBI) in high-risk patients.

Patients and Methods
In a multicenter, prospective, randomized controlled trial, 320 patients with ESCC were randomly assigned to primary WLI followed by NBI (n = 162) or primary NBI followed by WLI (n = 158) in a back-to-back fashion. The primary aim was to compare the real-time detection rates of superficial cancer in the H&N region and the esophagus between WLI and NBI. The secondary aim was to evaluate the diagnostic accuracy of these techniques.

Results
NBI detected superficial cancer more frequently than did WLI in both the H&N region and the esophagus (100% *v* 8%, $P < .001$; 97% *v* 55%, $P < .001$, respectively). The sensitivity of NBI for diagnosis of superficial cancer was 100% and 97.2% in the H&N region and the esophagus, respectively. The accuracy of NBI for diagnosis of superficial cancer was 86.7% and 88.9% in these regions, respectively. The sensitivity and accuracy were significantly higher using NBI than WLI in both regions ($P < .001$ and $P = .02$ for the H&N region; $P < .001$ for both measures for the esophagus, respectively).

Conclusion
NBI could be the standard examination for the early detection of superficial cancer in the H&N region and the esophagus.

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INTRODUCTION

Esophageal cancer is the eighth most common cancer worldwide, accounting for 462,000 new cases in 2002, and is the sixth most common cause of cancer-related death (386,000 deaths).[1] Squamous cell carcinoma (SCC) is the most common histologic type worldwide.[1] Head and neck (H&N) cancer accounted for 607,000 new cases and 261,000 deaths in 2002.[1] The most common histologic type of H&N cancer is also SCC.

The early detection of cancer offers the best prognosis. Currently, however, esophageal SCC (ESCC) and H&N SCC (HNSCC) are detected at a late stage and then have poor prognoses.[1] Early detection of these cancers is difficult by conventional endoscopic white light imaging (WLI). Lugol chromoendoscopy can be used to detect superficial ESCC, but it causes unpleasant adverse effects such as severe chest pain and chest discomfort,[2-4] and it cannot be used for HNSCC screening because of the risk of aspiration.

The narrow band imaging (NBI) system is an innovative optical image-enhanced technology that uses narrow bandwidth NBI filters.[5,6] The central wavelengths of the NBI filters are 415 and 540 nm and each has a bandwidth of 30 nm. This system is easily activated by pushing a button on the endoscope. NBI combined with magnifying endoscopy can clearly visualize the microvascular structure of the organ surface,[6,7] because the 415-nm light is well absorbed by hemoglobin. Surface microvascular irregularities provide useful landmarks for identifying an early neoplasm in the H&N region, bronchus,

