

RESEARCH COMMUNICATION

Clinico-Epidemiologic Study of the Metabolic Syndrome and Lifestyle Factors Associated with the Risk of Colon Adenoma and Adenocarcinoma

Rena Kaneko^{1,2*}, Yuzuru Sato¹, Yasuyosi An¹, Motoki Nakagawa¹, Satoshi Kusayanagi¹, Satoshi Kamisago¹, Tomoyuki Umeda¹, Masazumi Ogawa¹, Kazuo Munakata², Kyoichi Mizuno²

Abstract

Background: The numbers of patients with colorectal cancer and associated deaths have been increasing in Japan, probably due to rapid lifestyle changes. Prevention is clearly important and the present study aimed to clarify risk factors and to promote colon cancer screening. **Methods:** We investigated lifestyle factors, biochemical data, and pathological features of 727 individuals who underwent colonoscopy. Data were subjected to statistical analysis using SPSS software. **Results:** Low-grade adenoma was more frequent among the elderly and in men. All of the men and 87.5% of the women with high-grade adenoma or adenocarcinoma were aged ≥ 45 and ≥ 50 years, respectively. In women, a larger waist circumference (≥ 80 cm) increased the odds ratio for colon adenoma or adenocarcinoma (colon tumors) by 1.033 (95% confidence index (CI), 1.001-1.066; $p=0.040$). Metabolic syndrome significantly increased the odds ratio of colon tumors in men, but not in women. Cigarette smoking, drinking alcohol, and increased physical activity were significant risk factors for colon tumors in men, with odds ratios of 1.001 (95% CI, 1.000-1.002; $p=0.001$), 1.001 (95% CI, 1.000-1.003; $p=0.047$), and 1.406 (95% CI 1.038-1.904; $p=0.028$), respectively. **Conclusions:** Colon tumors have a high prevalence in the elderly. A larger waist circumference in women and metabolic syndrome in both men and women elevate the risk of colon tumors. In addition, smoking, drinking, and excessive physical activity are risk factors for adenoma and adenocarcinoma in men. For early detection of colorectal cancer, men older than 45 years and women older than 50 years with these risk factors are recommended to undergo colonoscopy.

Keywords: Colorectal adenoma - colorectal cancer - lifestyle - metabolic syndrome - excessive physical activity

Asian Pacific J Cancer Prev, 11, 975-983

Introduction

Colorectal cancer is the third most common cancer and the fourth most frequent cause of cancer death worldwide. More than 1 million new cases of colorectal cancer occur annually and nearly 530,000 individuals die from colorectal cancer each year (Parkin et al., 2005). In the United States, there were 146,000 new cases of colorectal cancer in 2004 and more than 56,000 Americans died of it that year. However, both the incidence of colorectal cancer and deaths due to this cancer have been decreasing recently, probably due to improvements of the lifestyle and more effective colorectal cancer screening. In contrast, the incidence of colorectal cancer and deaths from this tumor are still increasing in Japan. The number of deaths from colorectal cancer in 1950, 1989, and 2003 was 4,000, 23,663, and 38,909, respectively. The incidence rate in Japan is now among the highest in the world, and 40,000 Japanese die of colorectal cancer annually.

The rapid increase in the incidence of and death from colon cancer is considered to be related to adoption of a western diet rich in processed meat, high-fat foods, and refined rapidly digestible carbohydrates (Chao et al., 2005). Metabolic syndrome and physical inactivity have been reported to increase the risk of colorectal cancer (Ballard-Barbash et al., 1990; Slattery et al., 2002; Ahmed et al., 2006; Chiu et al., 2007). By improving the lifestyle, the Japanese death rate from colon cancer is expected to be reduced.

Death from colon cancer in Japan may also be reduced by improving cancer screening programs. The percentage of people undergoing cancer screening in the United States and Japan is approximately 80% and 30%, respectively. In the United States, colonoscopy is a routine screening test for people aged 50 years or older. Subsequent screening is then scheduled based on the initial findings, with a five- or ten-year recall period. In Japan, the fecal occult blood test (FOBT) is recommended as an initial screening

¹Department of Internal Medicine, Kanto Rosai Hospital, Japan Labor Health and Welfare Organization, Kizukisumiyoshi-cho, Nakahara-ku, Kawasaki City, Kanagawa, ²Department of Medicine, Nippon Medical School, Sendagi, Bunkyo-ku, Tokyo, Japan.
*For correspondence: s8030@nms.ac.jp

for people older than 40 years. A positive test is almost always an indication for colonoscopy, but people hesitate to undergo colonoscopy because of discomfort and the risk of complications. Virtual colonoscopy (CT colonoscopy) and examination of stool DNA are noninvasive screening options for colorectal cancer (Johnson et al., 2008). However, these new tools are not without problems such as poor detection of de novo carcinoma (Soetikno et al., 2008).

Under these circumstances, identifying high-risk people and recommending them to undergo colonoscopy is considered to be a feasible alternative. If the lifestyle is adequately modified and individuals are effectively screened for colorectal cancer, approximately 50% of deaths from this disease can be prevented (Coyle, 2009). In the present study, we performed statistical analysis to investigate risk factors and assess the importance of lifestyle modification. Another aim of the study was to assess recommendations for colon tumor screening.

Materials and Methods

Data from 727 individuals who underwent colonoscopy at our hospital in 2007 and 2008 were subjected to analysis. Among them, 375 people (223 men and 152 women) had been recommended to undergo colonoscopy because of a positive FOBT. In addition 138 subjects (90 men and 48 women) underwent colonoscopy because of symptoms such as abdominal pain, melena, diarrhea, or constipation. Follow-up colonoscopy was carried out for 126 people who had undergone colonic endoscopic submucosal resection or polypectomy (87 men and 39 women). Other reasons include voluntary screening, elevated serum tumor markers, and searching for the origin of metastatic lung or liver cancer.

Subjects completed a questionnaire about their diet, lifestyle, and medical history. Height, body weight, body mass index (BMI: weight in kilograms/square of height in meters), waist circumference (cm), and blood

pressure were measured before colonoscopy. Then blood samples were taken for laboratory tests. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by the following equation: fasting blood insulin ($\mu\text{U/ml}$)*fasting blood glucose (mg/dl)/405.

Metabolic syndrome was identified according to the criteria proposed by the Japanese Ministry of Health, Labor and Welfare. The components of the metabolic syndrome were an increased waist circumference (men \geq 85 cm, women \geq 90cm) and at least two out of elevated blood pressure (systolic blood pressure \geq 130mmHg and/or diastolic blood pressure \geq 85mmHg), elevated fasting glucose level (\geq 110mg/dl), and dyslipidemia (HDL $<$ 40mg/dl and/or TG \geq 150mg/dl). At the present time, a waist circumference \geq 90 cm for women is under question, so a waist circumference \geq 85cm or \geq 80cm was used as the criterion in some of our subjects.

Biopsy specimens were subjected to pathological studies. Adenoma was classified as low-grade adenoma or high-grade adenoma based on morphological findings and its potential for progression to cancer. High-grade adenomas contained atypical cells with the potential for malignancy.

The amount of smoking (Brinkmann index) was categorized into 5 groups (group 1 was $<$ 150, group 2 was 150 to 300, group 3 was 300 to 600, group 4 was 600 to 900, and group 5 was $>$ 900). Alcohol intake (g/week) was also categorized into 5 groups (group 1 was $<$ 105g/week, group 2 was 105 to 210, group 3 was 210 to 420, group 4 was 420 to 630, and group 5 was $>$ 630g/week). Furthermore, we categorized waist circumference into 5 groups (group 1 was $<$ 80, group 2 was 80 to 85, group 3 was 85 to 90, group 4 was 90 to 95, and group 5 was $>$ 95cm).

Physical activity was categorized into 4 groups according to the 2006 Exercise guide of the Japanese Ministry of Health, Labor and Welfare. Individuals in group 1 spend their days reading, shopping, walking median of physical activity calculated as METs*hours/

Table 1. Incidences of Colon Tumors

	Total	NO_T	LA	HA	AC	LA or HA or AC
Men	452	214 (47.3%)	181 (40.0 %)	38 (8.4%)	19 (4.2%)	238 (52.6%)
FOBT +	223	92 (41.3%)	95 (42.6%)	24 (10.8%)	12 (5.4%)	131 (58.7%)
Symptom +	90	54 (60%)	27 (30%)	6 (6.6%)	3 (3.3%)	36 (40%)
Follow up	87	39 (44.8%)	42 (48.2%)	6 (6.89%)	0 (0%)	48 (55.2%)
Drinker	298	130 (43.6%)	129 (43.2%)	25 (8.38%)	14 (4.69%)	168 (56.3%)
Smoker	263	105 (39.9%)	120 (45.6%)	26 (9.88%)	12 (4.56%)	158 (60.6%)
Women	275	170 (61.8%)	77 (28.0%)	13 (4.7%)	15 (5.4%)	105 (38.1%)
FOBT +	152	89 (58.5%)	44 (28.9%)	9 (5.9%)	10 (6.5%)	63 (41.4%)
Symptom +	48	36 (75%)	10 (20.1%)	0 (0%)	2 (4.16%)	12 (25%)
Follow up	39	22 (56.4%)	14 (36.8%)	2 (5.12%)	1 (2.56%)	17 (43.5%)
Drinker	63	41 (65.0%)	16 (25.3%)	4 (6.3%)	2 (3.17%)	22 (34.9%)
Smoker	31	23 (74.1%)	7 (22.5%)	0 (0%)	1 (3.2%)	8 (25.8%)
Total	727	384 (52.8%)	258 (35.4%)	51 (7.0%)	34 (4.6%)	343 (47.0%)
FOBT +	375	181 (42.2%)	139 (37.0%)	33 (8.8%)	22 (5.86%)	194 (51.7%)
Symptom +	138	90 (65.2%)	37 (26.8%)	6 (4.3%)	5 (3.62%)	48 (34.7%)
Follow up	126	61 (48.4%)	56 (44.4%)	8 (6.3%)	1 (0.79%)	65 (51.5%)
Drinker	361	171 (47.3%)	145 (40.1%)	29 (8.03%)	16 (4.43%)	190 (52.6%)
Smoker	294	128 (43.5%)	127 (43.1%)	26 (8.84%)	13 (4.42%)	166 (56.4%)

FOBT +, positive fecal occult blood test. Symptom +, symptoms such as diarrhea, constipation, bloody stools, etc.; Follow up, monitoring after the diagnosis and/or submucosal resection of colon tumors.

week=25). Those in group 2 spent more than 2 hours working in the upright posture (median physical activity=31). Those in group 3 did 1 hour of exercises like walking or cycling every day, or had jobs such as agriculture or fishing (median physical activity=34). Those in group 4 were doing hard work or vigorous exercise for 1 hour or more daily (median of physical activity=42). Physical activity is a discrete variable and the category numbers were used as discrete variables in multiple logistic regression analysis.

Data were subjected to statistical analysis by the t-test and multiple logistic regression analysis using SPSS for Windows (version 15.0). We estimated the odds ratio and the corresponding 95% confidence interval [CI] (with the p value of the significance of the estimate) for the association between various factors and colon tumors.

The study protocol was approved by the Ethics Committee of Kanto Rosai Hospital (Japan Labor Health and Welfare Organization) and written informed consent was obtained from the subjects.

Results

Table 1 summarizes the incidence of colon tumors among men and women enrolled in the present study. Colon tumors (adenomas and adenocarcinomas) were observed in 47% of the individuals who underwent colonoscopy (Table 1). The incidence differed between genders and was 52.6% and 38.1% in men and women, respectively. Colon adenoma was more frequent in men than women, while the gender difference was not remarkable for adenocarcinoma (Table 1). Low-grade adenoma was found in 42.6% of men and 28.9% of women with a positive FOBT, while adenocarcinoma was found in 5.4% of men and 6.5% of women who were FOBT-positive. Adenocarcinomas were found more frequently in FOBT-positive individuals than in those with abdominal symptoms or those undergoing follow-up studies (Table 1).

Age is a risk factor for colon tumors, and the incidence of colon adenoma increased markedly at 45 years (Table 2). All men and 87.5% of women with high-grade adenoma or adenocarcinoma were older than 45 years and 50 years, respectively (Table 2).

Among the 452 men, 67 (14.8%) were diagnosed as

having metabolic syndrome. Among these 67 men with metabolic syndrome, 44 (65.6%) were found to have colon tumors (Table 3A). The incidence of colon tumors was 1.30 times higher than that among men without metabolic syndrome (50.3%). The incidence of low-grade adenoma, high-grade adenoma, and adenocarcinoma among men with metabolic syndrome was respectively 1.23, 1.30 and 2.05 times higher than that for men without metabolic syndrome (Table 3).

Among the 275 women, metabolic syndrome was identified in 13 (4.7%). Among these 13 women with metabolic syndrome, colon tumors were detected in 6 (46.1%). The incidence was 1.22 times higher than that for women without metabolic syndrome (37.7%). The incidence of low-grade adenoma and adenocarcinoma among women with metabolic syndrome was respectively 1.10 and 3.12 times higher than that for women without metabolic syndrome.

Table 3 also shows the tumor incidence in women with or without metabolic syndrome stratified by waist circumference. When a waist circumference ≥85 cm was used as the criterion, 21 women (7.6%) were diagnosed as having metabolic syndrome and 12 of them (57.1%) had colon tumors. This incidence was 1.56 and 1.23 times higher than that for women without metabolic syndrome (36.6%) and that for women diagnosed by using a waist circumference ≥90cm (46.1%), respectively. The incidence of low-grade adenoma and adenocarcinoma was 1.57 and 3.02 times higher than that among women without metabolic syndrome, respectively. Similar results were obtained when a waist circumference ≥80cm was used to identify metabolic syndrome.

The incidence of colon tumors in women increased with an increase of waist circumference. Colon tumors were found in 25.2% of women with a waist circumference less than 80 cm. The incidence increased to 44.5%, 49%, and 55.5% among those with a waist circumference ≥80cm, ≥85cm, and ≥90cm, respectively. Waist circumference was ≥80cm for 73% of women with adenocarcinoma.

Clinical and laboratory data were compared between men with and without each type of colon tumor by the t-test (Table 4). Among men with low-grade adenoma, the mean age and the levels of glucose, insulin, TG, HOMA-IR, smoking and alcohol intake were all significantly higher. Among those with high-grade adenoma, the age,

Table 2. Age and the Incidence of Colon Tumors

Tumor	No. of Cases													
	Total	Age (years)												
		20	30	35	40	45	50	55	60	65	70	75	80	85
Men NO_T	211	4	10	13	18	17	19	21	31	25	23	17	12	1
LA	178	0	1	3	2	11	14	31	31	31	23	17	13	1
HA	38	0	0	0	0	3	0	9	6	6	7	4	3	0
AC	19	0	0	0	0	3	1	3	6	2	3	0	1	0
Women NO_T	168	3	3	11	12	14	15	17	21	21	22	19	8	2
LA	75	0	0	0	0	3	9	7	11	12	19	6	7	1
HA	12	0	0	0	1	0	1	2	0	3	3	2	0	0
AC	14	0	0	1	0	0	0	1	1	2	3	4	2	0

AD, adenoma; LA, low-grade adenoma; HA, high-grade adenoma; AC, adenocarcinoma; NO_T, no tumor.

Table 3. Metabolic Syndrome and Colon Tumors in Japanese Men and Women

		Total (%)	No_tumor	LA	HA	AC	LA, HA, or AC
		(%) †	(%) ‡	(%) ‡	(%) ‡	(%) ‡	(%) ‡
A	Men	452					
	Non_MetS	385 (85.1)	191 (49.6)	149 (38.7)	31 (8.4)	14 (3.63)	194 (50.3)
	MetS W≥85	67 (14.8)	23 (34.3)	32 (47.7)	7 (10.4)	5 (7.46)	44 (65.6)
B	Women	275					
	Non_MetS	262 (95.2)	163 (62.2)	73 (27.8)	13 (4.9)	13 (4.9)	99 (37.7)
	MetS W≥90	13 (4.7)	7 (53.8)	4 (30.7)	0 (0)	2 (15.3)	6 (46.1)
C	Women	275					
	Non_MetS	254 (92.3)	161 (63.3)	68 (26.7)	13 (5.1)	12 (4.7)	93 (36.6)
	MetS W≥85	21 (7.6)	9 (42.8)	9 (42)	0 (0)	3 (14.2)	12 (57.1)
D	Women	275					
	Non_MetS	244 (92.3)	156 (63.9)	64 (26.2)	12 (4.9)	12 (4.9)	88 (36.0)
	MetS W≥80	31 (11.2)	14 (45.1)	13 (41.9)	1 (3.2)	3 (9.6)	17 (54.8)
E	Women	275					
	W≥90	63 (22.9)	28 (44.4)	26 (41.2)	4 (6.3)	5 (7.9)	35 (55.5)
	W≥85	106 (38.5)	54 (50.9)	37(35.2)	7 (6.6)	8 (7.5)	52 (49.0)
	W≥80	184 (66.9)	102 (55.4)	65 (35.2)	6 (3.2)	11 (5.9)	82 (44.5)
	W<80	91 (33.0)	68 (74.2)	12 (13.1)	7 (7.6)	4 (4.3)	23 (25.2)

MetS, metabolic syndrome; W, waist circumference; LA, low-grade adenoma; HA, high-grade adenoma; AC, adenocarcinoma; † ratio to all men or women; ‡ ratio to men or women with or without metabolic syndrome.

Table 4. Risk Factors for Colon Tumors in Japanese Men and Women

	No tumor	LA	HA	AC	LA, HA, or AC
	Mean±SE (No.)	Mean±SE (No.)	Mean±SE (No.)	Mean±SE (No.)	Mean±SE (No.)
Age (years)					
Men	57.99±1.008 (211)	64.18±0.775* (178)	65.42±1.498* (38)	62.09±1.968 ^{NS} (19)	63.96±1.003* (235)
Women	60.28±1.091 (168)	66.72±1.182* (75)	67.00±3.421* (13)	68.00±3.362* (14)	66.61±1.040* (102)
Waist_C (cm)					
Men	84.90±0.541 (205)	86.17±0.604 ^{NS} (173)	85.67±1.432 ^{NS} (35)	85.19±1.949 ^{NS} (18)	86.15±0.539 ^{NS} (226)
Women	80.74±0.792(156)	86.11±1.151* (73)	80.62±3.081 ^{NS} (13)	86.00±2.918 ^{NS} (13)	85.61±1.011* (99)
BP (mmHg)					
Men	126.62±1.559 (181)	129.29±1.281 ^{NS} (155)	131.47±3.124 ^{NS} (32)	136.17±5.684 ^{NS} (18)	130.78±1.210* (205)
Women	124.81±1.818 (139)	130.12±2.385 ^{NS} (66)	138.00±4.654 ^{NS} (10)	127.58±11.58 ^{NS} (12)	130.77±2.421* (88)
Glucose (mg/dl)					
Men	97.16±1.396 (209)	102.43±1.744* (175)	99.53±2.270 ^{NS} (38)	103.16±3.736 ^{NS} (19)	102.30±1.410* (232)
Women	95.35±1.508 (164)	97.19±2.254 ^{NS} (72)	78.77±4.130 ^{NS} (13)	98.50±5.383 ^{NS} (14)	97.76±1.872 ^{NS} (99)
Insulin (µU/ml)					
Men	3.650±0.1528 (193)	4.209±0.1961* (173)	4.717±0.5523 ^{NS} (36)	3.330±0.503 ^{NS} (19)	4.207±0.182* (228)
Women	4.213±0.2675 (149)	4.066±0.3244 ^{NS} (68)	3.515±0.4289 ^{NS} (12)	6.791±1.804* (11)	5.300±0.999 ^{NS} (91)
HOMA_IR					
Men	0.706±0.042 (206)	0.966±0.064* (178)	1.0316±0.164 ^{NS} (36)	0.812±0.162 ^{NS} (19)	0.964±0.058* (233)
Women	0.862±0.090 (163)	0.794±0.094 ^{NS} (74)	0.633±0.134 ^{NS} (12)	2.87 5± 1.573 ^{NS} (15)	1.092±0.249 ^{NS} (101)
TG (mg/dl)					
Men	108.59±3.737 (202)	132.40±6.421* (177)	132.75±12.501* (36)	118.38±12.918 ^{NS} (18)	130.55±5.293* (231)
Women	89.24±4.477 (162)	114.96±18.115 ^{NS} (72)	115.42±10.411 ^{NS} (12)	125.07±16.984* (14)	118.05±13.741* (98)
HDL-C (mg/dl)					
Men	60.30±1.211 (198)	61.84±1.891 ^{NS} (173)	63.43±6.878 ^{NS} (37)	60.94±17.588 ^{NS} (18)	61.50±0.157 ^{NS} (228)
Women	70.05±1.884 (162)	67.13±2.193 ^{NS} (72)	62.92±4.507 ^{NS} (12)	55.08±3.234* (12)	65.19±1.816* (96)
LDL-C (mg/dl)					
Men	116.53±2.502 (197)	122.45±2.527 ^{NS} (174)	118.48±6.098 ^{NS} (37)	116.11±11.187 ^{NS} (18)	120.89±2.347 ^{NS} (229)
Women	117.82±3.117 (160)	128.76±4.090* (72)	126.25±11.20 ^{NS} (12)	146.67±8.918* (12)	130.97±3.578* (96)
Smoking (Brinkman index)					
Men	250.92±24.127 (207)	459.94±35.055* (172)	388.14±60.987* (37)	363.68±88.77 ^{NS} (19)	417.24±29.004* (228)
Women	39.86±9.189 (166)	34.80±16.933 ^{NS} (75)	15.38±11.855 ^{NS} (13)	35.71±35.714 ^{NS} (14)	32.45±13.39 ^{NS} (102)
Alcohol intake(g/week)					
Men	109.22±10.742 (212)	147.93±14.749*(180)	131.16±24.036 ^{NS} (36)	212.47±60.155* (19)	150.75±12.970* (235)
Women	21.31±5.096 (170)	20.27±5.147 ^{NS} (77)	55.62±26.996 ^{NS} (13)	3.730±2.590 ^{NS} (15)	22.26±5.140 ^{NS} (105)

NS, not significant (p≥0.050); *p<0.050; No., number of subjects; P, p value; BP, blood pressure; LA, low-grade adenoma; HA, high-grade adenoma; AC, adenocarcinoma; Waist_C, waist circumference.

TG, and smoking were significantly increased. Among men with adenocarcinoma, alcohol intake was the only factor that was increased significantly. Among men with colon tumors, the mean age, blood pressure, blood glucose,

insulin, HOMA-IR, triglycerides (TG), smoking, and alcohol intake were all significantly higher than among those without colon tumors.

On the other hand, among women with low-

Table 5. Estimated risk of colon tumors in Japanese men and women

	LA		HA		AC		LA, HA, or AC	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age (years)								
Men	1.054(1.032-1.076)	0.000	1.065(1.025-1.106)	0.010	1.033(0.987- 1.080)	0.160	1.055(1.030-1.076)	0.000
Women	1.045 (1.013-1.077)	0.005	1.082(1.013-1.134)	0.016	1.038(0.972-1.108)	0.271	1.041(1.014-1.069)	0.003
Waist_C (cm)								
Men	0.991(0.959-1.024)	0.614	0.985(0.894-1.019)	0.164	1.010(0.927-1.100)	0.819	0.999(0.961-1.023)	0.598
Women	1.054(1.016-1.092)	0.004	0.970(0.909-1.034)	0.344	0.998(0.923-1.078)	0.952	1.033(1.001-1.066)	0.040
Insulin (μU/ml)								
Men	1.148(1.025-1.287)	0.018	1.328(1.096-1.611)	0.004	0.926(0.638-1.349)	0.685	1.406(1.038-1.904)	0.013
Women	0.938(0.803-1.059)	0.300	0.937(0.711-1.234)	0.641	1.074(0.950-1.213)	0.255	1.009(0.961-1.060)	0.721
LDL-C (mg/dl)								
Men	1.007(1.000-1.015)	0.040	1.645(0.988-2.740)	0.056	1.004(0.986-1.021)	0.693	1.005(0.999-1.012)	0.129
Women	1.006(0.997-1.014)	0.187	1.011(0.996-1.027)	0.161	1.016(1.006-1.033)	0.055	1.007(0.999-1.015)	0.085
Smoking (Brinkman index)								
Men	1.001(1.000-1.002)	0.001	1.001(1.000-1.002)	0.053	1.000(0.999-1.002)	0.649	1.001(1.000-1.002)	0.001
Women	1.001(0.998-1.003)	0.679	0.996(0.985-1.007)	0.498	1.003(0.998-1.005)	0.304	1.001(0.998-1.003)	0.637
Alcohol intake (g/week)								
Men	1.001(1.00-1.003)	0.075	1.001(0.999-1.004)	0.276	1.002(0.999-1.014)	0.196	1.001(1.000-1.003)	0.047
Women	1.006(0.996-1.016)	0.222	1.028(1.010-1.046)	0.002	0.990(0.942-1.040)	0.676	1.008(0.999-1.017)	0.076
Pys.Act. (number of category group*)								
Men	1.230(0.871-1.783)	0.157	1.645(0.986-2.140)	0.056	2.667(1.504-4.729)	0.001	1.406(1.038-1.904)	0.028
Women	1.251(0.793-1.978)	0.336	0.540(0.172-1.689)	0.289	0.641(0.188-2.185)	0.477	1.100(0.721-1.679)	0.658

OR, odds ratio; CI, confidence interval; P, p value; LA, low-grade adenoma; HA, high-grade adenoma; AC, adenocarcinoma; Waist_C, waist circumference; Pys.Act., physical activity. *The group numbers were used as discrete variables.

grade adenoma, waist circumference and LDL-C were significantly higher. Among women with high-grade adenoma, age was significantly higher. Among women with adenocarcinoma, insulin, TG, and LDL-C values were significantly elevated, while HDL-C was significantly lower (Table 4). Among women with colon tumors, the mean age, waist circumference, blood pressure, TG, and LDL-cholesterol (LDL-C) were all significantly higher than for those without colon tumors, while HDL-cholesterol (HDL-C) was significantly lower.

Other data such as height, body weight, diastolic blood pressure, AST (GOT), ALT (GPT), γ-GTP, uric acid, CRP, CA19-9, HbA1c, family history, age of menopause, and the intake of calories, protein, fat, and carbohydrates were not significantly different between those with or without colon tumors (data not shown).

Logistic regression analysis was carried out with metabolic syndrome as the categorical variable and age, carbohydrate intake, protein intake, and lipid intake as

numerical variables. Among men, metabolic syndrome increased the odds ratio of low-grade adenoma, high-grade adenoma, adenocarcinoma, and colon tumors to 1.146 (95% CI 0.685-1.917; p=0.604), 2.374 (95% CI 1.094-5.154; p=0.029), 1.615 (95% CI 0.562-4.640; p=0.375), and 1.784 (95% CI 1.048-3.036; p=0.033), respectively. Among women, metabolic syndrome diagnosed by a waist circumference ≥90 or ≥80cm elevated the odds ratio for colon tumors to 1.119 (95% CI 0.361-3.421; p=0.843) and 1.727 (95% CI 0.732-4.072; p=0.212), respectively. Among women, there was no significant elevation of the odds ratios for low-grade adenoma, high-grade adenoma, and adenocarcinoma.

Logistic regression analysis was performed using age, waist circumference, insulin, LDL-C, smoking, and alcohol intake as continuous variables, with physical activity as a discrete variable (Table 5). In men, age, insulin, LDL-C, and smoking significantly elevated the odds ratio for low-grade adenoma, while age and insulin were risk factors for high-grade adenoma. Physical activity (category numbers were employed as discrete variables) significantly elevated the odds ratio for adenocarcinoma (Table 5), while age, insulin, smoking, drinking, and exercise all significantly increased the odds ratio for colon tumors.

The risk factors for colon tumors differed between men and women. In women, age and waist circumference significantly elevated the odds ratio for low-grade adenoma, while age and alcohol intake elevated the odds ratio for high-grade adenoma. As for adenocarcinoma, no factor significantly increased the estimated risk, but age and waist circumference significantly elevated the odds ratio for colon tumors (Table 5).

To investigate the effect of waist circumference in more detail, odds ratios were computed with waist circumference as the categorical variable and age, insulin,

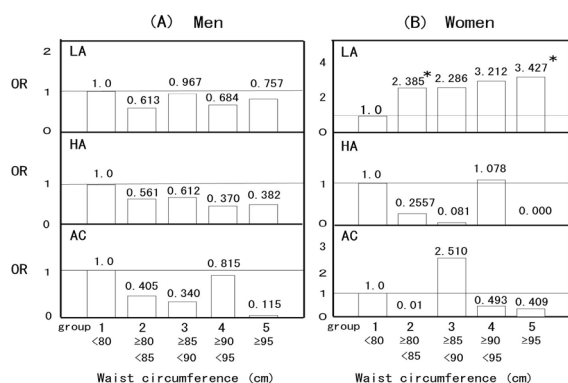


Figure 1. Influence of Waist Circumference on the Risk of Colon Tumors in Men (A) and Women (B). OR, odds ratio. *P<0.05. Ordinate: Waist circumference categorized as described in Materials and Methods. LA, low-grade adenoma; HA, high-grade adenoma; AC, adenocarcinoma

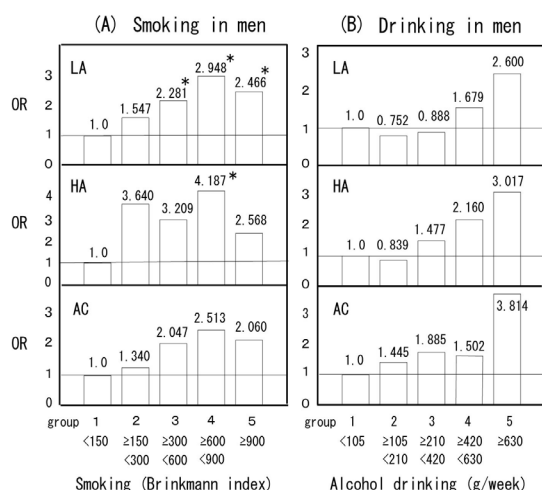


Figure 2. Influence of Smoking (A) and Alcohol Intake (B) on the Risk of Colorectal Tumors in Men. OR, odds ratio. *P<0.05. Brinkmann index (A) and alcohol intake (B) were categorized into 5 groups as described in Materials and Methods. LA, low-grade adenoma; HA, high-grade adenoma; AC, adenocarcinoma

LDL-C, and alcohol intake as continuous variables, and physical activity as the discrete variable (Figure 1). In women with an increase of waist circumference (≥80cm), the odds ratio for low-grade adenoma was ≥2.2 (Figure 1B). However, a larger waist circumference did not elevate the odds ratio among men (Figure 1A).

The prevalence of smoking was 58.1% in men (Table 1). The prevalence of smoking among men with no tumors, low-grade adenoma, high-grade adenoma, and adenocarcinoma was 49.0%, 66.2%, 68.4%, and 63.1%, respectively (Table 1), while the Brinkmann index of each group was 250, 459 (p=0.000), 388 (p=0.028), and 363 (p=0.092), respectively (Table 4). The index was highest for men with low-grade adenoma. Smoking increased the risk of colon tumors in men (Table 5). Logistic regression analysis was carried out with the Brinkmann index as the categorical variable, and age, waist circumference, insulin, LDL-C, and alcohol intake as continuous variables, and physical activity as the discrete variable (Figure 2A). Compared with the lowest Brinkmann index group, men in the higher groups had an elevated risk of adenoma and adenocarcinoma (Figure 2A). Statistically significant increases were observed for both low-grade adenoma and high-grade adenoma.

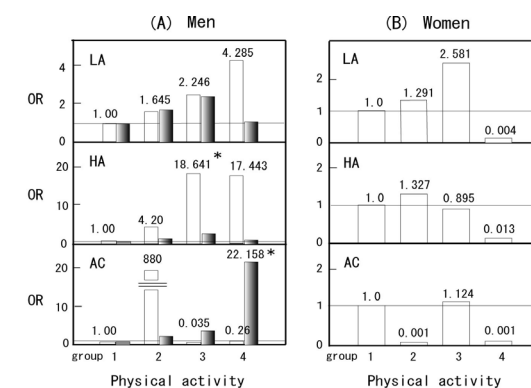


Figure 3. Influence of Physical Activity on the Risk of Colon Tumors in Men (A) and Women (B). Physical activity was categorized into 4 groups as described in Materials and Methods. OR odds ratio. *P<0.05. (A) Men: alcohol intake of 0 g/week=open rectangles, ≥1 g/week=shaded rectangles. (B) Women: drinkers + nondrinkers=open rectangles. LA, low-grade adenoma; HA, high-grade adenoma; AC, adenocarcinoma

The prevalence of smoking was 11.2% in women. The prevalence of smoking among women with no tumors, low-grade adenoma, high-grade adenoma, and adenocarcinoma was 13.5%, 9.0%, 0%, and 6.6%, respectively. Among 15 women with adenocarcinoma, only one was a smoker. The Brinkman index was not increased in women with colon tumors, and there was no excess risk of adenoma or adenocarcinoma among women who smoked.

The prevalence of drinking among men with no tumors, low-grade adenoma, high-grade adenoma, and adenocarcinoma was 60.7%, 71.2%, 65.7%, and 73.6%, respectively. The mean intake of alcohol (g/week) by individuals with no tumors, low-grade adenoma, high-grade adenoma, and adenocarcinoma was 109, 147 (p=0.029), 131 (p=0.412), and 212 (p=0.025), respectively. Alcohol intake increased the odds ratio for colon tumors in men. Logistic regression analysis was performed with alcohol intake as the categorical variable, and age, waist circumference, insulin, and LDL-C as continuous variables, and physical activity as the discrete variable (Figure 2B). Compared with the lowest alcohol intake group, men in the higher intake groups had an increased risk of both adenoma and adenocarcinoma (Figure 2B).

Among women, the prevalence of drinking was 22.9%

Table 6. Estimated Risk of Colon Tumors in Non-Drinking and Non-Smoking Japanese Men

	Non-drinkers (n=153)			Non-smokers (n=89)		
	OR (95% CI)	P		OR (95% CI)	P	
Age (years)	1.065 (1.025 - 1.106)	0.001		1.090 (1.048 - 1.133)	0.000	
Waist_C (cm)	1.000 (0.944 - 1.060)	0.999		0.999 (0.948 - 1.052)	0.968	
Glucose (mg/dl)	1.039 (1.003 - 1.077)	0.032		1.009 (0.987 - 1.032)	0.416	
Insulin (µU/ml)	1.057 (0.842 - 1.327)	0.632		0.989 (0.831 - 1.177)	0.902	
TG (mg/dl)	1.004 (0.993 - 1.015)	0.475		1.011 (1.001 - 1.021)	0.026	
LDL-C (mg/dl)	1.000 (0.977 - 1.027)	0.879		1.002 (0.989 - 1.015)	0.779	
HDL-C (mg/dl)	1.011 (0.996 - 1.027)	0.156		1.019 (0.996 - 1.042)	0.106	
Pys.Act.*	1.112 (0.640 - 1.931)	0.707		1.365 (0.850 - 2.191)	0.198	
Smoking (Brinkman index)	1.001 (1.000 - 1.002)	0.102				
Alcohol intake (g/week)				1.000 (0.997 - 1.003)	0.807	

Men with adenoma and/or adenocarcinoma were subjected to logistic regression analysis. OR, odds ratio; P, p value; BP, blood pressure; Waist_C, waist circumference; Pys.Act., physical activity. *The group numbers (1 to 4) were used as discrete variables.

(Table 1). The prevalence of alcohol intake among women with no tumors, low-grade adenoma, high-grade adenoma, and adenocarcinoma was 24.1%, 20.7%, 30.7%, and 13.3%, respectively (Table 1). The prevalence was highest in women with high-grade adenoma, which reflected a significantly elevated odds ratio (Table 5). In the case of low-grade adenoma or adenocarcinoma, however, alcohol intake did not elevate the odds ratio significantly.

Since alcohol intake is known to have a relationship with TG, HDL-C, and tobacco smoking, we calculated the odds ratio for colon tumors in nondrinkers and nonsmokers after eliminating smoking or alcohol from the variables (Table 6). Among nondrinkers, age and blood glucose significantly increased the odds ratio, while smoking did not. Among nonsmokers, age and TG significantly elevated the odds ratio, but alcohol intake did not.

Physical activity increased the risk of colon tumors (Table 5). Physically active men (groups 3 and 4) accounted for 9.8%, 10.2%, 18.7%, and 32.8% of those with no tumors, low-grade adenoma, high-grade adenoma, and adenocarcinoma, respectively. This suggested that the incidences of high-grade adenoma and adenocarcinoma was higher in more physically active men. Logistic regression analysis was performed with physical activity as the categorical variable and age, waist circumference, insulin, smoking, and alcohol intake as continuous variables. The results are shown in Figure 3. The odds ratio for colon tumors was elevated in the groups of men with higher physical activity in comparison to the group with the lowest activity (Figure 3A). The odds ratio for high-grade adenoma among nondrinkers and that for adenocarcinoma among drinkers were significantly elevated, indicating that the effect of physical activity was not entirely attributable to associated alcohol intake (Figure 3A). On the other hand, the percentage of women with higher physical activity (groups 3 and 4) was 8.6%, 12%, 0%, and 8% among females with no tumors, low-grade adenoma, high-grade adenoma, and adenocarcinoma, respectively. The risk of colon tumors was not significantly increased by physical activity in women (Figure 3B).

Discussion

The present study revealed that metabolic syndrome is a risk factor for colon tumors along with demographic factors such as age and gender. In addition, smoking, alcohol intake, and increased physical activity were shown to be important predictors of colon tumors among men, as was a larger waist circumference in women.

The incidence of adenomas was higher in elderly men and women (Table 2). All of the men and most of the women with high-grade adenoma or adenocarcinoma were older than 45 years and 50 years, respectively. The prevalence of advanced tumors is higher among older persons than younger persons (Rundl et al., 2008), and this age dependency is considered to be due to accumulation of genetic mutations, hypomethylation of DNA, and increased chromosomal fragility in the elderly. Hypomethylation of CpG islands decreases the activity of tumor suppressor genes (Worthley et al., 2010; Zuern

et al., 2010). The relationship between methylation and development of colon polyps is strong among persons with folic acid deficiency (Weinstein et al., 2008). These findings suggest that the incidence of colon adenoma can be reduced by changes to nutrition, 1-carbon metabolism, and methylation of colon mucosal cells (Worthley et al., 2010).

The incidence of colon adenomas was higher in men than in women. A similar gender difference has been reported before, and estradiol has been suggested to reduce the formation of preneoplastic lesions in the colon (Gao et al., 2008; Weige et al., 2009). It has been also suggested that chemoprevention of colorectal neoplasia may be achieved with estrogen-like drugs through the vitamin D receptor pathway (Protiva et al., 2009).

Many previous studies have shown that biological risk factors may be improved, but the feasibility remains to be studied. In contrast, risks related to the lifestyle are controllable. Metabolic syndrome has been reported to elevate the odds ratio for colon cancer by 1.5-fold (Ahmed et al., 2006; Chiu et al., 2007). In the present study, as well, odds ratio for colon tumor was elevated by 1.5-3-fold in people with metabolic syndrome. Metabolic syndrome is one of the targets of tumor prevention trials, and strategies to prevent it should also be useful for the primary prevention of colon tumors. In addition, screening by colonoscopy for persons with metabolic syndrome could be more efficient for the early diagnosis of colon cancer in both men and women.

In Japanese women, the prevalence of metabolic syndrome is not so high, and waist circumference may be more useful than metabolic syndrome or BMI for detection of women to undergo screening by colonoscopy (Moore et al., 2004). The present study disclosed that waist circumference is a clear predictor of colon tumors (Table 5). The waist circumference was more than 85 cm in 69% of women with colon tumors and more than 80 cm in 78% (Table 3, Figure 1). Therefore, it seems to be appropriate that women with a waist circumference ≥ 80 cm are recommended to undergo colonoscopy.

Blood pressure is a component of metabolic syndrome and has been reported to increase the risk of colon tumors (Ahmed et al., 2006; Stocks et al., 2008). In the present study, blood pressure was slightly elevated in the subjects with tumors (Table 4). However, the logistic analysis did not reveal any definite relation between blood pressure and colon tumors (Table 6). At the present time, a role of blood pressure in colon tumorigenesis seems to be controversial (Stürmer et al., 2006).

Metabolic syndrome reflects increased insulin resistance (Almendingen et al., 2001). Our data showed that elevated serum glucose and insulin levels were risk factors for colon tumors in men (Tables 5 and 6). Glucose increases sensitivity to oxidative stress, while insulin elevates the free IGF-1 level. These factors may play a role in the development of colorectal neoplasms (Rolo et al., 2006; Wei et al., 2006). Therefore, improvement of carbohydrate metabolism and insulin resistance is of crucial importance for the prevention of colon tumors.

In addition to carbohydrate metabolism, lipids are an important risk factor for colorectal tumors. TG had been

reported to be associated with increased development of colon adenoma, but not colon cancer (Ahmed et al., 2006; Tabuchi et al., 2008). In the present study, TG was significantly higher in men with adenoma and women with adenocarcinoma, but not in male nondrinkers. High HDL-C has been reported to be associated with a lower risk of colon cancer, while elevated LDL-C increases the risk (Bayerdörffer et al., 1993). In the present study, HDL-C was lower in women with adenocarcinoma (Table 4), but not in men with colon tumors. In addition, HDL-C and LDL-C did not elevate the odds ratio in male nondrinkers (Table 6). From these results, the effects of TG, HDL-C, and LDL-C are suggested to be at least partly related to alcohol intake. Nevertheless, as demonstrated in many reports, a low-fat diet is considered to be useful for the primary and secondary prevention of colon adenoma (Sansbury et al., 2009).

The present study showed that drinking alcohol elevated the risk of colon tumors in Japanese men, and its action seemed to be related to other factors such as dyslipidemia, smoking, and physical activity. Alcohol has been reported to enhance the development of cancer by stimulating the epithelial-mesenchymal transition through the epidermal growth factor receptor (EGFR)-Snail pathway or through disruption of one-carbon metabolism (Forsyth et al, 2010). High alcohol consumption and low folate and methylenetetrahydroforate reductase gene variants are risk factors for long interspersed nucleotide element-1 (LINE-1) hypomethylated cancer (Ashktorab et al., 2007; Schernhammer et al, 2009). Alcohol is metabolized to acetaldehyde, which binds to DNA and forms carcinogenic adducts, and alcohol drinkers with the aldehyde dehydrogenase 2*2 allele show high concentrations of acetaldehyde, indicating that genetic factors may be involved in its carcinogenic effects (Seitz et al., 2009).

Smoking is a risk factor for colon adenoma, as shown in the present study. Cigarette smoking has been more frequently reported to be associated with colorectal adenomatous polyps than colorectal cancer. However, a recent meta-analysis has demonstrated that smoking increases the risk of both formation and aggressiveness of adenomas (Botteri et al, 2008). Cigarette smoking is considered to have an additive effect with alcohol in elevating the risk of rectal cancer. A positive association of alcohol with colorectal cancer is present among smokers, but not among nonsmokers, so these two factors may share a common pathway in promoting rectal carcinogenesis (Tsong et al., 2007; Acott et al., 2008). In any case, smokers and alcohol drinkers are at higher risk, and this fact should be considered when developing screening programs for colon tumors (Cho et al., 2004; Acott et al., 2008).

Many reports have shown an association between physical inactivity and the risk of colon cancer (Ballard-Barbash et al, 1990). In contrast to these previous reports, the present study showed that men with higher physical activity had an elevated risk of the development of colon tumors. This may have been due to the small sample size of the present study. On the other hand, physical activity is considered to influence multiple mechanisms that

either stimulate or suppress the carcinogenic process. For example, physical activity has been reported to be associated with a high-risk diet (Slattery et al., 2002). In addition, a relation among work intensity, alcohol consumption, and the Brinkmann index has been reported in workers for small-scale enterprises (Kubo et al., 2004). These factors may provide a partial explanation for our present results, since our hospital is located in an area with many small-to-medium-sized enterprises. An increase in hard physical activity of factory workers may not have a beneficial effect, as reported recently (Isomura et al., 2006).

In conclusion, improvement of the metabolic syndrome and lifestyle factors is important for the primary prevention of colon cancer. In addition, we suggest that men older than 45 and women older than 50 years should undergo colonoscopy, especially when they have risk factors such as metabolic syndrome, an increased waist circumference, drinking, smoking, or high physical activity. For more efficient screening, further studies to develop a noninvasive method are necessary.

References

- Acott AA, Theus SA, Marchant-Miros KE, et al (2008). Association of tobacco and alcohol use with earlier development of colorectal cancer: Should we modify screening guidelines? *Am J Surg*, **196**, 915-8.
- Ahmed RL, Schmitz KH, Anderson KE, et al (2006). The metabolic syndrome and risk of incident colorectal cancer. *Cancer*, **107**, 28-36.
- Almendinger K, Hofstad B, Vatn MH (2001). Does high body fatness increase the risk of presence and growth of colorectal adenomas followed up in situ for 3 years? *Am J Gastroenterol*, **96**, 2238-46.
- Ashktorab H, Begum R, Akhgar A, et al (2007). Folate status and risk of colorectal polyps in African Americans. *Dig Dis Sci*, **52**, 1462-70.
- Ballard-Barbash R, Schatzkin A, Albanes D, et al (1990). Physical activity and risk of large bowel cancer in the Framingham study. *Cancer Res*, **50**, 3610-3.
- Bayerdörffer E, Mannes GA, Richter WO, et al (1993). Decreased high-density lipoprotein cholesterol and increased low-density cholesterol levels in patients with colorectal adenomas. *Ann Intern Med*, **118**, 481-7.
- Botteri E, Iodice S, Raimondi S, et al (2008). Cigarette smoking and adenomatous polyps: A meta-analysis. *Gastroenterology*, **134**, 388-95.
- Chao A, Thun MJ, Connell CJ, et al (2005). Meat consumption and risk of colorectal cancer. *JAMA*, **293**, 172-82.
- Chiu HM, Lin JT, Shun CT, et al (2007). Association of metabolic syndrome with proximal and synchronous colorectal neoplasm. *Clin Gastroenterol Hepatol*, **5**, 221-9.
- Cho E, Smith-Warner SA, Ritz J, et al (2004). Alcohol intake and colorectal cancer: A pooled analysis of 8 cohort studies. *Ann Intern Med*, **140**, 603-14.
- Coyle YM (2009). Lifestyle, genes, and cancer. *Methods Mol Biol*, **472**, 25-56.
- Forsyth CB, Tang Y, Shaikh M, et al (2010). Alcohol stimulates activation of Snail, epidermal growth factor receptor signaling, and biomarkers of epithelial-mesenchymal transition in colon and breast cancer cells. *Alcohol Clin Exp Res*, **34**, 19-31.
- Gao RN, Neutel CI, Wai E (2008). Gender differences in colorectal cancer incidence, mortality, hospitalizations and

- surgical procedures in Canada. *J Public Hlth (Oxf)*, **30**, 194-201.
- Isomura K, Kono S, Moore MA, et al (2006). Physical activity and colorectal cancer. The Fukuoka Colorectal Cancer Study. *Cancer Sci*, **97**, 1099-104.
- Johnson CD, Chen MH, Toledano AY, et al (2008). Accuracy of CT colonography for detection of large adenomas and carcinomas. *N Engl J Med*, **359**, 1207-17.
- Kubo N, Usami T, Haruyama Y, et al (2006). Characteristics of lifestyle and health status of workers in small-scale enterprises in Japan. *Ind Health*, **44**, 161-5.
- Moore LL, Bradlee ML, Singer MR, et al (2004). BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults. *Int J Obes Relat Metab Disord*, **28**, 559-67.
- Parkin DM, Bray F, Ferlay J, et al (2005). Global cancer statistics, 2002. *CA Cancer J Clin*, **55**, 74-108.
- Protiva P, Cross HS, Hopkins ME, et al (2009). Chemoprevention of colorectal neoplasia by estrogen: potential role of vitamin D activity. *Cancer Prev Res (Phila)*, **2**, 43-51.
- Rolo AP, Palmeira CM (2006). Diabetes and mitochondrial function: Role of hyperglycemia and oxidative stress. *Toxicol Appl Pharmacol*, **212**, 167-78.
- Rundl AG, Lebwohl B, Vogel R, et al (2008). Colonoscopic screening in average-risk individuals ages 40 to 49 vs. 50 to 59 years. *Gastroenterology*, **134**, 1311-5.
- Sansbury LB, Wanke K, Albert PS, et al (2009). The effect of strict adherence to a high-fiber, high-fruit and-vegetable, and low-fat eating pattern on adenoma recurrence. *Am J Epidemiol*, **170**, 576-84.
- Schernhammer ES, Giovannucci E, Kawasaki T, et al (2009). Alcohol and B vitamins in relation to LINE-1 hypomethylation in colon cancer. *Gut*, **59**, 794-9.
- Seitz HK, Stickel F (2009). Acetaldehyde as an underestimated risk factor for cancer development: role of genetics in ethanol metabolism. *Genes Nutr*, Oct 22.
- Slattery ML, Potter JD (2002). Physical activity and colon cancer: confounding or interaction? *Med Sci Sports Exerc*, **34**, 913-9.
- Soetikno RM, Kaltenbach T, Rouse RV, et al (2008). Prevalence of nonpolypoid (flat and depressed) colorectal neoplasms in asymptomatic and symptomatic adults. *JAMA*, **299**, 1027-35.
- Stocks T, Lukanova A, Johansson M, et al (2008). Components of the metabolic syndrome and colorectal cancer risk; A prospective study. *Int J Obes (Lond)*, **32**, 304-14.
- Stürmer T, Buring JE, Lee IM, et al (2006). Metabolic abnormalities and risk for colorectal cancer in the physicians' health study. *Cancer Epidemiol Biomarkers Prev*, **15**, 2391-7.
- Tabuchi M, Kitayama J, Nagawa H (2008). Hyperglycemia and hypertriglyceridemia may associate with the adenoma-carcinoma transition in colorectal epithelial cells. *J Gastroenterol Hepatol*, **23**, 985-7.
- Tsong WH, Koh W-P, Wang R, et al (2007). Cigarettes and alcohol in relation to colorectal cancer: The Singapore Chinese health study. *Br J Cancer*, **96**, 821-8.
- Wei WK, Ma J, Pollak MN, et al (2006). C-peptide, insulin-like growth factor binding protein-1, glycosylated hemoglobin, and the risk of distal colorectal adenoma in women. *Cancer Epidemiol Biomarkers Prev*, **15**, 750-5.
- Weige CC, Allred KF, Allred CD (2009). Estradiol alters cell growth in nonmalignant colonocytes and reduces the formation of preneoplastic lesions in the colon. *Cancer Res*, **69**, 9118-24.
- Weinstein SJ, Albanes D, Selhub J, et al (2008). One-carbon metabolism biomarkers and risk of colon and rectal cancers. *Cancer Epidemiol Biomarkers Prev*, **17**, 3233-40.
- Worthley DL, Whitehall VL, Buttenshaw RL, et al (2010). DNA methylation within the normal colorectal mucosa is associated with pathway-specific predisposition to cancer. *Oncogene*, **29**, 1653-62.
- Zuern C, Heimrich J, Kaufmann R, et al (2010). Down-regulation of MTUS1 in human colon tumors. *Oncol Rep*, **23**, 183-9.