ESDs were performed. Finally, there were no procedure-related mortalities at any of the institutions (Tables 1 and 2).

Independent risk factors for complications assessed by univariate and multivariate analysis

In the screening analysis for complication risk factors, tumor size, tumor location, macroscopic type, and histology had no significant association with the ESD complication rate (not significant), but there was a significantly decreased risk of complications corresponding to the increased number of ESDs performed at the 3 groups of institutions (group A, <50 ESDs, 17.6%; group B, ≥50 and <100 ESDs, 8.2%; and group C, ≥100 ESDs, 5.1%) ($P < .0001$) (Table 3). In the logistic regression models, the complication rate was independently higher for large tumors (≥50 mm) (multivariate analysis: odds ratio, 2.1; 95% confidence interval, 1.1-3.4; $P = .0198$), whereas the larger number of ESDs performed by groups B and C decreased the risk of complications (multivariate analyses: group B/group C: odds ratio, 0.4/0.2; 95% confidence interval, 0.2-0.9/0.1-0.5; $P = .0253/.0002$) (Table 4). There was no association, however, between the types of knives used during the ESDs and the complication rate (data not shown).

TABLE 3. Risk factors for ESD complications

Risk factors	Complications		
	No	Yes	*P* Value
ESDs	1039	72	
Sex, male	639	42	.595
Age, y, mean ± SD	66.2 ± 10.5	64.8 ± 9.5	.273
Tumor size, mm			
<50	851	52	
≥50	188	20	.0316
Tumor location			
Cecum	93	10	
Right colon	384	24	
Left colon	249	14	
Rectum	313	24	.451
Macroscopic type			
LST-NG	397	22	
LST-G	501	36	
Depressed (IIc)	30	0	
Protruded (Is)	54	8	
Recurrent tumor	39	5	
Submucosal tumor	18	1	.075
Histology			
Non-neoplastic	3	1	
Adenoma	328	28	
Mucosal cancer	487	32	
SM1 cancer	106	6	
SM2 cancer	96	5	
Others	19	0	.45
Institutions (no. of ESDs)			
Group A (<50)	56	12	
Group B (≥50 and <100)	201	18	
Group C (≥100)	782	42	<.0001
Trend			<.0001

ESD, Endoscopic submucosal dissection; *LST-NG*, nongranular type laterally spreading tumor; *LST-G*, granular type laterally spreading tumor; *SD*, standard deviation; *SM1*, submucosal invasion less than 1000 μm from the muscularis mucosae; *SM2*, submucosal invasion 1000 μm or more from the muscularis mucosae.

DISCUSSION

This is the first large prospective, multicenter cohort study of colorectal ESDs performed at specialized centers in Japan. There is increasing evidence of the effectiveness of colorectal ESD because the procedure makes it possible to treat large nongranular type LSTs (>20 mm) that had been treated by surgery in the past.[8] The longer procedure time and higher complication rate of ESD compared with conventional EMR have also been discussed previously.[3,6] In fact, a small number of analyses[12] conducted in an earlier Japanese multicenter study indicated a higher complication rate during colorectal ESDs and that standardization of the colorectal ESD procedure would be difficult.

This study is particularly important because more than 1000 colorectal ESD cases in 10 specialized centers were analyzed at a time when the use of colorectal ESD is spreading in Japan, and a number of trained endoscopists are starting to perform colorectal ESDs in Western countries as well.[21,22] The complication rate significantly decreased with the increased number of ESDs performed at an institution from 17.6% for group A (<50 ESDs) to 8.2% for group B (≥50 and <100 ESDs) to 5.1% for group C (≥100 ESDs), probably because of greater clinical experience in performing colorectal ESDs on a regular basis at group B institutions and even more so at group C institutions. There were no significant statistical differences for the mean procedure time, en bloc resection rate, and curative resection rate among the 3 groups, most likely because the mean tumor size was smaller and the locations differed as did the macroscopic types in group A,

TABLE 4. Risk factors for complications

	Univariate Analysis			Multivariate Analysis		
	OR	95 CI	*p* Value	OR	95 CI	*p* Value
Macroscopic Type						
LST-NG	1					
Recurrent Tumor	2.3	0.7-6.0	0.1088			
Others	1.3	0.8-2.3	0.2668			
Tumor Size						
<50 mm	1			1		
≥50 mm	1.7	1.0-2.9	0.0439	2.1	1.1-3.4	0.0198
Institutions (ESDs)						
A (<50)	1			1		
B (≥50, <100)	0.4	0.2-0.9	0.0351	0.4	0.2-0.9	0.0253
C (≥100)	0.3	0.1-0.5	0.0004	0.2	0.1-0.5	0.0002

CI, confidence interval; *OR*, odds ratio; *ESD*, endoscopic submucosal dissection.

suggesting that less-experienced endoscopists did not attempt to perform ESDs in more challenging cases.

To decrease the colorectal ESD complication rate in the future, it will be necessary to establish a learning curve based on the results of our large case series. In addition, conservative treatment of perforations should be possible in the future in those cases in which endoscopic clipping has already been shown to be effective.

The indications for ESD in this series were markedly different from those for conventional EMR,[17,36] and the overall perforation rate of 5.2% was higher compared with conventional EMR,[36] but considerably lower than the earlier Japanese multicenter analyses mentioned previously[12] in which delayed perforation cases were regarded as requiring emergency surgery because of the risk of peritonitis. Two of the 4 patients with delayed perforations in this series, however, were successfully treated conservatively as abdominal findings and inflammation changes based on laboratory data were slight. Taku et al[12] also reported that conservative treatment might be possible, even for cases of delayed perforation when abdominal findings and laboratory data are stable, but we must carefully follow patients with delayed perforation and continued close communication with consulting surgeons is essential because the number of such cases has been quite limited so far.

The other principal ESD complication involved postoperative bleeding, but the total postoperative bleeding rate was only 1.5%, and none of the 17 patients required a blood transfusion or emergency surgery. This relatively low rate of postoperative bleeding was probably a result of using the coagulation technique for exposed vessels during ESD procedures, and the incidence of postoperative bleeding also decreased as the total number of ESDs performed at the 3 respective groups of institutions increased.

Univariate and multivariate analysis revealed that large tumor size (≥50 mm) and less experience performing ESDs (group A, <50 cases) were independent risk factors for complications, so endoscopists should begin by performing colorectal ESDs on smaller lesions.

The mean ESD procedure time was considerably longer compared with that of conventional EMR,[36] but the indications for ESD and EMR were different, as were the tumor characteristics.[36] We should be comparing, therefore, the procedure times between ESD and surgery rather than ESD and EMR.

As for ESD devices, more than 2 knives were used in most institutions and CO_2 insufflation was used at 8 of the 10 institutions to reduce patient discomfort (Table 1). These factors also will need to be taken into account when considering costs in the future.

This was a prospective multicenter cohort study, but eligibility criteria for performing colorectal ESDs were sometimes unclear at some of the institutions. It will be necessary, therefore, to further assess the clinical outcome of using ESD for the treatment of large colorectal tumors in the future.

Another limitation of this study is that no long-term outcome data are available yet because a few of the institutions have only started performing colorectal ESDs in recent years. With more than 6 months of follow-up for cases at the National Cancer Center Hospital, there have been only 3 local recurrences (2%) in ESD cases (mean endoscopic follow-up period, 20.0 ± 12.9 months) compared with 33 recurrences (14%) in EMR cases (mean endoscopic follow-up period 25.9 ± 17.0 months).[36]

In conclusion, ESD performed by experienced endoscopists is a safe and very effective procedure for treating large superficial colorectal tumors such as nongranular type LSTs larger than 20 mm and granular type LSTs larger than 30 mm that would have previously been treated with surgery, as well as large villous tumors and intramucosal lesions, recurrent lesions, and residual mucosal lesions showing nonlifting sign after EMR.

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Adipocytokines as new promising markers of colorectal tumors: Adiponectin for colorectal adenoma, and resistin and visfatin for colorectal cancer

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Adipocytokines are adipocyte-secreted hormones associated with some malignancies such as colorectal, breast, and prostate cancer. We hypothesized that changes in the levels of adipocytokines may indicate the carcinogenesis and progression of colorectal cancer and adenoma, and investigated the association of the blood levels of several adipocytokines through a case-control study. Blood levels of adiponectin, leptin, resistin, visfatin, and C-peptide at diagnosis were measured in 115 colorectal cancer patients and 115 age-, sex-, and body mass index-matched controls. The same analysis was performed in 72 colorectal adenoma patients and 72 controls. Logistic regression models were used for estimating odds ratios and 95% confidence intervals, and one-way ANOVA was performed to determine the prevalence of each variable between two or more groups. Resistin and visfatin levels in cancer patients were significantly higher than those of controls on multivariate analysis ($P = 0.03$ and $P < 0.01$, respectively). Stage progression significantly correlated with resistin and visfatin levels ($P < 0.01$ for both). The adiponectin level in adenoma patients was significantly lower than that of controls on multivariate analysis ($P = 0.04$). Its level was inversely correlated with the number of adenoma ($P = 0.02$), but not correlated with the size of adenoma. Resistin and visfatin may be good biomarkers of colorectal malignant potential and stage progression. Adiponectin level may be a good biomarker of colorectal adenoma. (*Cancer Sci* 2010)

Adipocytokines, such as adiponectin, leptin, resistin, visfatin, tumour necrosis factor (TNF)-α, and interleukin (IL)-6 are cytokines secreted by visceral adipose tissue, and they have recently been suggested to be associated with obesity-related diseases.[1,2] Many epidemiologic studies have shown a positive correlation between obesity and increased risk of colorectal cancer and adenoma as well as other cancers at various sites (e.g. breast, prostate gland, and endometrium).[3–5]

In obesity mouse models, severe macrophage invasion was observed in the vascular/stromal compartment of adipose tissue, suggesting that excess adiposity is associated with chronic inflammation.[6,7] Other reports have shown that prostaglandin E2 stimulates leptin secretion from cultured human adipose tissue cells and that cyclooxygenase 2 inhibitors prevent an increase in leptin production.[8] In inflammation-associated colorectal cancers, such as those associated with inflammatory bowel diseases, non-genetic stimuli such as overexpression of IL-6 also enhance the survival and proliferation of preneoplastic cells.[9] Leptin was also reported to induce IL-6 production by $Apc^{Min/+}$ colon epithelial cells which leads to autocrine/paracrine trans IL-6 receptor signaling.[10] This results in the promotion and survival proliferation of preneoplastic cells. On the other hand, adiponectin reportedly inhibits inflammation and angiogenesis while leptin induces tumor angiogenesis.[11,12]

These findings in epidemiological and basic research suggest that adipocytokines may well contribute to the induction of carcinogenesis and tumor progression. Therefore, we hypothesized that changes in the levels of adipocytokines may indicate the carcinogenesis and progression of colorectal cancer and adenoma. To evaluate whether adipocytokines are stronger biomarkers of colorectal cancer and adenoma than body mass index (BMI), we performed a BMI-matched case-control study and investigated the association between the blood levels of several adipocytokines and colorectal cancer and adenoma.

Materials and Methods

Study population. After approval of the study protocol by the Institutional Review Board of the National Cancer Center, patients who underwent upper total colonoscopy at the hospital from February 1999 to February 2007, who were considered to have no active malignancies except colorectal cancer and no inflammatory bowel diseases, and whose blood samples at diagnosis before any treatments for colorectal cancer or adenoma could be obtained, were identified and invited to participate in the study. Patients who had been newly and pathologically diagnosed with colorectal cancer by biopsy using colonoscopy and treated at our hospital were identified as colorectal cancer patients among the enrolled patients. Age-, sex-, and BMI-matched controls (1:1) were identified among patients who had been diagnosed as free from colorectal cancer or adenoma by colonoscopy. Among the enrolled patients, we identified those patients who had been newly undergone hot-biopsy, polypectomy, or endoscopic mucosal resection and were pathologically diagnosed with colorectal adenoma at our hospital as colorectal adenoma patients. Age-, sex- and BMI-matched controls (1:1) were identified among patients who had been diagnosed as free from colorectal cancer or adenoma by colonoscopy. BMI at diagnosis was calculated based on the data in medical records as follows: weight (kg)/height $(m)^2$. All subjects (patients and controls) provided informed consent prior to the collection and analysis of blood samples. Clinical and pathological information for both groups was obtained from medical records.

Adipocytokines and C-peptide measurements. All blood samples were stored at −20°C until use. None of the samples were previously thawed. Blood levels of adiponectin, resistin,

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Table 1. Clinical characteristics of patients with colorectal cancer and controls

	Patients (n = 115)	Controls (n = 115)	P-values
Age (years)	63.7 ± 10.3	63.5 ± 10.5	0.99
Sex			
Female (%)	46 (40.0)	46 (40.0)	
Male (%)	69 (60.0)	69 (60.0)	1.00
Body mass index	22.9 ± 2.9	23.1 ± 2.7	0.897
Stage*			
0	23	–	–
I	23	–	–
II	19	–	–
III	23	–	–
IV	27	–	–
Location			
Right colon	55	–	–
Left colon	7	–	–
Rectum	53	–	–
Macroscopic type*			
0 – Ip	5	–	–
0 – Isp	6	–	–
0 – Is	10	–	–
0 – IIa	17	–	–
0 – IIb	0	–	–
0 – IIc	0	–	–
0 – III	0	–	–
1	1	–	–
2	73	–	–
3	1	–	–
4	1	–	–
5	1	–	–
Histological type*			
Well-differentiated adenocarcinoma	86	–	–
Moderately differentiated adenocarcinoma	21	–	–
Poorly differentiated adenocarcinoma	7	–	–
Mucinous adenocarcinoma	1	–	–

Data are presented as mean ± SD. *Japanese Classification of Colorectal Carcinoma 6th edition.

visfatin, and C-peptide at diagnosis were measured by SRL (Tokyo, Japan). Adiponectin was determined by enzyme-linked immunosorbent assay (ELISA) (Otsuka Pharmaceutical, Tokyo, Japan) with a sensitivity of 1.9 μg/mL, an intra-assay coefficient of variation of 3.5–5.1%, and an inter-assay coefficient of variation of 6.0–8.7%. Resistin was determined by ELISA (BioVender Laboratory Medicine, Brno, Czech Republic) with a sensitivity of 1.1 ng/mL, an intra-assay coefficient of variation of 2.8–3.4%, and an inter-assay coefficient of variation of 5.1–6.9%. Leptin was measured using radioimmunoassay kits (Linco Research, St. Charles, MO, USA) with a sensitivity of 0.5 ng/mL, an intra-assay coefficient of variation of 3.4–8.3%, and an inter-assay coefficient of variation of 3.0–6.2%. Visfatin was determined by ELISA (Adipo Gen, Seoul, Korea) with a sensitivity of 0.13 ng/mL, an intra-assay coefficient of variation of 4.4–10.4%, and an inter-assay coefficient of variation of 6.4–9.9%. C-peptide was determined by ELISA (Fujirebio, Tokyo, Japan) with a sensitivity of 0.04 ng/mL, an intra-assay coefficient of variation of 1.96–2.97%, and an inter-assay coefficient of variation of 1.06–2.60%. Duplicate measurements were performed in a single experiment.

Statistical analysis. The results of the comparison of clinical characteristics between patients and controls was evaluated by the χ^2-test for categorical variables and two-sample t-test for continuous variables. Conditional logistic regression models were used for estimating odds ratios and 95% confidence intervals to evaluate the association of each variable with colorectal cancer or adenoma. One-way ANOVA was performed to examine the prevalence of each variable between tumor stage groups. Log transformations were conducted on variables prior to analysis to achieve normal distribution. Differences with a P-value <0.05 were considered significant. All statistical analyses were carried out using the SAS system (version 9.1.3; SAS Institute, Cary, NC, USA).

Results

Adipocytokines and C-peptide, and colorectal cancer. The clinical characteristics and adipocytokine and C-peptide levels of the 115 colorectal cancer patients and 115 controls are shown in Tables 1 and 2. There was no significant difference in age, sex, and BMI between the two groups. Results of the univariate and multivariate logistic regression analyses are shown in Table 3. Resistin and visfatin levels were significantly higher in the colorectal cancer patients than in the controls on multivariate analysis (P = 0.03 and P < 0.01, respectiyely). Linear contrast analysis was conducted to evaluate the correlation between each variable and tumor stage defined by the Japanese Classification of Colorectal Carcinoma 6th edition (Table 4). Resistin and visfatin levels gradually increased with tumor stage progression (P < 0.01 and P < 0.01, respectively).

Adipocytokines and C-peptide, and colorectal adenoma. The clinical characteristics and adipocytokine and C-peptide levels of the 72 colorectal adenoma patients and 72 controls are shown in Tables 5 and 6. There was no significant difference in age, sex, and BMI between the two groups. Results of the univariate and multivariate logistic regression analyses are shown in Table 7. Multivariate analysis showed that adiponectin levels were significantly lower in the colorectal adenoma patients than in the control patients (P = 0.04). Linear contrast analysis was conducted to evaluate the correlation between each variable and the number of adenomas (Table 8a). Adiponectin level inversely correlated with the number of adenomas (P = 0.02). The size of the largest adenoma among all the adenomas of a patient showed no significant correlation with any variables (Table 8b).

Table 2. Blood adipocytokine levels in patients with colorectal cancer and controls

	Patients				Controls			
	n	Median value	25th quartile value	75th quartile value	n	Median value	25th quartile value	75th quartile value
Adiponectin (μg/mL)	115	8.9	6.6	13	115	8.9	5.7	12.9
Resistin (ng/mL)	115	4.5	3.1	6.4	115	3.1	2.2	4.7
Leptin (ng/mL)	115	3.7	2.4	5.7	114	4.2	2.3	6
Visfatin (ng/mL)	115	3.9	2.1	7.9	115	1.4	0.8	2.6
C-peptide (ng/mL)	114	0.2	0.1	0.4	111	0.3	0.1	0.6

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Table 3. Univariate and multivariate analysis of patients with colorectal cancer and controls

	Univariate analysis		Multivariate analysis	
	Odds ratios (95% confidence intervals)	*P*-values	Odds ratios (95% confidence intervals)	*P*-values
Adiponectin*	1.227 (0.653–2.307)	0.52	0.802 (0.321–2.003)	0.64
Resistin*	2.850 (1.700–4.777)	<0.01	2.067 (1.053–4.055)	0.03
Leptin*	0.799 (0.458–1.393)	0.43	1.057 (0.477–2.342)	0.89
Visfatin*	3.142 (2.064–4.783)	<0.01	2.985 (1.862–4.787)	<0.01
C-peptide*	0.711 (0.550–0.920)	0.01	0.983 (0.663–1.458)	0.93

*Log-transformed.

Table 4. Association between adipocytokine levels and stage progression of colorectal cancer

	Control		Stage 0		Stage 1		Stage 2		Stage 3		Stage 4		*P*-values
	n	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	
Adiponectin*	115	2.3 ± 0.5	23	2.3 ± 0.4	23	2.2 ± 0.6	19	2.3 ± 0.5	23	2.1 ± 0.5	27	2.3 ± 0.4	0.94
Resistin*	115	1.2 ± 0.5	23	1.3 ± 0.5	23	1.6 ± 0.5	19	1.5 ± 0.5	23	1.5 ± 0.6	27	1.7 ± 0.5	<0.01
Leptin*	114	1.4 ± 0.7	23	1.4 ± 0.7	23	1.4 ± 0.7	19	1.5 ± 0.8	23	1.3 ± 0.5	27	1.1 ± 0.6	0.11
Visfatin*	115	0.2 ± 1.1	23	0.8 ± 1.2	23	1.3 ± 1.1	19	1.0 ± 0.9	23	1.5 ± 1.0	27	1.8 ± 0.9	<0.01
C-peptide*	111	−1.4 ± 1.2	23	−1.6 ± 1.2	23	−1.6 ± 1.1	19	−1.9 ± 1.2	22	−1.8 ± 1.1	27	−1.6 ± 1.0	0.17

*Log-transformed. Data are presented as mean ± SD.

Linear contrast analysis was also conducted to evaluate the correlation between adiponectin and the adenoma-carcinoma sequence, and the result was not significant (data not shown).

Table 5. Clinical characteristics of patients with colorectal adenoma and controls

	Patients (*n* = 72)	Controls (*n* = 72)	*P*-values
Age (years)	66.8 ± 7.3	66.7 ± 7.1	0.99
Sex			
Female (%)	22 (30.6)	22 (30.6)	
Male (%)	50 (69.4)	50 (69.4)	1.00
Body mass index	23.0 ± 2.8	22.8 ± 2.8	0.74
Number of adenomas			
2>	44	–	–
≥3	28	–	–
Location			
Right colon	33	–	–
Left colon	27	–	–
Rectum	12	–	–
Macroscopic type*			
0 – Ip	4	–	–
0 – Isp	13	–	–
0 – Is	24	–	–
0 – IIa	31	–	–
0 – IIb	0	–	–
0 – IIc	0	–	–
0 – III	0	–	–
Histological atypia			
Moderate atypia	64	–	–
Severe atypia	78	–	–
Maximum size			
−5 mm	14	–	–
6–10 mm	24	–	–
11–20 mm	17	–	–
>20 mm	17	–	–

Data are presented as mean ± SD. *Japanese Classification of Colorectal Carcinoma 6th edition.

Discussion

The results of this case-control study suggest that resistin and visfatin may be good biomarkers of colorectal malignant potential independently from BMI, and also of stage progression of colorectal cancer. Adiponectin may be a good biomarker of colorectal adenoma independently from BMI. For gastric cancer, we have reported similar results, namely, resistin and visfatin levels in gastric cancer patients were significantly higher than those in controls, and gradually increased with tumor stage progression. Furthermore, adiponectin levels tended to be lower in early stage gastric cancer patients than in controls.[13]

Obesity is recognized as a strong risk factor for the development of several cancers.[3–5] However, many experimental and case-control studies have suggested that BMI is not the best and only marker for elucidating the physiology of obesity. Recently, adipocytokines produced by adipose tissue have been the subject of intense investigation as novel risk markers not only of metabolic syndrome but also of cancers, particularly those indicating a correlation between their risk of development and obesity such as colorectal cancer and adenoma.[14–20] To the best of our knowledge, however, the present study is the first report to evaluate a difference in visfatin level between colorectal cancer patients and controls, and the only one report has been reported for a difference in resistin level so far.[21]

Adiponectin suppresses the secretion of inflammatory cytokines such as TNF-α, and induces the secretion of anti-inflammatory cytokines such as IL-10 in the atherogenic process.[22–24] Furthermore, it has been reported to inhibit tumor growth by suppressing angiogenesis *in vitro* and *in vivo*.[25] In case-control studies, the correlation between adiponectin level and colorectal cancer remains controversial[19,26]. An inverse correlation between adiponectin level and colorectal adenoma has been also reported.[27] Our results showed an inverse correlation between adiponectin and colorectal adenoma. However, we had no information regarding body weight changes in the patients and controls before the sampling, and thus it was not possible to determine whether the decrease in adiponectin levels in the patients was caused by obesity before the sampling. It was also difficult to determine when the adiponectin level decreased, either before or after colorectal adenoma development. Instead

Table 6. Blood adipocytokine levels in patients with colorectal adenoma and controls

	Patients				Controls			
	n	Median value	25th quartile value	75th quartile value	*n*	Median value	25th quartile value	75th quartile value
Adiponectin (μg/mL)	72	7.5	5.4	10.3	72	8.8	6.3	13.6
Resistin (ng/mL)	72	3.1	2.4	4.8	72	2.8	1.9	3.9
Leptin (ng/mL)	71	3.3	2.4	5.4	72	3.3	1.8	5.4
Visfatin (ng/mL)	72	1	0.6	2.8	72	1.6	0.7	2.8
C-peptide (ng/mL)	71	0.3	0.1	0.7	69	0.2	0.1	0.5

Table 7. Univariate and multivariate analysis of patients with colorectal adenoma and controls

	Univariate analysis		Multivariate analysis	
	Odds ratios (95% confidence intervals)	*P*-values	Odds ratios (95% confidence intervals)	*P*-values
Adiponectin*	0.363 (0.169–0.780)	0.01	0.422 (0.189–0.946)	0.04
Resistin*	1.293 (0.706–2.368)	0.41	1.200 (0.595–2.420)	0.61
Leptin*	1.497 (0.772–2.901)	0.23	1.331 (0.662–2.677)	0.42
Visfatin*	0.883 (0.661–1.180)	0.40	0.872 (0.604–1.260)	0.47
C-peptide*	1.208 (0.893–1.634)	0.22	1.023 (0.704–1.484)	0.91

*Log-transformed.

Table 8. Association between adipocytokine levels and clinical features of colorectal adenoma. (a) Association between adipocytokine levels and number of colorectal adenomas. (b) Association between adipocytokine levels and maximum size of colorectal adenomas

	Control		≤2		≥3		*P*-values
	n	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	
(a)							
Adiponectin*	72	2.2 ± 0.5	44	2.0 ± 0.6	28	2.0 ± 0.4	0.02
Resistin*	72	1.1 ± 0.6	44	1.2 ± 0.5	28	1.1 ± 0.5	0.90
Leptin*	72	1.2 ± 0.6	43	1.2 ± 0.6	28	1.4 ± 0.5	0.15
Visfatin*	72	0.3 ± 1.2	44	0.2 ± 1.5	28	0.1 ± 1.1	0.40
C-peptide*	69	−1.5 ± 1.2	43	−1.2 ± 1.2	28	−1.2 ± 1.1	0.34

	Control		−5 mm		6–10 mm		11–20 mm		>20 mm		*P*-values
	n	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	
(b)											
Adiponectin*	72	2.2 ± 0.5	14	1.9 ± 0.4	24	1.9 ± 0.4	17	1.9 ± 0.5	17	2.3 ± 0.6	0.48
Resistin*	72	1.1 ± 0.6	14	1.2 ± 0.4	24	1.2 ± 0.6	17	1.4 ± 0.5	17	1.0 ± 0.4	0.81
Leptin*	72	1.2 ± 0.6	13	1.6 ± 0.7	24	1.2 ± 0.5	17	1.1 ± 0.6	17	1.3 ± 0.6	0.53
Visfatin*	72	0.3 ± 1.2	14	0.0 ± 1.4	24	0.3 ± 1.2	17	0.6 ± 1.5	17	−0.4 ± 1.2	0.31
C-peptide*	69	−1.5 ± 1.2	13	−0.9 ± 0.8	24	−1.1 ± 1.2	17	−1.6 ± 1.2	17	−1.3 ± 1.2	0.64

*Log-transformed. Data are presented as mean ± SD.

of these limitations, we evaluated the correlation between the number of adenomas, the size of adenomas and adenoma-carcinoma sequence, and adiponectin to speculate the possibilities as "risk factors" for colorectal adenoma. The results showed that adiponectin level was inversely correlated with the number of adenoma. However, we could not elucidate why the adiponectin level was not correlated with the size of adenoma. If many more patients were enrolled in this study, a significant correlation between adiponectin levels and adenoma sizes may have been detected.

We have performed the above additional investigations into the relationship between adiponectin levels and colorectal carcinoma; however, our study has a few limitations. The BMI levels of the selected target group are very important and can affect the results of the study. The mean of BMI level of the patients in this study was 22.9, which was lower than that reported previously; this low BMI level may be attributed to the fact that all the patients were Japanese. Further, it is possible that variables other than those evaluated in this study may be correlated with adiposity and may influence the levels of adipocytokines. Therefore, the implications of our findings should be carefully evaluated considering these limitations.

Leptin primarily controls body fat stores and has also roles in promoting cellular proliferation, inhibiting cellular apoptosis, and inducing angiogenesis.[28] Over the years, the association between leptin levels and the risk of colorectal cancer or adenoma has remained controversial.[20,29] The expression of the leptin receptor in normal human colon mucosa, adenomas, and cancers suggests that a direct effect of leptin may be involved in carcinogenesis.[30] In the present study, however, the level of leptin was not significantly different between controls and patients with colorectal cancer or adenoma. In our previous

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studies on the correlation between adipocytokines levels and gastric or esophageal cancer, we have shown that a strong correlation exists between leptin level and BMI. In this study, however, the BMI levels of patients and controls were similar; therefore, the value of leptin as a biomarker for colorectal could not be evaluated.[13,31]

Resistin has been demonstrated to be involved in inflammatory states corresponding to its predominant expression in mononuclear cells, particularly in atherosclerosis.[32,33] As for its correlation with cancer, three case-control studies on the risk of myelodysplastic syndrome, multiple myeloma, or colorectal cancer have been reported.[21,34,35] Dalamaga *et al.* demonstrated a decreased resistin level in myelodysplastic syndrome (MDS) patients, and speculated that it was due to a compensatory response to the up-regulation of other inflammatory factors etiologically linked to myelodysplasia. They also reported a decreased level of resistin in patients with multiple myeloma. Kumor *et al.* reported that the resistin levels in colorectal cancer patients are higher than those in controls and that the resistin levels in colorectal adenoma patients and controls were also significantly different. Our results showed that resistin levels, particularly in colorectal cancer patients, were significantly higher than those in controls independent of the BMI, and these levels gradually increased with progression in tumor stage. This may imply that resistin is a biomarker of colorectal malignant potential and stage progression.

Visfatin is a new insulinmimetic adipocytokine, which directly interacts with the insulin receptor but as the insulin-like growth factor receptor, and can subsequently promote cancer cell proliferation[36]. It is more highly expressed in primary colorectal cancer than in non-neoplastic mucosa.[37] Although the clinical correlations of visfatin with cancer have been rarely reported, we demonstrated here that it may be a novel and promising biomarker of colorectal cancer as well as resistin.

Taken together, the results suggest that resistin and visfatin may be good biomarkers of colorectal malignant potential independently of BMI, and also of stage progression of colorectal cancer. Adiponectin level may be a good biomarker of colorectal adenoma independently of BMI. Further investigations as to whether the changes in adipocytokine levels are the result and/or effects of colorectal cancer or adenoma development are needed, and the elucidation of this causative association will undoubtedly clarify the correlation between obesity and cancer. Histological studies on the expression of adipocytokines in cancer tissues also should be conducted to determine whether adipocytokines derived from cancer tissues or those derived from adipose tissues are important for carcinogenesis and tumor progression.

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Disclosure Statement

The authors have no conflict of interest.

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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

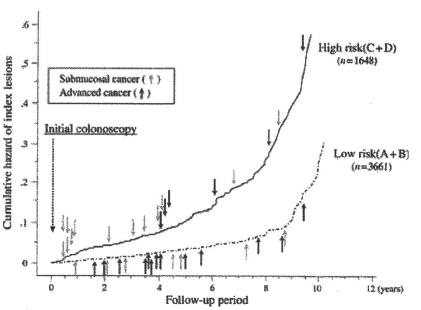

Figure 1. Comparison of cumulative incidence of index lesion and invasive colorectal cancer between risk groups.

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 ($n = 150$)	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 ARTICLES

Size does not determine the grade of malignancy of early invasive colorectal cancer

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Abstract

AIM: To clarify the clinicopathological characteristics of small and large early invasive colorectal cancers (EI-CRCs), and to determine whether malignancy grade depends on size.

METHODS: A total of 583 consecutive EI-CRCs treated by endoscopic mucosal resection or surgery at the National Cancer Center Hospital between 1980 and 2004 were enrolled in this study. Lesions were classified into two groups based on size: small (≤ 10 mm) and large (> 10 mm). Clinicopathological features, incidence of lymph node metastasis (LNM) and risk factors for LNM, such as depth of invasion, lymphovascular invasion (LVI) and poorly differentiated adenocarcinoma (PDA) were analyzed in all resected specimens.

RESULTS: There were 120 (21%) small and 463 (79%) large lesions. Histopathological analysis of the small lesion group revealed submucosal deep cancer (sm: ≥ 1000 μm) in 90 (75%) cases, LVI in 26 (22%) cases, and PDA in 12 (10%) cases. Similarly, the large lesion group exhibited submucosal deep cancer in 380 (82%) cases, LVI in 125 (27%) cases, and PDA in 79 (17%) cases. The rate of LNM was 11.2% and 12.1% in the small and large lesion groups, respectively.

CONCLUSION: Small EI-CRC demonstrated the same aggressiveness and malignant potential as large cancer.

Key words: Colorectal cancer; Submucosal invasion; Lymph node metastasis; Endoscopic mucosal resection

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INTRODUCTION

Colorectal cancer (CRC) is the third most important cause of cancer mortality in Japan, and its incidence is gradually increasing. To reduce CRC mortality, early detection and appropriate treatment are required. In general, small lesions are suspected of having a lower malignant potential than large ones, and hence are easy to remove endoscopically. Several authors have reported that the malignant potential of early invasive colorectal cancer (EI-CRC) increases with lesion size[1-3]. Therefore, lesion size is considered to be indicative of the depth of invasion and presence of lymph node metastasis (LNM). In contrast, flat, and in particular depressed lesions, are considered to have a tendency to invade rapidly the submucosal layer, even when small[4-6]. However, clinicopathological features of small EI-CRCs have still

not been studied extensively.

The aim of this retrospective study was to clarify the clinicopathological characteristics of small and large EI-CRCs and their implications for endoscopic treatment.

MATERIALS AND METHODS

Subjects

Five hundred and eighty-three patients (374 male and 209 female) with EI-CRC that had been resected surgically or endoscopically at the National Cancer Center Hospital, between January 1980 and January 2004, were examined retrospectively. In all of these patients, cancer cells invaded through the muscularis mucosa into the submucosal layer but did not extend deeply into the muscularis propria. Eligibility also required the lesions to be macroscopically non-pedunculated (sessile, flat and depressed). Patients with synchronous advanced CRC, multiple EI-CRCs, inflammatory bowel disease, hereditary non-polyposis colorectal cancer and familial adenomatous polyposis were excluded from the study.

Methods

All lesions were classified into two groups according to their endoscopic image size: small (≤ 10 mm) and large (> 10 mm). Furthermore, lesions were classified into three categories (sessile, 0- I s, I s+ II a; flat, 0- II a; and depressed, 0- II c, II a+ II c, I s+ II c) according to the Paris classification[7]. Clinicopathological features, incidence of LNM and risk factors for LNM, such as depth of invasion, lymphovascular invasion (LVI) and poorly differentiated adenocarcinoma (PDA) were analyzed in all resected specimens.

Histopathology

Resected specimens were fixed in 10% formalin and examined histopathologically following hematoxylin and eosin staining. Histopathological diagnosis was based on the World Health Organization (WHO) criteria[8]. Submucosal invasion was measured from the muscularis mucosa to the deepest portion. When the muscularis mucosa could not be identified because of cancer invasion, the vertical length was measured from the surface of the lesion to the deepest portion according to Kitajima's classification[9]. Tumors with a vertical length of < 1000 μm in the submucosal layer were classified as submucosal superficial invasive cancers (sm-superficial), and lesions with a length ≥ 1000 μm were classified as submucosal deep invasive cancers (sm-deep). The tumor growth patterns were histopathologically divided into polypoid growth (PG) and non-polypoid growth (NPG) types. Shimoda *et al*[10] have reported polyp cancers with protrusions caused by intramucosal proliferation of the carcinoma or coexistent adenoma that behaved as PG type carcinoma, while flat/depressed type carcinoma without polypoid proliferation of intramucosal tumor behaved as NPG type carcinoma.

Statistical analysis

The significance of differences in proportions was assessed by the χ^2 test, Fisher's exact test and the Wilcoxon matched-pairs signed-ranks test using SPSS statistical software (SPSS for Windows , version 16.0J, Tokyo, Japan). Statistical significance was defined as $P < 0.05$.

RESULTS

A total of 583 EI-CRCs were retrospectively evaluated, with 120 (21%) small and 463 (79%) large lesions identified (Table 1). The gender ratio (male/female) was 2.4 and 1.7, and the mean age was 61.5 and 62.4 years in the small and large lesion groups, respectively. Mean size of the small and large lesions was 8.3 and 22.1 mm, respectively.

Macroscopic type, growth type and location

Macroscopic assessment of small lesions identified 51 cases as sessile (42%), 14 as flat (12%), and 55 as depressed (46%). Similarly, large lesion groups comprised 233 sessile (50%), 64 flat (14%), and 166 depressed (36%) type. PG types were identified in 32% (38/120) and 54% (250/463) of small and large lesions, respectively. In contrast, the prevalence of NPG type in the small lesion group was significantly higher than in the large lesion group (68% *vs* 46%, $P < 0.0001$). Regarding tumor location, there were 33 (27%) rectal, 56 (47%) distal colon and 31 (26%) proximal colon cancers in the small lesion group. In contrast, there were 213 (46%) rectal, 139 (30%) distal colon and 111 (24%) proximal cancers in the large lesion group. The incidence of rectal cancer in the large lesion group was significantly higher than in the small lesion group ($P = 0.02$).

LNM

Among the lesions treated surgically, the incidence of LNM was 11.2% (10/89) and 12.1% (46/381) in small and large lesion groups, respectively ($P = 0.85$) (Table 2).

Depth of invasion/LVI/PDA

Histopathological analysis of the small lesion group revealed sm-deep cancer in 90 (75%) cases, LVI in 26 (22%) and PDA in 12 (10%). Similarly, the large lesion group exhibited sm-deep cancer in 380 (82%) cases, LVI in 125 (27%), and PDA in 79 (17%). Therefore, in relation to depth of invasion, LVI and PDA, there were no significant differences between the groups.

Treatment strategy

Among the small lesion group, 62 (52%) cases were initially treated with endoscopic mucosal resection (EMR), while 58 (48%) cases were surgically resected. In contrast, among the large lesion group, 133 (29%) cases were initially treated with EMR, while 330 (71%) cases were surgically resected. Among all lesions treated by EMR, there were no differences in the rate of positive and unknown vertical and/or lateral cut margins in the small (18%, 11/62) and large lesion groups (20%, 26/133). Furthermore, among all positive cut margin cases in the small and large lesion groups, there were 11 (100%) and 18 (69%) positive vertical margin cases (Table 3, Figures 1 and 2).

Table 1 Comparison of clinicopathological and endoscopic characteristics for 583 study cases

	Small (≤ 10 mm)	Large (> 10 mm)	*P* value
No. of lesions, *n* (%)	120 (21)	463 (79)	
Gender (M/F)	85/35	289/174	0.09
Age (yr), mean (range)	61.5 (39-84)	62.4 (30-90)	0.86
Macroscopic type, *n* (%)			
Sessile (0-Is, Is+IIa)	51 (42)	233 (50)	0.13
Flat (0-IIa)	14 (12)	64 (14)	
Depressed (0-IIc, IIa+IIc, Is+IIc)	55 (46)	166 (36)	
Size (mm), mean ± SD	8.3 ± 1.6	22.1 ± 9.6	
Growth pattern (PG/NPG)	38/82	250/213	< 0.0001
Location, *n* (%)			
Rectum	33 (27)	213 (46)	0.02
Distal colon[1]	56 (47)	139 (30)	
Proximal colon[2]	31 (26)	111 (24)	

[1]Descending-sigmoid colon; [2]Cecum-transverse colon.

Table 3 Comparison of treatment strategy and positive rate of cut margin *n* (%)

	Small (≤ 10 mm)	Large (> 10 mm)	*P* value
Initial treatment			
EMR	62 (52)	133 (29)	< 0.0001
Surgery	58 (48)	330 (71)	
Positive rate of cut margin[1]	11 (18)	26 (20)	0.81
In EMR cases			
Lateral	0 (0)	8 (31)	0.08
Vertical	11 (100)	18 (69)	

[1]Positive and unknown cut margin. EMR: Endoscopic mucosal resection.

According to the initial treatment, there were 134 (69%) and 336 (87%) sm-deep cancers in the EMR and surgery groups, respectively. Furthermore, there were 33 (17%) and 118 (30%) LVI-positive, and 18 (9%) and 73 (19%) PDA-positive cases in the EMR and surgery groups, respectively. There were 37 (19%) positive cut margin cases, including 29 (78%) positive vertical margins in the EMR group. In contrast, there were no positive cut margin cases in the surgery group. In the EMR group, 82 (42%) patients underwent additional surgery with LN dissection after EMR within 6 mo. The incidence of LNM was 11.0% (9/82) and 12.1% (47/388) in the EMR and surgery groups, respectively ($P = 0.79$) (Table 4).

DISCUSSION

Several authors have reported a strong association between lesion size and submucosal invasion or risk of LNM when referring to the grade of malignancy of early CRC. Large lesion size has been considered an indicator of deep submucosal invasion and presence of LNM. However, in this large retrospective study, small EI-CRC demonstrated a similar aggressive behavior and malignant potential to those of large lesions, with a similar risk of LNM , LVI and PDA among both groups.

Intramucosal CRC is thought generally to have no potential for LNM. In contrast, it has been reported that

Table 2 Incidence of LNM and clinicopathological characteristics based on tumor size *n* (%)

	Small (≤ 10 mm)	Large (> 10 mm)	*P* value
LNM	10/89 (11.2)	46/381 (12.1)	0.85
Depth of invasion			
sm-superficial (< 1000 μm)	30 (25)	83 (18)	0.08
sm-deep (≥ 1000 μm)	90 (75)	380 (82)	
LVI	26 (22)	125 (27)	0.23
PDA	12 (10)	79 (17)	0.06

LVI: Lymphovascular invasion; PDA: Poorly differentiated adenocarcinoma; LNM: Lymph node metastasis.

Table 4 Comparison of clinicopathological characteristics and incidence of LNM based on the treatment strategy *n* (%)

	EMR (*n* = 195)	Surgery (*n* = 388)	*P* value
Depth of invasion			
sm-superficial (< 1000 μm)	61 (32)	52 (13)	< 0.0001
sm-deep (≥ 1000 μm)	134 (69)	336 (87)	
LVI	33 (17)	118 (30)	0.0006
PDA	18 (9)	73 (19)	0.0006
Positive rate of cut margin[1]	37 (19)	0 (0)	< 0.0001
Lateral	8 (22)	0 (0)	
Vertical	29 (78)	0 (0)	
Additional surgical operation	82 (42)	-	
LNM	9/82 (11.0)	47/388 (12.1)	0.79

[1]Positive and unknown cut margin.

LNM occurs in 6%-13% of patients with submucosal invasive CRC[11-15]. Therefore, radical surgery with LN dissection is recommended strongly in these cases. At present, EMR provides an endoscopic cure of early stage CRC when there is no risk of LNM. Advances in endoscopic instruments and techniques have increased the detection rates of early stage CRC and have expanded the indications for EMR[16].

In the past 20 years, many investigators have proposed the following histopathological criteria when considering additional surgery after EMR of submucosal cancers: massive submucosal invasion (≥ 1000 μm), and/or LVI, and/or PDA[17-22]. Among these factors, LVI and PDA are impossible to predict before resection. At this point, it is crucial to predict the vertical depth of invasion of submucosal cancers prior to EMR. In our center, we use routinely a magnifying colonoscope to decide on the adequate treatment of early stage CRC. Magnifying chromoendoscopy (MCE) is a standardized validated method that facilitates detailed analysis of the morphological architecture of colonic mucosal crypt orifices (pit pattern), in a simple and rapid manner. We have reported previously the efficacy of MCE to diagnose an invasive pattern as a typical finding of sm-deep cancers, and have demonstrated that it provides a good correlation between pit pattern and tumor depth in flat and depressed CRC[23-27].

Many authors have reported that depressed and/or NPG type lesions are considered to have a high malignant potential, compared to the polypoid type lesions of similar