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

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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,

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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

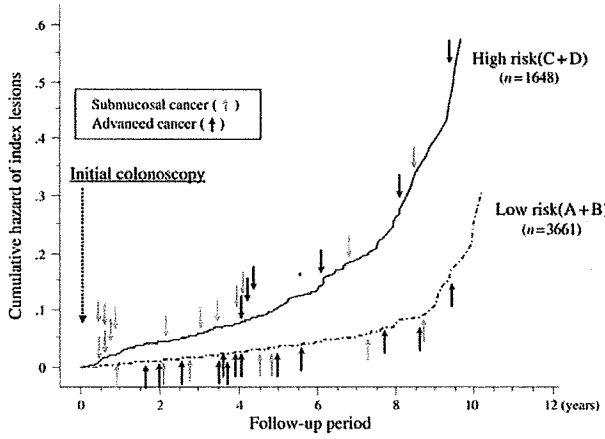

Figure 1. Comparison of cumulative incidence of index lesion and invasive colorectal cancer between risk groups.

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					
Age (year)/sex	Category (group)	Months since initial colonoscopy	Location	Size/macroscopic type	Depth of lesion (T-stage)
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

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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

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Clinical Trials repository link available on JCO.org.

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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,

and the GI tract.[7-15] We previously reported that NBI was useful for identifying HNSCC at an early stage.[8] Watanabe et al[16,17] also reported the usefulness of NBI rhinolaryngovideoscopy for the diagnosis of HNSCC. Yoshida et al[18] reported that NBI improves the accuracy of magnifying WLI in the assessment of ESCC.

However, the diagnostic yield of NBI in the early detection of superficial SCC has not been investigated. We conducted a prospective randomized study to directly compare WLI and NBI in the early diagnosis of SCC in the H&N region and the esophagus among high-risk patients.

PATIENTS AND METHODS

Study Rationale

Because ESCC patients frequently develop multiple intraesophageal SCC and second primary HNSCC synchronously and metachronously,[4,19-22] they provide a good cancer screening model. Whereas massively invasive SCC is easy to detect by endoscope, superficial cancer has been difficult. Furthermore, detection of high-grade intraepithelial neoplasia (HGIN) is clinically important because HGINs have the potential to become malignant invasive cancers.[23,24] Therefore, in this study, we targeted only macroscopic superficial cancer including HGIN that appeared as slightly elevated lesions lower than 5 mm, flat lesions, and lesions with a shallow depression. Lesions with an apparent elevation greater than 5 mm or those with apparent deeper ulceration were not evaluated.

The primary analysis of this study was a comparison of the detection rates of superficial cancer (HGIN, carcinoma in situ, and microinvasive SCC) using WLI and NBI. The secondary analysis was a comparison of the diagnostic accuracy (sensitivity and specificity) of the two imaging methods, size of the lesion detected, and the examination time. To evaluate diagnostic accuracy, we used the histologic diagnosis from a biopsy specimen as the gold standard diagnosis.

Study Populations

The protocol and consent form for this study were approved by the institutional review board at each participating institution, and written informed consent was obtained from all patients. The inclusion criteria were histologically confirmed present or previous ESCC and an age of 20 years or older. Although this study included patients with advanced ESCC, we evaluated only concomitant superficial cancer but not primary advanced cancer. Patients who had been previously treated for ESCC by endoscopic mucosal resection were included, because their esophagus was preserved with minimal damage. Patients with prior chemotherapy, radiotherapy, chemoradiotherapy, or surgical resection for ESCC or HNSCC were excluded, because their esophagus or pharynx was removed or too damaged to evaluate. Patients referred from another hospital with newly diagnosed ESCC were also included because they required more detailed examination (Fig 1) . The endoscopists were blinded to the endoscopic information. Patients with esophageal stricture, esophageal varices, or allergy to lugol dye solution were excluded.

Study Design

Patients were randomly assigned to receive primary WLI or primary NBI. To investigate whether a lesion detected by primary imaging could be identified subsequently by the other type of imaging, or whether a lesion missed by primary imaging could be identified subsequently by the other type of imaging, we performed both imaging methods in a back-to-back fashion so that primary WLI was followed by NBI and primary NBI was followed by WLI. To avoid affecting the first imaging results, the report of the first examination was completed before the second imaging was started.

To improve the quality of the reporting in the diagnostic accuracy study, we complied with the Standards for Reporting of Diagnostic Accuracy (STARD) initiative.[25] We set WLI as reference standard and NBI as index test.

Random assignment was performed in each case by an investigator using a computer-aided system on Medical Research Support Web site (Kyoto, Japan). This Web site was available only to the study participants. Using a minimization algorithm, the selection of the primary examination was balanced with respect to five stratification variables: institution, age (< 60 and ≥ 60 years), sex, alcohol consumption, and smoking habit.

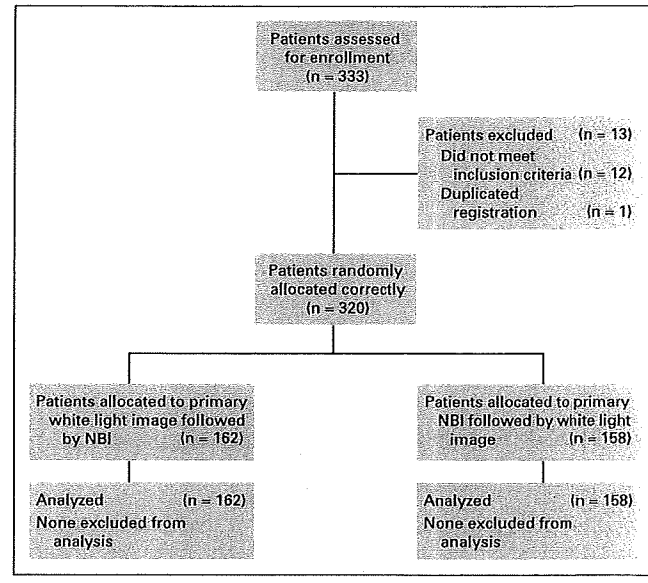

Fig 1. CONSORT diagram; overview of the study design. NBI, narrow band imaging.

Calculation of the Sample Size

For the purposes of this study, we set the probability for error (α) to .05 with a power of 0.80 (reflecting a β error of .2). Because there are no published comparative studies of NBI in ESCC patients, we estimated that the NBI system would increase the detection yield for superficial cancer by at least threefold compared with conventional WLI. This resulted in a calculated sample size of 250 patients (125 per group). Finally, we recruited an additional 50 patients in anticipation of instances of ineligibility or withdrawal during the examination because of discomfort (25 per group).

Endoscopic Examination

We used the same magnifying endoscope, with the capability for 80 times optical magnification (GIF-Q240Z, Olympus Medical Systems, Tokyo, Japan) for both WLI and NBI. The two imaging methods can be performed in a same video-endoscopy system (EVIS LUCERA system, Olympus Medical Systems, Tokyo, Japan). The details of the NBI system have been published elsewhere.[1,2,26,27] To maintain the quality of the endoscopic images, we used the same liquid-crystal color display for both imaging methods. Before the study started, all the participating endoscopists were trained using a central review of demonstrable NBI images of superficial squamous lesions (13 neoplasias and seven non-neoplastic lesions).

All endoscopic observations were made according to the protocol. During the first imaging, all parts of the oropharynx and hypopharynx were evaluated. The nasopharynx was not included the examination. After the first imaging was completed, an assistant physician immediately recorded the results on the case record form (CRF). After completion of the first imaging CRF, the second imaging of the oropharynx and hypopharynx was performed and the results were recorded on the CRF.

Next, all parts of the esophagus were evaluated using the same imaging as used for the H&N region. The endoscope was inserted to gain a view from the cervical esophagus to the esophagogastric junction, and the results were recorded on the CRF. The second imaging was performed on withdrawal of the endoscope, and the results were recorded on the CRF. During the procedure, we measured the examination time from start to finish of each imaging at each site. These procedure times included the evaluation of the lesion but not the biopsy procedure. The findings obtained by lugol chromoendoscopy are not included in this study.

Endoscopic Evaluation of Superficial Cancers

In this study, the real-time on-site diagnosis was evaluated because making an accurate diagnosis during an examination is clinically more important than a retrospective evaluation using a stored database. On WLI, if the lesion showed both a reddish color with uneven surface and disappearance of the vascular network pattern (Fig 2A), we diagnosed it as endoscopically suspected "superficial cancer." On NBI, if the lesion exhibited a well-demarcated brownish area as well as irregular microvascular patterns (Fig 2B), we diagnosed it as endoscopically suspected "superficial cancer." Details of these findings have been described previously.[7,8] If the lesion did not show these characteristics, the lesion was diagnosed as "non-cancer." Mucosal abnormalities were recorded with regard to endoscopic diagnosis, location, and size of the lesion.

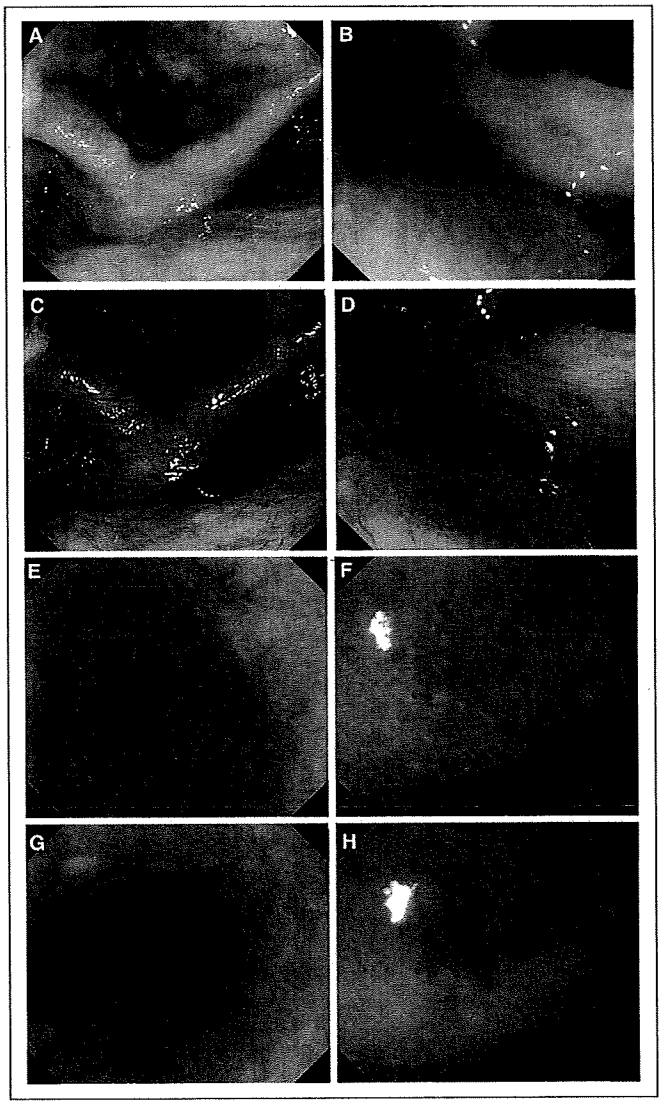

Fig 2. Superficial cancer in the head and neck region and esophagus. (A) White light imaging (WLI) shows a small reddish area (arrows) in the posterior wall of the hypopharynx. (B) Magnifying WLI shows a slightly reddish area with tiny microdots. (C) Narrow band imaging (NBI) shows a well-demarcated brownish area (arrows) in the posterior wall of the hypopharynx. (D) Magnifying NBI shows many tiny dots in the brownish area. This lesion was diagnosed histologically as squamous cell carcinoma in situ. (E) WLI shows a slightly reddish and depressed lesion (arrows) in the esophagus, although it is difficult to detect by WLI alone. (F) Magnifying WLI shows a slightly reddish area with an irregular microvascular pattern. (G) NBI shows a well-demarcated brownish area (arrows). (H) Magnifying NBI shows many tiny dots in the brownish area. This lesion was diagnosed histologically as high-grade intraepithelial cancer.

Pathologic Evaluation

Biopsy specimens were taken from each lesion after the completion of both types of imaging. Histologic evaluation was performed by central review by four experienced pathologists (H.S., A.O., T.S., and H.W.) who were blinded to the recorded endoscopic assessment. Histologic diagnoses were made according to WHO criteria[23] and were classified into two groups. One group included superficial cancers and the other group included non-cancers such as parakeratosis and inflammation. Microinvasion was estimated by the subepithelial invasion. The final pathologic diagnosis was made by the agreement of three of the four pathologists.

Statistical Analysis

The absolute and relative frequencies for qualitative variables were calculated for each group. Statistical analysis was performed using SPSS version

Table 1. Characteristics of Patients

Characteristic	Primary WLI (n = 162) No.	%	Primary NBI (n = 158) No.	%	P
Age, years					
Median	64		64		
Range	39-84		46-84		.99
Male sex	143	88	141	89	.86
Alcohol habit					
Drinking duration, years	157	97	148	94	.19
Median	41		40		.17
Range	10-63		5-60		
Favorite beverage					
Beer	61	38	59	37	1.00
Shochu	66	41	55	35	.30
Sake	43	27	48	30	.71
Whisky	22	14	24	15	.75
Wine	8	5	7	4	1.00
Others	1	0.6	0	0	1.00
Hot flashes					
Formerly had hot flashes	117	72	109	69	.62
Currently has hot flashes	75	46	70	44	.91
Smoking habit					
No. of smokers	145	90	142	90	1.00
Smoking duration, years					
Median	37		40		
Range	1-61		5-61		.41
No. of packs per day					
Median	1		1		
Range	0.05-4		0.125-4		.64
No. of packs per year					
Median	41		42		
Range	0.5-180		1.3-160		.89
Esophageal cancer					
No. of patients newly diagnosed	110	68	115	73	.39
Previously treated EMR	52	32	43	27	.39
Duration from previous EMR, years					
> 1	17	10	20	13	.60
1	45	28	33	21	.16
Depth of invasion					
Tis-T1a	74	46	67	42	.57
T1b	25	15	20	13	.27
T2	12	7	22	14	.07
T3	49	30	46	29	.90
T4	2	1	3	2	.68

Abbreviations: WLI, white light imaging; NBI, narrow band imaging; EMR, endoscopic mucosal resection.

17 software (SPSS, Chicago, IL). The continuous variables are expressed as medians and ranges. Continuous data were compared using the Mann-Whitney U test. Pearson's χ^2 test or Fisher's exact test was used to analyze categoric data to compare proportions. All P values were two-tailed, and a P value of $< .05$ was considered significant.

RESULTS

Between March 2005 and December 2005, 333 patients were enrolled onto this study (Fig 1). Twelve patients did not meet the inclusion criteria, and one was registered twice, so the remaining 320 patients were randomly assigned correctly into two groups: (1) 162 patients who underwent primary WLI followed by NBI, and (2) 158 patients who were examined by primary NBI followed by WLI.

The characteristics of the two groups are listed in Table 1. The two groups did not differ significantly in age, sex, alcohol consumption, smoking habits, or history of esophageal cancer treatment. In both groups, approximately 70% of the patients had newly diagnosed ESCC. Sixty-three (39%) patients in the primary WLI group and 71 (45%) patients in the primary NBI group had advanced ESCC deeper than the submucosal layer.

Table 2 provides the distribution of histologically confirmed superficial cancers. The total numbers of superficial cancer in the H&N region and the esophagus were 28 and 212, respectively. Total numbers of histologically confirmed non-cancer were 36 and 38 in each region. In all patients, superficial cancers were detected in 8% (26 of 320) in the H&N region and in 38% (121 of 320) in the esophagus. Multiple cancers were found in 0.6% of the patients in the H&N region and in 12% in the esophagus. The number of patients with superficial cancer, total number of superficial cancers, and their sizes and distribution did not differ between the two groups.

The diagnostic yields for superficial cancer using primary WLI and primary NBI detection are summarized in Table 3. The total numbers of superficial cancers detected by primary imaging differed between the two groups. In the H&N region, primary NBI detected all (100%; 15 of 15) of the superficial cancers, but primary WLI detected only one lesion (8%; 1 of 13). In the esophagus, only 58 (55%) lesions were detected by primary WLI, whereas 104 (97%) lesions were detected by primary NBI. All these differences were statistically significant ($P < .001$). The detection rate was significantly higher with primary NBI than with primary WLI, even for small lesions (< 10 mm in diameter) in both the H&N region ($P < .001$) and the esophagus ($P = .03$).

In the back-to-back analysis, secondary NBI after primary WLI significantly increased the detection rate in both the H&N region (8% *v* 77%; $P < .001$) and esophagus (55% *v* 95%; $P < .001$; Appendix Table A1, online only). In contrast, secondary WLI after NBI significantly decreased the detection rate (Appendix Table A1). Moreover, 16 (57%) superficial cancers in the H&N region and 48 (23%) superficial cancers in the esophagus were detected only by NBI (Appendix Table A2, online only). In contrast, no lesion was detected only

Table 2. Distribution of Histologically Confirmed Superficial Cancer According to Lesion in the Head and Neck Region and the Esophagus

Variable	Primary WLI (n = 162)			Primary NBI (n = 158)			P
	No.	%	95% CI	No.	%	95% CI	
Head and neck region							
No. of patients	12	7	3.3 to 11.4	14	9	4.4 to 13.3	.66
No. of lesions per patient							
1	12	7	3.3 to 11.4	14	9	4.4 to 13.3	> .999
≥ 2	1	0.6	−0.6 to 1.8	1	0.6	−0.5 to 1.9	
Total No. of superficial neoplasias	13			15			
Size threshold, mm							
< 10	7			10			.50
11-20	5			5			
≥ 21	1			0			
Histologic diagnosis							
High-grade intraepithelial neoplasia or carcinoma in situ	10			15			.09
Microinvasive cancer	3			0			
Esophagus							
No. of patients	58	36	28.4 to 43.2	63	40	32.2 to 47.6	.49
No. of lesions per patient							
1	39	24	17.4 to 30.7	43	27	20.3 to 34.2	> .999
≥ 2	19	12	6.7 to 16.7	20	13	7.4 to 17.9	
Total No. of superficial cancers	105			107			
Size threshold, mm							
< 10	18			18			.91
11-20	21			19			
≥ 21	66			70			
Histologic diagnosis							
High-grade intraepithelial neoplasia or carcinoma in situ	73			84			.16
Microinvasive cancer	32			23			

Abbreviations: WLI, white light imaging; NBI, narrow band imaging.

Table 3. Diagnostic Yield of Primary WLI and Primary NBI for Detection of Superficial Cancer in the Head and Neck Region and the Esophagus

Variable	Primary WLI (n = 162)			Primary NBI (n = 158)			P
	No.	%	95% CI	No.	%	95% CI	
Head and neck region							
No. of superficial cancers	1/13	8	0.2 to 36.0	15/15	100	78.2 to 100	< .001
Size of superficial cancer, mm							
< 10	0/7	0	0 to 41.0	10/10	100	69.2 to 100	< .001
11-20	1/5	20	0.5 to 71.6	5/5	100	48.7 to 100	.12
≥ 21	0/1	0	0.0 to 0.0	to			—
Esophagus							
No. of superficial cancers	58/105	55	45.2 to 65.0	104/107	97	92.0 to 99.4	< .001
Size of superficial cancer, mm							
< 10	7/18	39	17.3 to 64.3	17/18	94	72.7 to 99.9	.03
11-20	7/21	33	14.6 to 57.0	18/19	95	74.0 to 99.9	.02
≥ 21	44/66	67	54.0 to 77.8	69/70	99	92.3 to 100	< .005

Abbreviations: WLI, white light imaging; NBI, narrow band imaging.

by WLI, except one lesion of > 20 mm in the esophagus. No lesions were undetected by both WLI and NBI in either region.

Table 4 summarizes the diagnostic performance of primary WLI and primary NBI for detecting superficial cancer. The sensitivity of primary NBI was significantly higher than that of primary WLI in both the H&N region (100% *v* 7.7%; $P < .001$) and the esophagus (97.2% *v* 55.2%; $P < .001$). Accuracy was also significantly higher for primary NBI than for primary WLI in both regions (85.7% *v* 62.9%, $P = .02$ and 88.9% *v* 56.5%, $P < .001$, respectively). Specificity was not significantly different in the two regions ($P = .28$ and $P = .33$, respectively). The positive predictive value did not differ between the two imaging techniques, but the negative predictive value was significantly higher for primary NBI than for primary WLI in both the H&N region ($P = .02$) and the esophagus ($P < .002$).

The median procedure times of primary WLI and primary NBI for the H&N region were 120 seconds (range, 34 to 275 seconds) and 162 seconds (range, 30 to 525 seconds), respectively. Those for the esophagus were 95 seconds (range, 30 to 360 seconds) and 135 seconds (range, 30 to 616 seconds), respectively. These differences were statistically significant ($P < .001$). The procedure times in the secondary imaging in the back-to-back experiments also differed significantly between WLI and NBI in both regions (Appendix Table A3, online only). There were no serious adverse events related to examination with either procedure. All patients tolerated both procedures well.

DISCUSSION

This study clearly demonstrates that NBI is a more sensitive method for detecting and diagnosing superficial SCC in the H&N region and the esophagus. According to the concept of "field cancerization,"[28] patients with ESCC or HNSCC are at high risk for the development of multiple SCCs. In the clinical context, the early detection strategy for superficial SCC is the same between patients at high risk and those at risk because of heavy drinking, smoking, or aldehyde dehydrogenase 2 deficiency.[20-35] In addition, detection technique should not only be sensitive but should also be easily applicable. From this perspective, NBI is easily applied with a modicum of experience and will have a rapid learning curve compared with WLI. Thus, NBI is the ideal method for effectively detecting superficial SCC.

Table 4. Diagnostic Performance of Primary WLI and Primary NBI Observation for Detection of Superficial Cancer in the Head and Neck Region and the Esophagus

Variable	Primary WLI			Primary NBI			P
	No.	%	95% CI	No.	%	95% CI	
Head and neck							
Sensitivity	1/13	7.7	0.2 to 36.0	15/15	100	100	< .001
Specificity	21/22	95.5	77.2 to 99.9	11/14	78.6	54.6 to 98.1	.28
Accuracy	22/35	62.9	47.6 to 76.4	26/29	86.7	72.6 to 97.8	.02
PPV	1/2	50	1.3 to 98.7	15/18	83.3	58.6 to 96.4	.37
NPV	21/33	63.6	54.1 to 79.6	11/11	100	100	.02
Esophagus							
Sensitivity	58/105	55.2	45.2 to 65.0	104/107	97.2	92.0 to 99.4	< .001
Specificity	12/19	63.2	38.4 to 83.7	8/19	42.1	20.3 to 66.5	.33
Accuracy	70/124	56.5	47.3 to 65.3	112/126	88.9	82.1 to 93.8	< .001
PPV	58/65	89.2	79.1 to 95.6	104/115	90.4	85.3 to 95.1	.80
NPV	12/59	20.3	11.0 to 32.8	8/11	72.8	39 to 94	< .002

Abbreviations: WLI, white light imaging; NBI, narrow band imaging; PPV, positive predictive value; NPV, negative predictive value.

Detecting cancer at an early stage is an optimal strategy for preventing the development of advanced cancer and improving survival. Furthermore, early detection uses a minimally invasive treatment (eg, endoscopic resection) with curative intent.[8,36-38] In fact, in our study, 75% (21 of 28) of the superficial HNSCCs were completely removed by endoscopic resection or biopsy alone, while early detection of HNSCC had been quite difficult. These results provide us with new diagnostic and treatment strategies for ESCC patients, because the risk of development of HNSCC after esophagectomy is quite high.[21]

As the criteria for diagnosing superficial SCC by NBI, we used two endoscopic findings: a well-demarcated brownish area and an irregular microvascular pattern.[7-9] Using only these two findings, the sensitivity of primary NBI for the diagnosis of superficial SCC was 100% in the H&N region and 97.2% in the esophagus. The diagnostic accuracy was nearly 90%. These results indicate that these NBI findings are quite useful for the accurate diagnosis of superficial SCC.

Lugol chromoendoscopy is useful for the detection of superficial ESCC.[2-3] However, the administration of lugol solution is time-consuming, and accurate diagnosis by lugol chromoendoscopy is difficult[4] because the staining pattern shows wide variations.[2] This increases the incidence of false-positive lesions and leads to unnecessary biopsies. In contrast, NBI is easily manipulated and shows high sensitivity. Thus, NBI could reduce the number of unnecessary biopsies and shorten examination time. Furthermore, lugol chromoendoscopy is more invasive than both WLI and NBI, and WLI is still the gold standard for cancer screening. Therefore, we did not compare the diagnostic yield of NBI and lugol chromoendoscopy, and we used WLI as the standard reference to compared the diagnostic yield of WLI and NBI.

NBI required a significantly longer examination time than WLI. This might be related to the high detection rate and more frequent time spent in magnification during NBI, because if the lesions were not seen by WLI, no magnification was performed. The actual time difference between NBI and WLI was only 20 to 42 seconds. This is clinically acceptable, because the important time issue is not that NBI takes slightly longer than WLI, but rather that endoscopists spend more time in the careful observation of high-risk patients.

In this study, ESCC patients referred from another hospital were included. Even if the biopsies were previously done, the earlier biopsy sites were healed by the time of this study and were not generally detectable by either imaging method. Therefore, we thought that it was not a confounding factor.

The same endoscopists performed both imaging procedures in this study, whereas the endoscopists ideally should be separated and blinded to each imaging procedure. However, it was clinically impossible to change and blind the endoscopists during this series of examinations. Furthermore, the result produced with NBI first followed by WLI might underestimate the benefit of NBI because NBI is more sensitive than WLI. However, the detection and diagnosis of superficial SCC by NBI was significantly better than that using WLI in both the H&N region and the esophagus, regardless of whether NBI was primary or secondary. These results indicate that NBI should be the standard examination.

Significant detection results seen in this study were all achieved without the newest generation high-definition endoscope. If we use the newest high-definition endoscope with NBI, the rates of detection might increase compared with those found in this study. Furthermore, the endoscopy system used in this study and in most Asian countries was different from those used in North America and Europe.[26,27] However, we previously reported that even the nonmagnifying laryngoscope based on same system as that used in North America and Europe could dramatically improve the visualization of both the brownish area and irregular microvascular patterns.[39] Therefore, we believe that differences in the system are no longer as important as careful observation by NBI.

In conclusion, NBI combined with magnifying endoscopy significantly improved the detection rates for SCC with quite high sensitivity, and this new image-enhanced technology can be applied easily in clinical practice. Furthermore, early detection facilitates the potential of minimally invasive treatment, such as endoscopic resection or partial surgical resection.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Excessive Fat Restriction Might Promote the Recurrence of Colorectal Tumors

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The incidence of colorectal cancer is rapidly increasing in Japan. This trend has been suggested to be caused by an increasing fat intake as a result of the Westernized diet among Japanese. We investigated whether dietary instruction optimizing the fat energy ratio suppresses the recurrence of colorectal tumors. The subjects, 373 men and women, were the participants in a randomized clinical trial of colorectal cancer prophylaxis. At entry, each participant completed a 3-consecutive-day food record on which dietary instruction was given to restrict fat energy ratio to 18–22%. Data obtained before and after the intervention were examined by cohort analysis. The primary endpoint was the presence or absence of colorectal tumor(s) at colonoscopy after 4 yr. Unexpectedly, the recurrence of tumor increased as the subjects reduced their fat intake. The lowest tumor recurrence among the men was observed in the group with 23.8–26.4% fat energy ratio after the intervention. Furthermore, in men, the risk of tumors decreased significantly as the intake of linoleic acids per body weight increased. For women, similar trends were observed. These results suggest that extreme fat restriction is highly likely to promote the recurrence of colorectal tumors, which may be partly attributable to linoleic acid deficiency.

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INTRODUCTION

Over the last several decades, the Japanese dietary habit has changed considerably. According to the National Nutrition Survey in Japan, fat intake, of animal fat in particular, has been increasing remarkably since around 1960. As compared to 1946, when the first National Nutrition Survey was conducted, fat intake had increased threefold by 1970 and even fourfold by 1995. Animal fat intake in 1995 was 4.6 times greater than that in 1955. At the same time, the disease structure in the Japanese population has been greatly changing, too. The incidence and mortality of colorectal cancer have been increasing rapidly (1,2), which resulted in colorectal cancer gaining the leading position in terms of cancer mortality among Japanese women in 2003 (1). It appears that the increase in colorectal cancer incidence followed the increase of fat intake with about a 20-yr lag (3).

Nakaji et al. (4) reported a significant correlation between fat intake and colon cancer in their cross-sectional analysis. Also, the incidence of colorectal cancer among Japanese migrants to Hawaii was, as their fat intake increased, reported to have increased much rapidly compared with that in Japanese people in Japan (5). On the other hand, Howe et al. (6) performed a meta-analysis of 13 case-control studies from all over the world. Their analysis suggested that there was no association between intakes of total fat or saturated fatty acids (SFA) and colorectal cancer (6). The second expert report issued by the World Cancer Research Fund and American Institute for Cancer Research listed only animal fat as a risk factor among fats, although judging it as "limited evidence" for its causal relation to colorectal cancer (7).

However, as far as Japanese studies are concerned, several recent results have suggested an association between fat intake and colorectal cancer. According to The Japan Public Health Center-based Prospective Study, the Western dietary pattern characterized by high intake of fat and meat was positively associated with colon cancer risk in women (8). Also, the Japan Collaborative Cohort Study indicated positive association of chicken and egg consumption with colon cancer (9).

A few clinical trials examining the preventive effects of fat-restricting dietary intervention on colorectal cancer have been reported (10–12). However, with regard to the Japanese, whose fat intake has been rapidly increasing, no such trials have ever been reported. Furthermore, most of the epidemiological studies on colorectal cancer (13–16) applied the Semi-Quantitative Food Frequency Questionnaire (FFQ). Thus far, no study has applied a 3-day diet record (DR) to all the subjects for this purpose. Since 3-day DR is based on actual intakes, it is considered to give better estimates of absolute amount of intakes for energy and fats than an FFQ (17). In addition, due to a large variety of the Japanese diet, FFQ might lack many food items actually consumed by Japanese subjects.

In this study applying a 3-day DR for dietary assessment, we investigated whether dietary instruction optimizing the fat intake could suppress the recurrence of colorectal tumors. The subjects were recruited to participate in a randomized clinical trial of colorectal cancer prophylaxis by administration of wheat bran and/or *Lactobacillus casei* performed at the Osaka Medical Center for Cancer and Cardiovascular Diseases (18).

SUBJECTS AND METHODS

Study Design and Population

The subjects were the participants of a randomized clinical trial of colorectal cancer prophylaxis by administration of wheat bran and/or a *Lactobacillus casei* preparation (18). The details of this study were previously reported (19). In brief, the subjects were 406 men and women aged 40 to 65 yr who had had at least two colorectal tumors (adenomas and/or early cancers) removed endoscopically within 3 mo before recruitment. Excluded were subjects with other malignant tumors, a history of intestinal or gastric resection (except appendectomy), familial adenomatous polyposis, and severe illness.

The subjects were randomly allocated into 4 groups to receive wheat bran, *Lactobacillus casei* preparation, both, or neither. Each subject received dietary instruction individually so that his or her fat intake would constitute 18–22% of the total energy intake.

The subjects were recruited at the Osaka Medical Center for Cancer and Cardiovascular Diseases between June 1993 and September 1997. The study protocol was approved by the Ethics Committee of this institution. All the subjects gave written informed consent.

Colonoscopy

Total colonoscopy for observation was performed 2 and 4 yr after the start of the regimen. All polyps discovered by this procedure were resected and examined histologically. The primary endpoint was the presence or absence of colorectal tumor(s) after 4 yr.

Dietary Assessment

Dietary assessments were conducted by means of a 3-day DR at entry, at 3 mo, and at 4 yr after the start of the intervention. Trained dietitians interviewed each subject individually for about 1 h to assess and record the contents of his or her meals. In principle, male participants were accompanied by a family member. Intakes of energy and nutrients were calculated using the Food Composition Database developed by the Osaka Medical Center for Cancer and Cardiovascular Diseases (19). The intake of wheat bran biscuit was included in dietary assessment after 3 mo and after 4 yr. Intakes of other health foods including food supplements were excluded from the assessment. Intake amounts of energy and nutrients before and after the intervention were represented by the mean values of 3 days at entry and those after 3 mo, respectively.

Dietary Intervention

The core of the dietary instruction was to optimize the fat intake of the subjects. Based on the results of the dietary survey at entry, each subject was advised on the selection of food items, food preparation methods, and so forth so that the energy from fat would constitute 18–22% of total energy intake. We recommended reducing both animal and vegetable fats equally. Those whose fat intake was too low were instructed to increase it. Dietary instruction was given during the interview immediately after the dietary survey at entry followed by additional comments and an individually calculated diet assessment sent by post. Compliance with the instructions was evaluated at dietary checkup 3 mo after the start of the intervention. If necessary, instruction was given again at that time. Furthermore, the subjects were encouraged to adhere to their dietary instruction by means of written dietary information handed over at the follow-up visit after 1 yr and sent by post after 2 yr.

Other Variables

Colonoscopic findings in the past, height, past medical history, medication history, and family history of the subjects were recorded at entry. Body weight was measured at entry and at each consultation. Subjects' information about drinking, smoking, physical activity, and use of health foods and/or supplements was recorded during the initial interview by the dietitian.

Statistical Analysis

Drinking and smoking status were represented by baseline values. Body weight was represented by baseline value (before) and the measurement after 3 mo (after). Crude nutrients were used in t-tests for intake of nutrients. For analysis of the rate of subjects in each category of fat energy ratio before and after the intervention, χ^2 test was used. Before relative risk analysis, nutrients were adjusted for total energy intake using the residual method (20). Energy and nutrient intakes were analyzed for men and women separately. Statistical significance was established at $P < 0.05$ for the 2-tailed test. Men were equally divided into quintiles, and women were divided into tertiles based on height, body weight, body mass index [(BMI); weight (kg)/height $(m)^2$], and energy and nutrient intakes. On the basis of unconditional logistic regression models, the lowest quintile/tertile was taken as the reference in estimating the relative risk as the odds ratio (OR) adjusted for age, BMI (<18.5, 18.5–25, and ≥25), amount of alcohol consumption (never, ≤23 g/day, and >23 g/day), current smoking status (smoker or nonsmoker), physical activity level (light or moderate), and randomization group. Linear trends in logistic regression analysis were evaluated using medians of each quintile/tertile. SPSS statistical analysis software version 15 (SPSS, Inc., Chicago, IL) was used.

RESULTS

The initial dietary survey was conducted between June 1993 and April 1998. Colonoscopy after 4 yr was completed in February 2002. Among 406 subjects who participated in the initial dietary survey, 373 subjects completed colonoscopic examination after 4 yr as well as dietary assessment/instruction after 3 mo.

Table 1 shows the baseline characteristics of the subjects consisting of 305 men and 68 women; approximately 80% were men. More than 80% of both sexes had low levels of physical activity. By colonoscopy after 4 yr, recurrence of colorectal tumors was diagnosed in 53.1% of men and 47.1% of women; that is, 51.7%–52.0% of subjects overall. Virtually all cases were precancerous lesions, including adenoma and intramucosal cancer, and only one case of colorectal cancer was diagnosed as adenoma with severe dysplasia. Elevated risk of colorectal cancer was associated with higher values of age, body weight, and height; whereas no significant correlation was found between the colorectal cancer risk and physical activity, drinking, or smoking.

For the data analysis after intervention, mean values of 3 days at 3 mo were used throughout. An alternative analysis using mean values of 6 days, 3 days each at 3 mo and at 4 yr was also performed with the similar but somewhat obscured results (data not shown). The number of subjects with fat energy ratio of 18–22% increased significantly from 97 (26.0%) at baseline to 112 (30.0%) after the intervention ($P = 0.01$) as shown in Fig. 1. Among the subjects with the highest fat energy ratio at baseline (>22%), the risk of developing colorectal tumors increased substantially in the subjects who reduced the ratio after the intervention. When the subjects with unchanged fat energy ratio (>22%) after the intervention was taken as reference, OR of those with the ratio reduced to 18–22% was 2.16 and OR of those with the ratio reduced to <18% was 4.45.

TABLE 1
Baseline characteristics of subjects

	Men ($n = 305$)	Women ($n = 68$)
Age (yr)[a]	54.8 ± 6.1	56.3 ± 6.3
Height (cm)[a]	166.5 ± 6.0	153.4 ± 4.5
Body weight (kg)[a]	65.4 ± 9.4	53.8 ± 6.7
Body mass index (kg/m^2)[a]	23.9 ± 2.6	22.9 ± 2.8
Physical activity[b]		
Light	256 (83.9)	55 (80.9)
Moderate	49 (16.1)	13 (19.1)
Current smokers[b]	151 (49.5)	12 (17.6)
Alcohol intake[b]		
Never	41 (13.4)	46 (67.6)
≤23.0 g/day	112 (36.7)	17 (25.0)
>23.0 g/day	152 (49.8)	5 (7.4)

[a]Values are means ± SD.
[b]Values are number; values in parentheses are percent.

Energy and major nutrient intakes before and after the intervention are shown in Table 2. In both men and women, the intake of dietary fiber was significantly increased after the intervention. In men, the intakes of energy, total fat, carbohydrate, calcium, iron, and vitamin C were significantly decreased; whereas in women, significant decreases were found in energy and carbohydrate intakes.

Table 3 and 4 show energy and energy-adjusted nutrient intakes at baseline in relation to tumor recurrence for men and women, respectively. A significant decrease in OR was found only in the third quintile for linoleic acid (LA) intake per body weight in men [OR = 0.36, 95% confidence interval (CI) = 0.17–0.77].

Energy and energy-adjusted nutrient intakes after the intervention in relation to tumor recurrence for men is shown in Table 5. OR decreased significantly in the fourth quintile, with fat energy ratio of 23.8–26.4% compared with the lowest quintile (OR = 0.23, 95% CI = 0.11–0.50). As for total fat, OR in the fourth quintile showed a significant decrease. Furthermore, OR decreased significantly in the fifth quintile for saturated fatty acids (SFA) and in the fourth and fifth quintiles for monounsaturated fatty acids (MUFA). For polyunsaturated fatty acids (PUFA), a