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, respectively). 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

doi: 10.1111/j.1349-7006.2010.01518.x

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

doi: 10.1111/j.1349-7006.2010.01518.x

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.

Acknowledgment

This work was supported by the Ministry of Health, Labor and Welfare of Japan.

Disclosure Statement

The authors have no conflict of interest.

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doi: 10.1111/j.1349-7006.2010.01518.x