RESEARCH ARTICLE

A New Index of Abdominal Obesity which Effectively Predicts Risk of Colon Tumor Development in Female Japanese

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Abstract

Background: A relation between abdominal obesity and colorectal tumor development has been reported repeatedly, and is believed to be more remarkable in man than in women. However, the details vary depending on scientific reports. This may be due at least partly to the selected surface anthropometric index in addition to the influence of gender and ethnic groups. To cope with this, we considered a new index of abdominal obesity and evaluated its risk prediction potential. Materials and Methods: Six hundred ninety five Japanese (262 women and 433 men) who had a colonoscopy were studied. The new index was named as waist circumference to height index (WHI) and was calculated by the formula of waist circumference (cm)/height (m)/height (m). Biochemical and lifestyle factors were investigated preceding the colonoscopy. Statistical analysis was performed using SPSS for Windows. Results: Increase of WHI was associated with altered metabolism of carbohydrate and lipid in both women and men. WHI was positively related with the development of colon tumor of women, while not with that of men. Logistic regression analysis performed for stratified age groups (45-54, 55-64 and 65-74 years) showed that WHI significantly increased odds ratio to 1.31 (CI 1.05-1.64 p=0.01) in women of 55-65 years. In contrast, in men this index WHI reduced the odds ratio insignificantly, while low density lipoprotein and triglyceride significantly increased the odds ratio to 1.01 (CI 1.00-1.03 p=0.02) in the 55-65 year group and to 1.02 (CI 1.00-1.03 p=0.02) in the 45-55 year group. Conclusions: In Japanese the risk factors for colon tumor development are different between women and men. WHI is a simple and efficient predictor of colon tumor risk in Japanese women and may be used to select those who should have colonoscopy.

Keywords: Colon cancer - waist circumference - central obesity- waist to height index - Japanese gender differential

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Introduction

Colorectal cancer is the third most common cancer worldwide. Incidence rates vary by up to 25-fold among countries, with the highest rates observed in North America, Australia, and Western Europe and the lowest rates in Africa and Asia (Parkin et al., 2002). In Japan, the number of colon cancer patients is rapidly increasing, and it is of urgent need to reduce the cancer mortality by either avoiding risk factors or early diagnosis.

Obesity caused by excess intake of fat-rich foods and less exercise is known as a statistically significant risk factor for colorectal cancer. Recent meta-analysis demonstrates that general obesity measured using body mass index (BMI) and central obesity measured using waist circumference (WC) increases the risk of colorectal cancer 1.33 and 1.45-fold, respectively (Ma et al., 2013). Indexes of abdominal obesity such as WC and waist-to-hip-ratio are more sensitive than those of overall obesity, and the abdominal fat is of particular relevance to the cancer in both women and men (Dai et al., 2007; Larsson et al., 2007).

In many previous reports, abdominal obesity has been shown to be a strong risk factor of colon cancer in men but a weaker risk factor in women (Giovannucci et al., 1995). However, it have also been shown that the differences in the relation between obesity and colon tumor between genders and ethnic groups exist. Therefore, it is conceivable that the causal relation between abdominal obesity and colon tumor may not be simple as we understand. In European Americans WC is strongly associated with colon adenoma, while in African Americans waist-to-hip ratio is the only index associated with colon adenoma (Wise et al., 2008; Thompson et al., 2012). These may suggest that in addition to different environmental conditions and hereditary factors the selection of anthropometric indices to substitute abdominal obesity may have profound effects on the prediction of colon cancer risk.

It has been reported recently that waist-to-height ratio (cm/cm) is associated with cardio-metabolic risks. Among Taiwanese adults, a waist-to-height ratio greater than 0.5 is a simple, yet effective indicator of centralized obesity and

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associated cardio-metabolic risk, even among individuals deemed 'healthy' according to BMI and WC (Li et al., 2013). Recent systemic review and meta-analysis also demonstrate that waist-to-height ratio is a better screening tool than WC and BMI in predicting cardio-metabolic risk (Ashwell et al., 2012). As far as we know, however, no data have been reported about the association between waist-to-height ratio and colon cancer.

Under these circumstances, we studied a new index of abdominal obesity which comprises an attribute of height in addition to waist circumference. This index is defined by a formula of WC (cm)/height (m)/height (m), and is named as waist circumference to height index (WHI). Its possible efficacy in predicting colon tumor risk in Japanese is presented in the present report.

Materials and Methods

Participants

Data from 695 individuals (433 men and 262 women) who underwent colonoscopy at our hospital in 2009 and 2010 were subjected to analysis. Fifty-eight % of men and 11% of women were smokers, while 65% of men and 22.9% of women were drinkers.

Surface anthropometric measurement

Preceding the endoscopic examination, patients completed a questionnaire about their diet. Height (m), weight (kg) and WC (cm) were measured by trained interviewers, which were used for the calculation of WHI (WC in cm/height in m/height in m).

Blood chemistry and calorie intake

Blood samples for laboratory tests were taken before endoscopic examination, and were assayed for low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride (TG) and insulin. Dietary calorie intakes (kcal/day) were evaluated using a food frequency questionnaire.

Pathological study

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

Data were subjected to statistical analysis using SPSS for windows (version 13.0)

Logistic regression was used to calculate odds ratio (OR) and 95% confidence interval (CI) after stratifying age to three groups, namely 45-54 years, 55-64 years and 65-74 years.

Ethics statement

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 subject.

Results

WC, WHI, BMI and age of the patients with or without colon tumors are summarized in Table 1. The values of these surface anthropometric indices were significantly increased in women with colon adenoma. In women with colon cancer, WHI but not WC or BMI was significantly increased. In contrast, in men these indices were not significantly different between those with and without colon tumors. On the other hand, both women and men with colon tumors were significantly older than those without tumor except for men with colon cancer (Table 1).

Table 2 summarizes the data of clinical biochemistry, blood pressure and calorie intake. In women with tumors, the serum levels of HDL was significantly lower while LDL and TG were significantly higher. In men with colon tumors, only TG was significantly increased. Serum

Table 1. Surface Anthropometric Indices in Men and Women With or Without Colon Tumors

Sex	Normal	Grade adenoma		Cancer	Adenoma or cancer
		High	Low		
Women	n=160	n=74	n=15	n=13	n=102
WC	80.85±9.87	86.33±9.713	80.62±11.110	86.00±10.520	85.61±10.006
		p=0.000	p=0.940	p=0.074	p=0.000
WHI	34.08±5.29	36.48±5.11	33.71±3.40	37.51±4.52	36.50±4.85
		p=0.001	p=0.805	p=0.036	p=0.001
BMI	22.0±3.22	23.2±3.67	21.7±2.58	23.6±3.88	23.1±3.59
	p=0.013	p=0.779	p=0.099	p=0.011	
Age	60.40±14.07	66.28±9.86	67.87±11.68	68.00±13.02	66.61±10.6
		p=0.001	p=0.048	p=0.045	p=0.000
Men	n=209	n=171	n=35	n=18	n=224
WC	84.90±7.72	86.28±8.02	86.00±8.07	85.22±9.19	86.15±8.07
		p=0.090	p=0.441	p=0.869	p=0.110
WHI	30.33±3.33	31.07±3.37	30.60±3.12	29.24±3.59	30.83±3.38
		p=0.05	p=0.730	p=0.167	p=0.187
BMI	23.1±2.39	23.2±2.78	23.2±2.99	22.2±3.09	23.1±2.83
		p=0.400	p=0.683	p=0.264	p=0.727
Age	58.19±14.39	63.94±10.58	65.13±9.4	61.42±9.78	63.79±10.41
		p=0.000	p=0.004	p=0.190	p=0.000

*WC=waist circumference, WHI=waist circumference to height index (waist circumference/height^2 in cm/m^2), BMI=body mass index (weight/height^2 in kg/m^2)

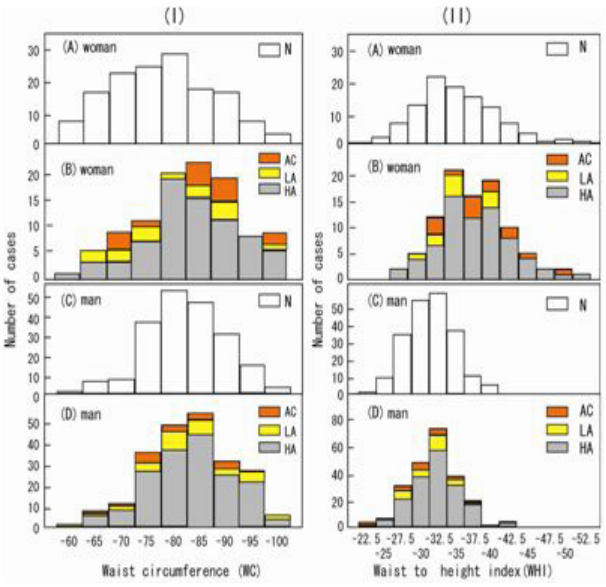

Figure 1. Frequency Distribution of Waist Circumference (I) and Waist to Height Index (II). N normal, AC adeno-carcinoma, LA low-grade adenoma, HA high-grade adenoma

insulin was significantly increased in men with colon tumors but not in women with colon tumor. Systolic blood pressure was increased significantly in both women and men with colon tumors. In both genders, the calorie intake was not different depending on the presence of colon tumors (Table2).

Figure 1 (I) and Figure 1 (II) shows the histogram of WC and WHI, respectively. Women without colon tumor distributed loosely on the smaller WC divisions (Figure 1 IA). In contrast, the histogram deviated toward larger WC in the case of women with colon tumors (Figure 1, IB). This tendency became more apparent in the histogram of WHI (Figure 1, IIA and IIB). In 9 (69%) of 13 women with adenocarcinoma, WC is larger than 80 cm (Figure 1, IB) and WHI is larger than 35 (Figure 1, IIB).

On the other hand, the histogram of WC was not remarkably different between men with and without colon tumors (Figure 1, IC and ID). In the histogram of WHI as well, no remarkable difference was observed between those with and without colon tumors (Figure 1, IIC and IID). WHI was less than 35 in 94.5% of men with adenocarcinoma (Table 1 IID).

The histogram of BMI is shown in Figure 2. BMI of women with colon tumor appeared to be distributed at slightly larger division of BMI (Figure 2 A and B), but the difference was not remarkable compared with WHI shown in Figure 1, IIA and IIB. In men, the histogram of BMI was not different between those with or without colon tumor (Figure 2 C and D).

The possible association between WHI and clinical data was examined next. Since WHI was 35 or more in 69% of women with colon cancer, clinical data were compared between WHI of 34 or less versus (vs) 35 or more (Table 3). Both women and men of WHI 35 or more were significantly older than those with WHI of 34 or less. In women with WHI of 35 or more, the level of HDL

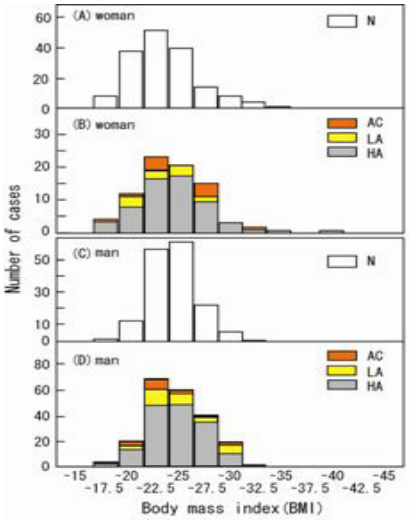

Figure 2. Number of Cases with or Without Colon Tumors in Different BMI Groups. BMI kg/m^2, AC adenocarcinoma, LA low-grade adenoma, HA high-grade adenoma

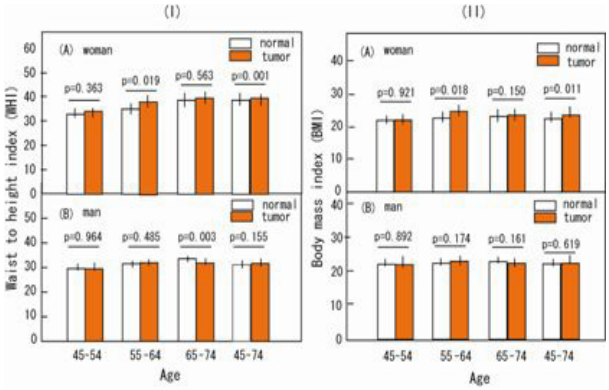

Figure 3. I) Waist to Height Index (WHI) in Different Age Groups of Women (A) and Men (B). WHI cm/m^2, age years. **II) Body Mass Index (BMI) in Different Age Groups of Women (A) and Men (B).** BMI in kg/m^2, age in years

Table 2. Serum Levels of Clinical Data and Food Intake in Women and Men with or without Colon Tumors

Index	Women			Men		
	without tumors (n=160)	with tumors (n=102)		without tumors (n=209)	with tumors (n=224)	
HDL (mg/dl)	71.9±23.9	65.1±17.7	(p=0.01)	60.1±17.0	61.50±23.5	(p=0.41)
LDL (mg/dl)	118.1±39.3	130.9±35.0	(p=0.00)	116.7±34.9	120.8±35.6	(p=0.23)
TG (mg/dl)	89.3±56.7	118.8±136.0	(p=0.01)	108.3±53.3	130.7±80.0	(p=0.00)
Insulin (μU/ml)	4.2±3.	5.3±9.5	(p=0.20)	3.66±2.1	4.20±2.7	(p=0.02)
Systolic BP (mmHg)	124±21	130±22	(p=0.04)	126±20	131±17	(p=0.02)
Diastolic BP (mmHg)	72±12	73±14	(p=0.52)	77±11	78±9	(p=0.15)
Total intake (kcal/day)	3019±384.03	2966±332.5	(p=0.25)	2881.0±393.5	2836.2±356.3	(p=0.15)
Protein intake (kcal/day)	606.3±116.0	589.7±75.3	(p=0.20)	568.5±74.9	576.3±84.6	(p=0.31)
Lipid intake (kcal/day)	948.6±148.6	941.6±141	(p=0.70)	895.6±199.6	862.9±151.1	(p=0.05)
Carbohydrate intake (kcal/day)	1485.2±203.9	1431.7±254.6	(p=0.06)	1426.0±251.0	1397.0±221.9	(p=0.21)

*BP=blood pressure

Table 3. Relation between WHI and Clinical Data

Index	Women		p	Men		p
	WHI<35	WHI≥35		WHI<35	WHI≥35	
Age (years)	57±13	67±9	0.01	59±12	68±8	0.41
HDL (mg/dl)	72.9±24.6 (n=131)	65.6±18.6 (n=113)	0.01	61.7±21.6 (n=363)	54.2±12.4 (n=38)	0.04
LDL (mg/dl)	120.8±38.3 (n=130)	126.9±39.6 (n=112)	0.22	118.5±35.8 (n=365)	118.8±32.9 (n=39)	0.96)
TG (mg/dl)	83.0±45.9 (n=131)	110.4±61.0 (n=113)	0.00	118.8±69.8 (n=367)	123.5±56.3 (n=38)	0.68
Insulin (μU/ml)	3.6±2.1 (n=121)	5.7±9.1 (n=110)	0.01	3.7±2.3 (n=357)	5.4±3.0 (n=39)	0.00
Systolic BP (mmHg)	122.4±19.2 (n=119)	130±22.6 (n=101)	0.00	128.6±19.8 (n=330)	131.7±14.5 (n=36)	0.24
Diastolic BP (mmHg)	71.7±13.3 (n=102)	74.0±13.2 (n=101)	0.21	78.3±11.4 (n=302)	78.9±10.5 (n=32)	0.75

*BP=blood pressure

Table 4. Estimated Risk of Colon Tumor in Japanese Women in Different Age Groups

	45≤age<55 (n=23)		55≤age≤65 (n=49)		65≤age<75 (n=56)	
	OR(95%CI)	p	OR(95%CI)	p	OR(95%CI)	p
WHI	1.317(0.881-2.140)	0.226	1.318(1.057-1.644)	0.014	1.044(0.916-1.190)	0.518
HDL(mg/dl)	0.863(0.712-1.046)	0.132	0.982(0.934-1.032)	0.466	1.009(0.970-1.050)	0.657
LDL(mg/dl)	0.952(0.878-1.031)	0.227	1.006(0.991-1.022)	0.403	1.010(0.995-1.026)	0.188
TG(mg/dl)	0.99(0.970-1.012)	0.382	0.993(0.980-1.006)	0.31	1.009(0.990-1.028)	0.35
Insulin(μU/ml)	0.936(0.312-2.809)	0.906	1.066(0.857-1.325)	0.567	1.114(0.898-1.382)	0.324
sBP(mmHg)	0.896(0.758-1.059)	0.198	0.998(0.962-1.035)	0.908	0.992(0.996-1.019)	0.554
tCal(Kcal/day)	0.992(0.980-1.005)	0.228	1.000(0.999-1.002)	0.576	0.999(0.998-1.001)	0.308

*OR: odds ratio; CI: confidence index; p: p value; WHI: waist circumference to height index; BP:blood pressure

Table 5. Estimated Risk of Colon Tumor in Japanese Men in Different Age Groups

	45≤age<55 (n=23)		55≤age≤65 (n=49)		65≤age<75 (n=56)	
	OR(95%CI)	p	OR(95%CI)	p	OR(95%CI)	p
WHI	0.862(0.652-1.139)	0.297	0.953(0.804-1.130)	0.581	0.837(0.700-1.281)	0.049
HDL(mg/dl)	1.0228(0.996-1.082)	0.447	1.007(0.982-1.032)	0.604	1.025(0.990-1.061)	0.163
LDL(mg/dl)	0.997(0.976-1.022)	0.819	1.016(1.002-1.031)	0.023	0.991(0.976-1.006)	0.222
TG(mg/dl)	1.021(1.003-1.039)	0.024	1.007(0.997-1.016)	0.157	1.003(0.996-1.011)	0.386
Insulin(μU/ml)	1.055(0.763-1.457)	0.747	1.196(0.984-1.454)	0.073	1.019(0.815-1.275)	0.866
sBP(mmHg)	0.985(0.928-1.046)	0.625	0.998(0.964-1.012)	0.332	1.000(0.975-1.025)	0.984
tCal(Kcal/day)	0.999(0.997-1.001)	0.437	0.999(0.997-1.000)	0.123	1.000(0.998-1.002)	0.746

*OR: odds ratio; CI: confidence index; p: p value; WHI: waist circumference to height index; BP:blood pressure

was significantly decreased, while TG was significantly increased. In men with WHI of 35 or more, HDL was significantly decreased. Insulin was increased significantly in women and men with WHI 35 or more. Systolic blood pressure was increased in women with WHI of 35 or more. From these it was indicated that increased WHI was associated with abnormal clinical indices related with life style related disease and aging.

Since women and men with colon tumor are significantly older, a possibility exists that the increase in both tumor incidence and WHI is attributable to aging. Therefore, to exclude the possible effect of age as confounder, the women and men stratified into three age groups, and the relation between WHI and colon tumor was examined about each group (Figure 3). In women, WHI increased in parallel with age (Figure 3 I A). In addition, in the age group of 55-64 years, WHI of women with colon tumor (36.8±5.1 n=23) was significantly larger (p=0.01) than that of those without colon tumor (33.7±4.5 n=36). In all age groups (45-74 years), the WHI of women with tumor (36.5±4.8 n=94) was also significantly increased (p=0.00) in comparison with that of women without tumors (34.1±5.2 n=153) (Figure 3 I A). In contrast, WHI was significantly smaller in those men with colon tumor (31.0±3.0 n=66) than without tumor (32.7±2.5 n=44) in age group of 65-74 years (p=0.00). Except this age group, however, the difference was not significant between those men with or without colon tumors (Figure 3 I B).

Figure 3 II demonstrates BMI of women (A) and men (B) of the stratified three age groups. In the age group of 55-64 years, BMI of women with tumor (24.2±3.5 n=24) was significantly larger (p=0.01) than those without tumor (22.2.±3.2 n=38). In all age groups (45-74 years), similar significant difference was recognized (23.1±2.5 n=10 vs 22.0±3.2 n=162 p=0.01) (Figure 3 II A). In men, BMI was not significantly different between those with and without colon tumor in three age groups (Figure3 II B).

Logistic regression analysis was carried out for each stratified age group using age, WHI, HDL, LDL, TG, insulin, systolic blood pressure and total calorie intake as numerical variables. Estimated risks of colon tumor in women and men were shown in Table 4 and 5, respectively. Among women with age group of ≥55 and <65 years, WHI significantly increased the odds ratio (OR) to 1.31 (CI 1.05-1.64 p=0.01). HDL, LDL, TG, insulin, blood pressure, and total calorie intake did not increase the ORs(Table 4). In other two age groups, these variables did not increase ORs (Table 4). In men, WHI decreased OR insignificantly in the three age groups (Table 5). In contrast, LDL significantly increased OR to 1.01 (CI 1.00-1.03 p=0.02) in the age group of ≥55 and <65 years, and TG significantly increased OR to 1.02 (CI 1.02-1.03 p=0.02) in group of ≥45 and <55 years (Table 5).

Discussion

As shown in the present study, WHI is a simple yet effective predictor of colon tumor risk in Japanese, and its effectiveness appears to be superior to BMI and WC. As far as we know, this is the first report which demonstrates the usefulness of WHI in predicting the risk of colon tumor.

Past reports demonstrate that WC and waist-to-hip ratio are stronger predictors of colon cancer risk than BMI (Martínez et al., 1997; Moore et al., 2004). However, the association between these indices and colon cancer varies depending on genders, ethnic groups and reports. The exact cause of these conflicting results is not known, but a possibility exists that the selected indices for abdominal obesity are not appropriate. Recent reports demonstrate that waist-to-height ratio is more useful than WC for the prediction of diabetes, hypertension, high total cholesterol, high triglycerides, and low HDL-cholesterol.

Robust statistical evidence from studies involving more than 300,000 adults in several ethnic groups shows the superiority of waist-to-height ratio over WC for detecting cardio-metabolic risk factors in both sexes (Ashwell et al., 2012). These suggested that a new index which includes a factor of height provide an answer to the conflicting data of surface anthropometric indexes, at least partly.

Our present study demonstrates that WHI was associated with alterations of lipid and carbohydrate metabolism, insulin level and systolic blood pressure in Japanese (Table 3). Furthermore, WHI is shown to be a more sensitive index than WC and BMI in predicting risk of colon tumors of Japanese women. Although WHI increased with age in women, the increase of WHI in women with colon tumor was still recognized after stratification of age (Figure 3). In addition, as shown in the logistic regression analysis carried out for each stratified age group, WHI increased OR of women of 55-64 years (Table 4). These indicate that the association between WHI and an increased tumor incidence in Japanese women are independent of age.

Our results show that WHI is positively related with colon tumors in women. In contrast, WHI was reduced in men with colon tumors, although the reduction was not significant. This is clearly different from the results of the past reports which demonstrated that the relation was stronger in men. In the past reports from Westernized countries , BMI, WC and waist-to-hip ratio were strong risk factors for colon cancer in men (Giovannucci et al., 1995 and 1996; Caan et al. 1998). In Asian peoples as well, the association was statistically significant in men only (Larsson et al., 2007; Li et al., 2012). On the other hand, a few past reports have shown that the positive relation between obesity and colon tumor exists in women, as well (Pischon et al., 2006; Wise et al., 2008; Li et al., 2012; Thompson et al., 2012). In one of them, obesity of women is shown to be associated with an elevated risk of adenomas rather than cancer (Giovannucci et al., 1996). In a recent report, obesity and weight gain are shown to be associated with early colorectal carcinogenesis (Morois et al., 2010). Therefore, the relation between abdominal obesity and colon tumor still remain to be clarified especially in women in Asian countries.

In men, WHI did not increase the risk of colon tumors (Table 5). Instead, LDL and TG significantly increased OR to 1.016 and 1.021, respectively (Table 5). In Japanese men, excessive alcohol drinking rather than abdominal obesity may contribute to the increases of serum LDL and TG and odds ratio of colon tumors (Table 5). Other possibilities such as that smoking, socio-economic conditions, and genetic predisposition may be playing important role in the development of colon tumor cannot be ruled out completely (Kaneko et al., 2010). The mechanisms by which abdominal obesity in women and altered lipid metabolism in men increase the colon tumor risk are not known. Still unknown factors which exacerbate chronic inflammation and increase the risk of colon tumors remained to be studied.

WHI is well correlated with the alterations in serum levels of LDL, TG and HDL, and is an useful predictor of abnormal lipid metabolism in addition to colon tumors (Table 3). Positive energy balance leads to the development of abdominal obesity and altered lipid metabolism, which elevates adipokine secretion and reactive oxygen species. Resulting metabolic stresses exacerbate chronic inflammation, leading to the increased risk of colon cancer (Műzes et al., 2012; Liang et al., 2013). The anticancer effect of caloric restriction in addition to moderation in drinking and stopping smoking has been demonstrated. For many people, however, these are considered to be abstemious, and are not welcome as a strategy for cancer prevention. Therefore, attention must be focused to early diagnosis of colon cancer by colonoscopy, as well. Our present study may suggest that those women with WHI of 35 or more (Figure 1, IIA and IIB) and with age of 55 or more (Figure 3) are recommended to undergo colonoscopy.

In conclusion, WHI is a simple surface anthropometric index representing abdominal obesity. This is an effective predictor of colon tumor and metabolic state and has significantly greater discriminatory power than WC and BMI. WHI is associated with elevated risk of colon tumors in Japanese women, and those women of age 55 or more and/or with WHI of 35 or more are recommended to undergo colonic endoscopy. Apparently, however, more detailed study are necessary to conclude this.

References

Ashwell M, Gunn P, Gibson S (2005). Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. *Obes Rev*, **13**, 275-86.

Caan BJ, Coates AO, Slattery ML, et al (1998). Body size and the risk of colon cancer in a large case-control study. *Int J Obes Relat Metab Disord*, **22**, 178-84.

Dai Z, Xu YC, Niu L (2007). Obesity and colorectal cancer risk: a meta-analysis of cohort studies. *World J Gastroenterol*, **13**, 4199-206.

Giovannucci E, Ascherio A, Rimm EB, et al (1995). Physical activity, obesity, and risk for colon cancer and adenoma in men. *Ann Intern Med*, **122**, 327-34.

Giovannucci E, Colditz GA, Stampfer MJ and Willett WC (1996). Physical activity, obesity, and risk of colorectal adenoma in women (United States). *Cancer Causes Control*, **7**, 253-63.

Kaneko R, Sato Y, An Y, et al (2010). Clinico-epidemiologic study of the metabolic syndrome and lifestyle factors associated with the risk of colon adenoma and adenocarcinoma. *Asian Pac J Cancer Prev*, **11**, 975-83.

Larsson SC, Wolk A (2007). Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies1,2,3. *Am J Clin Nutr*, **86**, 556-65.

Li H, Yang G, Xiang YB, et al (2005). Body weight, fat distribution and colorectal cancer risk: a report from cohort studies of 134255 Chinese men and women. *Int J Obes*, [Epub ahead of print].

Li WC, Chen IC, Chang YC, et al (2013). Waist-to-height ratio, waist circumference, and body mass index as indices of cardiometabolic risk among 36,642 Taiwanese adults. *Eur J Nut*, **52**, 57-65.

Liang J, Nagahashi M, Kim EY, et al (2013). Sphingosine-1-phosphate links persistent STAT3 activation, chronic intestinal inflammation, and development of colitis-associated cancer. *Cancer Cell*, **23**, 107-20.

Ma Y, Yang Y, Wang F, et al (2013). Obesity and risk of colorectal

cancer: a systematic review of prospective studies. *PLoS One*, **8**, 53916.

Martínez ME, Giovannucci E, Spiegelman D, et al (1997). Leisure-time physical activity, body size, and colon cancer in women. Nurses' Health Study Research Group. *J Natl Cancer Inst*, **89**, 948-55.

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.

Morois S, Mesrine S, Josset M, Clavel-Chapelon F, Boutron-Ruault MC (2010). Anthropometric factors in adulthood and risk of colorectal adenomas: The French E3N-EPIC prospective cohort. *Am J Epidemiol*, **172**, 1166-80.

Műzes G, Molnár B, Sipos F (2012). Regulatory T cells in inflammatory bowel diseases and colorectal cancer. *World J Gastroenterol*, **18**, 5688-94.

Parkin DM, Bray F, Ferlay J, Pisani P (2002). Global cancer statistics. *CA Cancer J Clin*, **55**, 74-108.

Pischon T, Lahmann PH, Boeing H, et al (2006). Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *J Natl Cancer Inst*, **98**, 920-31.

Thompson CL, Berger NA, Chak A, Li L (2012). Racial differences in measures of obesity and risk of colon adenoma. *Obesity*, **20**, 673-7.

Wise LA, Rosenberg L, Palmer JR, Adams-Campbell LL (2008). Anthropometric risk factors for colorectal polyps in African-American women. *Obesity*, **16**, 859-68.