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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

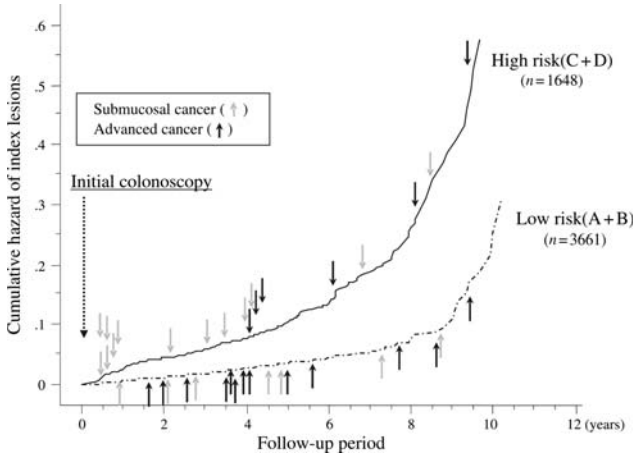

Figure 1. Comparison of cumulative incidence of index lesion and invasive colorectal cancer between risk groups.

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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