COLORECTAL CANCER

Incidence and recurrence rates of colorectal adenomas estimated by annually repeated colonoscopies on asymptomatic Japanese

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Background: Whereas high recurrence rates of colorectal adenomas after polypectomy are widely recognised, little is known of the natural incidence in those with no neoplastic lesions initially. It is also known that single colonoscopy has a significant miss rate.

Aims: To elucidate the incidence and recurrence rates of colorectal neoplasms from a large cohort of asymptomatic Japanese patients on the basis of annually repeated colonoscopies.

Methods: A total of 6225 subjects (4659 men and 1566 women) participating in an annual colonoscopic screening programme and completing three or more colonoscopies were analysed during the 14 year period between 1988 and 2002. Patients were divided into three groups according to the findings of the initial two colonoscopies: 4084 subjects with no neoplasm, 1818 with small adenomas <10 mm, and 323 with advanced lesions, including carcinoma in situ, severe dysplasia, or large adenomas ≥10 mm. Mean age at the second colonoscopy was 48.8 years.

Results: For all types of colorectal neoplasms, the incidence rate in those with no initial neoplasm was 7.2%/year whereas recurrence rates in those with small adenomas and advanced lesions were 19.3% and 22.9%/year, respectively. For advanced colorectal lesions, the incidence rate was 0.21%/year whereas recurrence rates in those with small adenomas and advanced lesions were 0.64% and 1.88%/year, respectively. Colorectal neoplasms were in general more likely to develop in males and older subjects.

Conclusions: Although recurrence rates after polypectomy were elevated, the incidence rates in subjects with no neoplastic lesions initially were quite high.

Colorectal adenomas are reputed to be precancerous lesions that develop into colorectal cancers on the basis of the adenoma-carcinoma sequence.^{1–2} The effects of screening for colorectal cancer and removing precancerous lesions or early stage cancers on the prevention of colorectal cancer development or death have been established.^{3–6} Because of the high recurrence rates of colorectal adenomas in patients who have undergone polypectomy, regular surveillance by colonoscopy has been recommended.^{7–8}

On the other hand, colorectal adenomas are much more common lesions than colorectal cancers, and tiny colorectal adenomas are frequently discovered by particularly vigorous colonoscopy.^{9–12} In this regard, recent prevalence studies based on screening colonoscopy of asymptomatic adults have reported colorectal adenomas in approximately 30% of patients aged >50 years whereas the prevalence of invasive cancer is less than 1%.^{10–11–13}

Regarding the new development of colorectal adenomas, there have been many reports on the recurrence rates of colorectal adenomas after polypectomy.^{7–14–17} However, reports on the incidence rates of colorectal adenomas from subjects free of neoplastic lesions on initial colonoscopy are scarce, and the sample sizes of the few previous studies were rather small.^{18–19}

In this study, we aimed to determine the actual incidence rates of colorectal adenomas from a large cohort that was initially adenoma free. To obtain precise rates, repeated annual colonoscopies were conducted. As it is known that single colonoscopy has a significant miss rate,^{20–22} the initial colorectal findings were confirmed by the second of two serial colonoscopies. Hence analysis was based on at least the third or even later colonoscopy. Then, the incidence rates were compared with recurrence rates after polypectomy. Our

results should represent fundamental data that can be used for the study of colorectal neoplasms and the planning of cancer prevention programmes.

METHODS

Subjects

We consecutively enrolled asymptomatic Japanese subjects who underwent total colonoscopy as part of their annual medical health checkup at Kameda General Hospital and Makuhari Clinic between 1988 and 2002. They had no visible rectal bleeding, recent change in bowel habits, or recent or current lower abdominal pain. They had not been screened by faecal occult blood tests or other examinations for colorectal cancer, and they underwent colonoscopy as the first choice examination to check for colorectal lesions. Subjects with a personal history of colorectal cancer, colorectal polyps, or inflammatory bowel disease were excluded. All subjects were encouraged to undergo annual follow up examinations by total colonoscopy, irrespective of the results of previous examinations. Subjects undergoing a third or greater annual colonoscopies were entered into the analysis.

Endoscopic procedures

Two litres of polyethylene glycol electrolyte solution were ingested for bowel preparation. Medium length paediatric colonoscopes were used (mainly PCF200 and PCF230; Olympus, Tokyo, Japan). "Simple total colonoscopy" (no fluoroscopic assistance, no sedation or analgesia, one man method) was performed. During the procedure, the location and size of all polyps were determined and documented before their removal. The size of each polyp was estimated with open biopsy forceps (=8 mm). All polyps ≥5 mm and lesions <5 mm suspected of neoplasia were resected

endoscopically or by surgical operations. All pathological specimens were evaluated by the same pathologists at Kameda General Hospital. Neoplastic lesions were classified into colorectal invasive cancer, carcinoma in situ, and adenoma.

Classification of subjects

Subjects were classified into three groups according to the most advanced colorectal lesion found by the first and second colonoscopies. The first group consisted of subjects with no neoplastic lesions during the initial two colonoscopies. The second group consisted of subjects with small adenomas of <10 mm at most. The third group consisted of subjects with advanced lesions, including carcinoma in situ, or with severe dysplasia, and adenomas ≥ 10 mm. Subjects with invasive cancer were referred for medical care outside of our health check programme and were excluded from further analysis.

The incidence rate of colorectal adenomas was estimated by newly developed adenomas from subjects with no neoplastic lesions on the first two examinations. Recurrence rates of colorectal adenomas were estimated by newly detected adenomas after neoplasms were endoscopically resected either on the first or second colonoscopy. Two end points, all neoplastic lesions and advanced lesions, were subjected to analysis.

Statistical analysis

The incidence and recurrence rates of adenomas or advanced lesions were determined on the basis of the Kaplan-Meier method. Hazard ratios with 95% confidence intervals (CI) controlling for sex, age at the second colonoscopy, and initial colorectal lesions were calculated using the Cox proportional hazard model. A two sided *p* value of less than 0.05 was considered statistically significant. Analyses were performed with SAS for Windows software (SAS Institute Inc., North Carolina, USA).

RESULTS

Subjects and findings of the initial two colonoscopies

A total of 68 053 screening colonoscopies were performed from January 1988 to March 2002, of which 22 395 were first time cases. Mean (SD) age was 48.1 (9.4) years; 15 956 were men and 6439 were women. Of the total, 17 933 (80.1%) had no neoplastic lesions, 3699 (16.5%) had small adenomas <10 mm, 692 (3.1%) had advanced lesions, including carcinoma in situ, severe dysplasia, or large adenomas ≥ 10 mm, and 71 (0.32%) had invasive carcinoma.

Among these, 7620 subjects underwent a second colonoscopy within 1.5 years after the first one, and 6356 (83.4%) had no neoplasm, 1187 (15.6%) had small adenomas, 74 (0.97%) had advanced lesions, and three had invasive cancer at the second colonoscopy. When the results of the first and second procedures were combined, 5069 subjects (66.5%) had no neoplasm, 2142 (28.1%) had small adenomas, 393 (5.2%) had advanced lesions, and 16 (0.21%) had invasive carcinoma.

Of the 7604 subjects without invasive carcinoma, 6225 went on to have a third or more annual colonoscopies. Mean (SD) age at the second colonoscopy was 48.8 (8.4) years; 4659 were men and 1566 were women. Of these, 4084 subjects (65.6%) had shown no neoplasm, 1818 (29.2%) had shown small adenomas, and 323 (5.2%) had shown advanced lesions during the initial two colonoscopies. The results of the third or more colonoscopies on these cohorts were analysed.

Incidence and recurrence rates of colorectal neoplasms according to initial colonoscopic findings (table 1, fig 1)

Of 4084 subjects with no neoplasm at the initial two colonoscopies, 848 (20.8%) developed some type of colorectal

neoplasm during a mean follow up of 2.89 years. The annual incidence rate was estimated to be 7.2%.

Of 1818 subjects with small adenomas removed during the initial two colonoscopies, 821 (45.2%) developed some type of colorectal neoplasm during a mean follow up period of 2.34 years. The annual recurrence rate was estimated to be 19.3%.

Of 323 subjects with advanced lesions removed during the initial two colonoscopies, 162 (50.2%) presented with some form of colorectal neoplasm during a mean follow up of 2.19 years, the annual recurrence rate being 22.9%.

Hazard ratios controlling for sex and age of the subjects with no neoplasm initially were 2.4 (95% CI 2.2–2.7; *p*<0.001) in those with small adenomas and 2.6 (2.2–3.1; *p*<0.001) in those with advanced lesions.

Incidence and recurrence rates of colorectal neoplasms according to sex and age

Males or older subjects had a greater likelihood of developing more adenomas than females or younger subjects. The incidence or recurrence rates in males and females were 12.4% and 6.5%/year, respectively. Rates for the age groups <40, 40–49, 50–59, and ≥ 60 years were 6.1%, 9.7%, 13.5%, and 16.3%/year, respectively (table 1).

Sex and age were shown to be independent risk factors for newly developed colorectal neoplasias according to multivariate analysis. The male to female hazard ratio was 1.8 (95% CI 1.6–2.0; *p*<0.001), and those for the age groups 40–49, 50–59, and ≥ 60 years relative to the <40 year age group were 1.5 (1.3–1.8; *p*<0.001), 2.0 (1.6–2.3; *p*<0.001), and 2.2 (1.8–2.7; *p*<0.001), respectively (table 1).

When the group with no initial neoplasia was stratified by sex and age, the incidence rates of colorectal adenomas in male subjects were 4.7%, 8.2%, 10.1%, and 11.4%/year at ages <40, 40–49, 50–59, and ≥ 60 years, respectively, and those in female subjects were 3.1%, 3.2%, 6.7%, and 7.3%/year, respectively (table 2).

When the group with initial small adenomas was stratified by sex and age, the incidence rates of colorectal adenomas in males were 15.1%, 18.9%, 22.2%, and 25.1%/year at age of <40, 40–49, 50–59, and ≥ 60 years, respectively, and those in females were 7.9%, 11.4%, 14.1%, and 20.4%/year, respectively (table 2).

Males with initial advanced lesions stratified by age had incidence rates of colorectal adenomas of 14.7%, 24.6%, 26.7%, and 24.4%/year at <40, 40–49, 50–59, and ≥ 60 years, respectively, and females had rates of 0.0%, 3.2%, 16.3%, and 10.7%/year, respectively (table 2).

Incidence and recurrence rates of advanced lesions according to initial colonoscopic findings (table 3, fig 2)

Of 4084 subjects with no neoplasm found at the initial two colonoscopies, 30 (0.73%) subjects developed advanced colorectal lesions during a mean follow up of 3.45 years. The annual incidence rate was estimated to be 0.21%.

Of 1818 subjects with small adenomas removed at the initial two colonoscopies, 40 (2.2%) developed advanced colorectal lesions during a mean follow up of 3.46 years. The annual recurrence rate was estimated to be 0.64%.

Advanced lesions were removed from 323 subjects during the initial two colonoscopies, and during a mean follow up of 3.29 years, 20 (6.2%) showed recurrence of advanced colorectal lesions, a rate of 1.88%/year.

Hazard ratios controlling for sex and age of subjects with no initial neoplasm were 2.6 (95% CI 1.6–4.2; *p*<0.001) in those with small adenomas and 6.6 (3.7–12; *p*<0.001) in those with advanced lesions.

Table 1 Incidence and recurrence rates of colorectal neoplasia—all neoplasias

	No of subjects	All neoplasias	Mean time (y)	Annual incidence rate (%/year)	Hazard ratio	95% CI	p Value
Total	6225	1831	2.69	10.9			
Sex							
Female	1566	266	2.62	6.5	1		
Male	4659	1565	2.71	12.4	1.8	1.6–2.0	<0.001
Age (y)*							
<40	806	151	3.07	6.1	1		
40–49	2738	754	2.84	9.7	1.5	1.3–1.8	<0.001
50–59	1975	656	2.46	13.5	2.0	1.6–2.3	<0.001
≥60	706	270	2.35	16.3	2.2	1.8–2.7	<0.001
Initial lesion							
None	4084	848	2.89	7.2	1		
Small adenoma	1818	821	2.34	19.3	2.4	2.2–2.7	<0.001
Advanced lesion	323	162	2.19	22.9	2.6	2.2–3.1	<0.001

*Age groups were classified according to age at the second colonoscopy.

Figure 1 Cumulative incidence and recurrence rates of colorectal neoplasia according to initial lesions by the Kaplan-Meier method—all neoplasias.

Incidence and recurrence rates of advanced lesions according to sex and age

Older subjects were more likely to develop advanced lesions than younger subjects but there was no difference between the sexes. The incidence or recurrence rates in male and female subjects were 0.42% and 0.40%/year, respectively. Rates according to the age groups <40, 40–49, 50–59, and ≥60 years were 0.10%, 0.29%, 0.56%, and 0.97%/year, respectively (table 3).

Age, but not sex, was shown to be an independent risk factor for the new development of advanced lesions by multivariate analysis. The male to female hazard ratio was 0.9 (95% CI 0.5–1.5; $p = 0.9$), and those for the age groups

40–49, 50–59, and ≥60 years relative to that of the <40 year age group were 2.3 (0.7–7.6; $p = 0.17$), 3.6 (1.1–12; $p = 0.04$), and 5.5 (1.6–19; $p < 0.01$), respectively (table 3).

When the group with no initial neoplasia was stratified by sex and age, the incidence rates of advanced colorectal lesions in male subjects were 0.05%, 0.18%, 0.25%, and 0.48%/year at ages <40, 40–49, 50–59, and ≥60 years, respectively, and those in female subjects were 0.00%, 0.16%, 0.31%, and 1.00%/year, respectively (table 4).

When the group with initial small adenomas was stratified by sex and age, the incidence rates of advanced colorectal lesions in males were 0.21%, 0.43%, 0.67%, and 1.36%/year at ages <40, 40–49, 50–59, and ≥60 years, respectively, and those in females were 3.55%, 0.56%, 0.51%, and 1.30%/year, respectively (table 4).

Males with initial advanced lesions stratified by age had incidence rates of advanced colorectal lesions of 0.00%, 1.87%, 2.56%, and 0.96%/year at <40, 40–49, 50–59, and ≥60 years, respectively, and females had rates of 0.00%, 0.00%, 2.05%, and 2.26%/year, respectively (table 4).

Incidence and recurrence rates according to initial colonoscopic findings in subjects ≥50 years old

Age groups ≥50 years old consisting of 2681 subjects (males/females 1918/763, mean age at second colonoscopy 56.8 years) were separately analysed according to initial colorectal findings. Colorectal cancer screening has been generally recommended for this population worldwide.

The annual incidence or recurrence rates of some type of colorectal neoplasm were 9.2%/year (364/1507 cases during a

Table 2 Incidence and recurrence rates of colorectal neoplasia in detail—all neoplasias

Initial lesion	Sex	Age group (y)			
		<40	40–49	50–59	≥60
None	Female	3.1 [1.3–6.3] 7/86×2.66	3.2 [2.4–4.2] 53/576×2.90	6.7 [5.4–8.4] 74/451×2.46	7.3 [4.5–11.3] 19/104×2.50
	Male	4.7 [3.9–5.9] 88/567×3.28	8.2 [7.5–9.2] 336/1348×3.02	10.1 [9.0–11.7] 198/722×2.70	11.4 [9.1–14.2] 73/230×2.79
Small adenoma	Female	7.9 [1.0–27.0] 2/11×2.29	11.4 [8.1–15.9] 33/117×2.47	14.1 [10.5–18.9] 42/121×2.46	20.4 [14.1–29.4] 25/56×2.19
	Male	15.1 [11.7–19.8] 51/130×2.60	18.9 [17.2–21.3] 289/606×2.52	22.2 [20.3–25.2] 264/543×2.19	25.1 [21.4–29.7] 115/234×1.96
Advanced lesion	Female	0.0 [0.0–70.8] 0/1×3.01	3.2 [0.1–16.7] 1/12×2.63	16.3 [6.4–32.8] 6/20×1.84	10.7 [3.0–25.4] 4/11×3.38
	Male	14.7 [3.2–37.9] 3/11×1.86	24.6 [18.8–32.4] 42/79×2.16	26.7 [22.0–33.1] 72/118×2.28	24.4 [17.8–32.9] 34/71×1.96

Each cell represents “annual incidence rate (%/year) [95% confidence interval]” in the top row, and “number of cases with adenomas”/“number of subjects followed up “×” mean follow up time (year)” in the bottom row.

Table 3 Incidence and recurrence rates of colorectal neoplasia—advanced lesions							
	No of subjects	Advanced lesion	Mean time (y)	Annual incidence rate (%/year)	Hazard ratio	95% CI	p Value
Total	6225	90	3.44	0.42			
Sex							
Female	1566	19	3.02	0.40	1		
Male	4659	71	3.59	0.42	0.9	0.5–1.5	0.9
Age (y)*							
<40	806	3	3.56	0.10	1		
40–49	2738	29	3.61	0.29	2.3	0.7–7.6	0.17
50–59	1975	36	3.24	0.56	3.6	1.1–12	0.04
≥60	706	22	3.22	0.97	5.5	1.6–19	<0.01
Initial lesion							
None	4084	30	3.45	0.21	1		
Small adenoma	1818	40	3.46	0.64	2.6	1.6–4.2	<0.001
Advanced lesion	323	20	3.29	1.88	6.6	3.7–12	<0.001

*Age groups were classified according to age at the second colonoscopy.

Figure 2 Cumulative incidence and recurrence rates of colorectal neoplasia according to initial lesions by the Kaplan-Meier method—advanced lesions.

mean time of 2.63 years) in those with no neoplasm, 21.6%/year (446/954 over 2.17 years) in the small adenoma group, and 24.0%/year (116/220 over 2.17 years) in the advanced lesion group. Hazard ratios relative to those with no neoplasm initially were 2.2 (95% CI 1.9–2.6; $p<0.001$) in those with small adenomas and 2.4 (2.0–3.0; $p<0.001$) in those with advanced lesions.

The annual incidence or recurrence rates of advanced lesion were 0.35%/year (17/1507 over 3.24 years) in those with no neoplasm, 0.85%/year (26/954 over 3.22 years) in the small adenoma group, and 2.05%/year (15/220 over 3.32 years) in the advanced lesion group. Hazard ratios relative to those with no neoplasm initially were 2.3 (95% CI

1.2–4.3; $p<0.001$) in those with small adenomas and 5.3 (2.6–11; $p<0.001$) in those with advanced lesions.

DISCUSSION

Studies on the endoscopic surveillance of patients at high risk have reported high recurrence rates of colorectal adenomas after polyp removal. Recurrence rates of 15–60% within 3–4 years after previous polypectomy have been reported.^{7 14–17} Sex, age, index adenoma size, number, and pathology have also been reported as risk factors involved in higher recurrence rates of colorectal adenomas.^{7 14–17} Our results were in general agreement with these reports. Recurrence rates of colorectal neoplasm were estimated to be 19.3%/year in those with small adenomas and 22.9%/year in those with advanced lesions.

Little is known of the incidence rates of colorectal adenomas in those who are free of neoplasms at their initial examination although they are widely believed to be lower than recurrence rates following polypectomy.¹⁸ In previous studies, Neugut and colleagues¹⁸ reported a cumulative incidence rate of 16% among 99 subjects at three years, and Rex and colleagues,¹⁹ following 154 subjects for a mean of 5.5 years, reported an incidence rate of 27%. Certainly, incidence rates were generally lower than recurrence rates but they seemed to be extremely high compared with those of invasive cancer from post-polypectomy subjects who were thought to be at high risk (reported to be 0.3–0.5% at 3 years).⁷

Significant miss rates of single colonoscopies, especially for small adenomas, have been estimated on the basis of tandem

Table 4 Incidence and recurrence rates of colorectal neoplasia in detail—advanced lesions						
Initial lesion	Sex	Age group				
		<40	40–49	50–59	≥60	
None	Female	0.00 [0.00–1.53] 0/86×2.82	0.16 [0.03–0.49] 3/576×3.16	0.31 [0.09–0.80] 4/451×2.88	1.00 [0.21–2.94] 3/104×2.88	
	Male	0.05 [0.00–0.27] 1/567×3.69	0.18 [0.08–0.34] 9/1348×3.75	0.25 [0.09–0.54] 6/722×3.39	0.48 [0.13–1.23] 4/230×3.63	
Small adenoma	Female	3.55 [0.09–19.0] 1/11×2.56	0.56 [0.07–2.02] 2/117×3.08	0.51 [0.06–1.84] 2/121×3.26	1.30 [0.16–4.73] 2/56×2.75	
	Male	0.21 [0.01–0.19] 1/130×3.65	0.43 [0.21–0.79] 10/606×3.88	0.67 [0.35–1.18] 12/543×3.30	1.36 [0.66–2.52] 10/234×3.14	
Advanced lesion	Female	0.00 [0.00–70.8] 0/1×3.01	0.00 [0.00–10.3] 0/12×2.88	2.05 [0.05–11.1] 1/20×2.44	2.26 [0.06–12.0] 1/11×4.03	
	Male	0.00 [0.00–12.3] 0/11×2.59	1.87 [0.62–4.38] 5/79×3.38	2.56 [1.30–4.58] 11/118×3.64	0.96 [0.12–3.46] 2/71×2.93	

Each cell represents “annual incidence rate (%/year) [95% confidence interval]” in the top row, and “number of cases with adenomas”/“number of subjects followed up “×”mean follow up time (year)” in the bottom row.

colonoscopies.²⁰⁻²² Miss rates of 15–24% for all types of adenomas and 0–6% for adenomas ≥ 10 mm have been reported. Therefore, the studies cited above regarding the incidence rates of adenomas from the normal colon assumed that many of the detected adenomas had probably been missed in the initial procedure.¹⁸⁻¹⁹ In fact, since they evaluated incidence rates only from the results of second follow up colonoscopies,¹⁸⁻¹⁹ a considerable number of missed lesions must have been blended into the results, and the actual contribution of missed lesions to the incidence rates is uncertain. In order to avoid this obfuscating problem of missed neoplasms as much as possible in the present study, we performed two serial colonoscopies, using the second to confirm the findings of the first. Then the incidence and recurrence rates were determined from the results of the third or even more colonoscopies.

In our study, even subjects with no initial neoplasm showed an incidence rate of colorectal neoplasm of as much as 7.2%/year. Moreover, the yearly incidence rate seemed constant according to the Kaplan-Meier curve. The present study is, to our knowledge, the largest in terms of number of subjects, and the most precise that has ever been reported on this topic. We believe that this high incidence of colorectal neoplasm reflects the actual situation, at least in the Japanese population. Colorectal adenomas are much more common lesions than colorectal cancers, as a high prevalence has also been reported by screening colonoscopy studies.^{9-11, 23}

The incidence and recurrence rates of all adenomas were associated with sex and age in our study. The association of incidence rates with sex and age was not significant in previous studies, perhaps because of small sample size or other biases.¹⁸⁻¹⁹ Our results paralleled those of prevalence studies.^{9-11, 23} It can be concluded that colorectal adenomas are more likely to develop in males and in older subjects. When considering only advanced lesions, association with sex was uncertain. This may be due to sample size or it may be related to a rising risk in female subjects as they grow older.

On the basis of the extremely high incidence and recurrence rates of colorectal neoplasia, small adenomas would seem to be a common disease. The result may be too high even when compared with the high prevalence obtained from cross sectional studies.^{9-11, 23} Hofstad and colleagues²⁴ suggested the possibility of regression of small adenomas, which may partly explain our observation. On the other hand, the development of advanced lesions was highly correlated with the initial colorectal findings. It was much more likely to develop in the subject with a past history of colorectal adenoma, and especially with a history of an advanced stage. In fact, advanced lesions might be better candidates as a target of colorectal cancer screening and surveillance programmes instead of all neoplastic lesions, including small adenomas.^{8, 25}

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