

# Overweight as an Additional Risk Factor for Colorectal Neoplasia in Lean Population

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## Abstract

**Background:** Overweight in Thailand is not as common as in Western countries. We sought to evaluate overweight as the additional risk factor that can increase the prediction of colorectal neoplasia (CRN) detection in Thais apart from the Asia-Pacific Colorectal Screening (APCS) score. **Methods:** We prospectively enrolled asymptomatic 338 subjects who underwent screening colonoscopy between November 2016 and September 2017. All risk factors according to APCS, BMI and the presence of metabolic syndrome were collected. Overweight was defined as BMI  $\geq 23$  kg/m<sup>2</sup>. By APCS score, subjects were categorized into 1) high-risk and 2) average-risk. Using the combination of APCS score and overweight, subjects were stratified into 4 groups; high-risk with overweight (G1), average-risk with overweight (G2), high-risk with normal weight (G3) average-risk and with normal weight (G4). Logistic regression analysis was used to estimate the risk of detecting CRN. **Results:** The prevalence of CRN in the high-risk subjects was higher than that of in the average-risk subjects (49%vs.32%; OR, 2.00; 95%CI, 1.17-3.41). After adjustment for APCS risk factors and metabolic syndrome, overweight significantly increased the risk of detecting CRN (OR, 2.52; 95%CI, 1.57-4.05). Among the 4 groups, the detection rates of CRN were significantly different (G1=64%, G2=40%, G3=32% and G4=21%,  $p < 0.01$ ). The relative risk of detecting CRN increased when G1 (OR 6.49; 95%CI, 2.87-14.67), and G2 (2.42; 1.39-4.21) were compared with G4. **Conclusions:** In addition to the APCS score, overweight is an independent risk factor for detecting CRN. In Thai population, combining overweight and APCS score may be useful to improve the prediction for CRN.

**Keywords:** Colorectal adenoma- colorectal cancer screening- colonoscopy- risk stratification- body mass index

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## Introduction

Incidence of colorectal cancer (CRC) has been increasing in Asia and also in Thailand (Sung et al., 2005). Although colonoscopy is the best single colonic examination and provides an opportunity for polypectomy, its cost and nature of the technique that requiring endoscopist attribute to tremendous burden on healthcare systems in the resource-limited countries.

To reduce the cost and workload of colonoscopy, the updated Asia-Pacific Consensus on CRC proposed a risk stratified approach to select a high-risk subject for an early colonoscopy (Sung et al., 2015). The Asia-Pacific Colorectal Screening (APSC) score has been developed across 11 countries in Asia and Pacific region (Yeoh et al., 2011). It has been validated in Asian and Western population (Aniwan et al., 2015; Corte et al., 2016; Aniwan et al., 2017; Quach et al., 2018). The score that composed of 4 traditional CRC risk factors; age, sex,

family history of CRC and smoking, ranges from score 0 to 7. These scores are grouped into low-risk, average-risk, and high-risk (Table 1). When compared with the low-risk group, the relative risk of detecting advanced CRN was 2.6-fold in the average-risk and 4.3-fold in the high-risk (Yeoh et al., 2011)

In addition to the traditional CRC risk factors, overweight was found as an environmental factor for developing CRC (Harriss et al., 2009). The proposed mechanism is an increase in insulin-like growth factor, leptin, vascular endothelial growth factor leading patients to chronic inflammation and cancer (Stattin et al., 2004; Byrne et al., 2005; Pollak, 2008; Braun et al., 2011; Hursting and Hursting, 2012). A recent meta-analysis including Western and Asian studies showed the positive association between overweight and the detection rate of colorectal adenoma (Okabayashi et al., 2012). Over the last decade, overweight has become a global burden throughout world (Kelly et al., 2008). Although

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overweight in Thailand is not as common as in Western countries, one-fifth of Asian population were overweight in 2005 and the estimated prevalence of overweight has been projected to approximately 50% of Asian population by 2030 (Kelly et al., 2008). Since the original APCS score did not include overweight as a parameter, hence the potential increase in the prediction of CRN detection by adding overweight as additional factor to the APCS score in Thai population is uncertain. To confirm this hypothesis, this study was taken to evaluate the association between the combination of overweight and the APCS score and the detection rate of CRN in asymptomatic Thais who presented for CRC screening.

## Materials and Methods

### Study population

We conducted a prospective cross-sectional study including consecutive asymptomatic subjects who attended the CRC screening clinic at the King Chulalongkorn Memorial Hospital between 1 November 2016 and 30 September 2017. Asymptomatic subjects, aged 50 to 75 years were recruited. Exclusion criteria were history of CRC, history of inflammatory bowel disease and family history of hereditary CRC ( $\geq 2$  first-degree relatives with CRC or  $\geq 1$  first degree relative diagnosed with CRC before age of 60 years). All subjects provided written informed consent. This study was approved by the Chulalongkorn Institutional Review Board.

### Data collection

All subjects were interviewed to determine their clinical risk score by the research assistant (N.K.). We stratified subjects into 2 groups according to APCS score; 1) average-risk defined as APCS score of 2-3 and 2) high-risk defined as APCS score of 4-7 (Table 1) (Yeoh et al., 2011). Data on demographic characteristics, body weight, height, waist circumference, medical history were collected. Serum triglyceride, serum high-density lipoproteins (HDL) cholesterol, and serum fasting glucose at colonoscopy screening or within one year before were collected. Using body mass index (BMI) cutoff at 23 kg/m<sup>2</sup> for Asian population (WHO, 2004), we categorized subjects into 1) overweight (BMI  $\geq 23$  kg/m<sup>2</sup>); 2) normal weight (BMI  $< 23$  kg/m<sup>2</sup>). According to metabolic syndrome diagnostic criteria of National Cholesterol Education Program, Adult Treatment Panel III, metabolic syndrome was defined as meeting at least three of the following criteria; 1) waist circumference  $\geq 90$  cm for Asian men or  $\geq 80$  cm for Asian women.; 2) serum triglyceride  $\geq 150$  mg/dL; 3) HDL cholesterol  $< 40$  mg/dL for men or  $< 50$  mg/dL for women; 4) fasting glucose  $\geq 110$  mg/dL (National Cholesterol Education Program Expert Panel on Detection, 2002).

Bowel preparation and total colonoscopy were performed as described previously (Aniwan et al., 2016). All detected polyps were removed. Each polyp was measured by open biopsy forceps, 7-mm in diameter. Polyp was classified by pathology to 1) colorectal neoplasia 2) colorectal non-neoplasia. Colorectal neoplasia (CRN) was defined as adenoma (i.e. tubular adenoma, villous

adenoma, tubulovillous adenoma, sessile/traditional serrated adenoma) or CRC. CRN was further classified as advanced CRN and non-advanced CRN. Advanced CRN was defined as adenoma with size  $\geq 10$  mm. or high grade dysplasia or villous (at least 25%) or CRC.

### Statistical analysis

To compare categorical variables, Chi-square test or Fisher exact test was used. To compare continuous variables, Student's t-test or Mann-Whitney U-test was used. Logistic regression analysis was used to assess the association between the potential risk factors (i.e. age, sex, family history of CRC, smoker, overweight and metabolic syndrome) and CRN. Any variables with  $p < 0.10$  in the univariate analysis were included in the multivariate analysis to estimate the odds ratio (OR) and 95% confidence interval (CI). In order to evaluate whether the combination between overweight and the APCS score improve the detection of CRN, subjects were stratified by 4 groups; 1) subject with high-risk and overweight group (G1); 2) subject with average-risk and overweight group (G2); 3) subject with high-risk and normal weight group (G3); 4) subject with average-risk and normal weight group (G4).

We hypothesized that subject with high-risk and overweight would have the highest prevalence of CRN. In Thailand, the prevalence of CRN was 27% (Aniwan et al., 2015) and the prevalence of the high-risk was 29% (Aniwan et al., 2017). Assuming the detection rate of CRN in subject with average-risk and normal body weight was 20% and that of subject with high-risk and overweight was 50%. We estimated the prevalence of subjects with high-risk and overweight was 12%. Therefore, a sample size of at least 300 subjects was required to detect 30% difference with a power of 80% at a two-sided significance level of 0.05. Statistical analyses were performed by using SPSS statistical software (version 23.0; PSS Inc, Chicago III).

## Results

A total of 338 subjects were enrolled. All subjects had a complete colonoscopy. Mean age was 62.7 $\pm$ 8.6 years. Two hundred and nine subjects (62%) were female. Mean BMI was 23.9 $\pm$ 3.7 kg/m<sup>2</sup>. Of 338 subjects, overweight was found in 192 subjects (57 %) and metabolic syndrome was diagnosed in 136 subjects (40%). The overall detection rates of CRN, advanced CRN, and CRC were 120 (36%), 25 (7%), and 2 (0.6%), respectively. Demographic characteristics are shown in Table 2.

### Overweight and metabolic syndrome

The detection rates of CRN and advanced CRN in subjects with overweight were higher than those of subjects with normal weight (for CRN 44% vs. 24%;  $p < 0.01$  and for advanced CRN 12% vs. 2%;  $p < 0.01$ , respectively) The detection rates of CRN and advanced CRN between subjects with metabolic syndrome and those without metabolic syndrome were not significantly different (for CRN 38% vs. 34%;  $p = 0.39$  and for advanced CRN 7% vs. 7%;  $p = 1.00$ , respectively). Table 3 shows the univariate and multivariate analysis for the

Table 1. Asia-Pacific Colorectal Screening Scoring System for Predicting the Risk for Colorectal Neoplasm

Variables Criteria	Points
Age	
<50	0
50-69	2
≥70	3
Sex	
Female	0
Male	1
Family history of colorectal cancer in a first-degree relative	
Absent	0
Present	2
Smoking	
Never	0
Current or past	1

low-risk group, score of 0-1; average-risk group, score of 2-3; high-risk group, score of 4-7

association between potential risk factors and the risk of CRN detection. In multivariate logistic regression, after adjusting for traditional risk factors for CRC, there was statistically significant association between overweight and the CRN detection (OR, 2.57; 95% CI, 1.57-4.20). When the model of analysis was adjusted with the high-risk score, overweight remained an increased risk for the CRN detection (OR, 2.68; 95% CI, 1.65-4.36). For advanced CRN, the detection rates of advanced CRN were numerically higher in subjects with traditional CRC risk factors as compared to subjects without traditional CRC risk factors ( $p > 0.05$  for all comparisons). Only overweight significantly increased the risk for detecting advanced CRN (OR, 6.17; 95% CI, 1.81-21.0) (Supplement Table 1).

#### APCS scoring system

Stratification by APCS score, there were 268 subjects (79%) with average-risk and 70 subjects (21%) with

Table 2. Demographic Characteristics of 338 Subjects

Variables	N = 338
Age (year), mean (SD)	62.7 (8.6)
50-69 years (n, %)	272 (80%)
≥ 70 years (n, %)	66 (20%)
Male (n, %)	129 (38%)
First degree relative with colorectal cancer (n, %)	28 (8%)
Current or former smoker (n, %)	39 (12%)
Body mass index (kg/m <sup>2</sup> ), mean (SD)	23.9 (3.7)
BMI ≥ 23 kg/m <sup>2</sup> (n, %)	192 (57%)
Metabolic syndrome <sup>a</sup> (n, %)	136 (40%)
APCS score <sup>b</sup> (n, %)	
Average risk	268 (79%)
High risk	70 (21%)
Prevalence of colorectal neoplasia (n, %)	
All colorectal neoplasia	120 (36%)
Advanced colorectal neoplasia	25 (7%)
Cancer	2 (0.6%)

SD, standard deviation; APCS score, Asia-Pacific Colorectal Screening score; a, Metabolic syndrome was defined according to National Cholesterol Education Program (NCEP), Adult Treatment Panel III (ATP III); b, Average risk was defined as an APCS score of 2-3, and high risk was defined as an APCS score of 4-7.

high-risk, respectively. The detection rate of CRN was 49 % for subjects with high-risk and was 32% for subjects with average-risk ( $p=0.01$ ). The detection rate of advanced CRN was 9% for subjects with high-risk and 7% for subjects with average-risk ( $p=0.67$ ). Subjects with high-risk significantly had an increased risk for CRN detection when compared with subjects with average-risk (OR, 2.00; 95% CI 1.17-3.41) (Table 4).

#### Combination between overweight and APCS scoring system

With the combination of overweight and the APCS score, subjects were classified into 4 groups; 36 subjects (11%) were categorized as high-risk group with

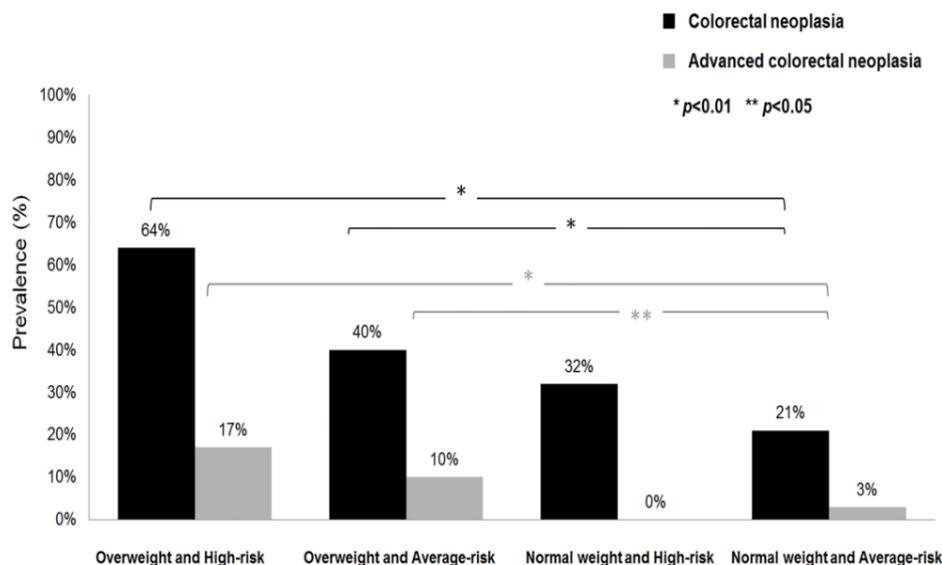


Figure 1. Prevalence of Colorectal Neoplasia and Advanced Colorectal Neoplasia Classified by Overweight and Asia-Pacific Colorectal Scoring System

Table 3. Univariate and Multivariate Analysis for the Association between Potential Risk Factors and the Detection Rate of Colorectal Neoplasia

Model 1 <sup>a</sup>	Colorectal neoplasia (n=120) (prevalence, %)	Univariate analysis		Multivariate analysis <sup>c</sup>	
		Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age (per 1-year increase)		1.03 (1.00–1.05)	0.05	1.03 (1.00-1.06)	0.05
Sex					
Male (n=129)	57 (44%)	1.84 (1.16-2.90)	<0.01	1.61 (1.00-2.59)	0.05
Female (n=209)	63 (30%)	reference		reference	
First-degree relative with CRC					
Present (n=28)	16 (57%)	2.64 (1.21-5.79)	0.02	2.95 (1.29-6.72)	0.01
Absent (n=310)	104 (36%)	reference		reference	
Smoking				--	--
Current/former (n=39)	15 (39%)	1.16 (0.58-2.30)	0.68		
Never (n=299)	105 (35%)	reference			
Body mass index					
≥23 kg/m <sup>2</sup> (n=192)	85 (44%)	2.52 (1.57-4.05)	<0.01	2.57 (1.57-4.20)	<0.01
<23 kg/m <sup>2</sup> (n=146)	35 (24%)	reference		reference	
Metabolic syndrome					
Present (n=136)	52 (38%)	1.22 (0.78-1.92)	0.39	--	--
Absent (n=202)	68 (34%)	reference			
Model 2 <sup>b</sup>					
APCS score					
High risk (n=70)	34 (49%)	2.00 (1.17-3.41)	0.01	2.23 (1.28-3.88)	<0.01
Average risk (n=268)	86 (32%)	reference		reference	
Body mass index					
≥23 kg/m <sup>2</sup> (n=192)	85 (44%)	2.52 (1.57-4.05)	<0.01	2.68 (1.65-4.36)	<0.01
<23 kg/m <sup>2</sup> (n=146)	35 (24%)	reference		reference	
Metabolic syndrome					
Present (n=136)	52 (38%)	1.22 (0.78-1.92)	0.39	--	--
Absent (n=202)	68 (34%)	reference			

CRC, colorectal cancer, APCS score; Asia-Pacific Colorectal Screening score; a Model 1, was the analysis for the association between overweight and metabolic syndrome and the risk of CRN detection after adjustment for the individual traditional CRC risk factors; b Model 2, was the analysis for the association between overweight and metabolic syndrome and the risk of CRN detection after adjustment for the APCS risk stratification; c, Any variables with  $p < 0.1$  in the univariate analysis were included in the multivariate analysis.

Table 4. Prevalence of Colorectal Neoplasia According to Overweight, APCS Score and the Combination of Overweight and the APCS Score

All subjects (n=338)	Colorectal neoplasia		
	Prevalence	Odds ratio (95% CI)	p-value
Overweight			
Present (n=192)	85 (44%)	2.52 (1.57-4.05)	<0.01
Absent (n=146)	35 (24%)	reference	
APCS scoring system			
High risk (n=70)	34 (49%)	2.00 (1.17-3.41)	0.01
Average risk (n=268)	86 (32%)	reference	
APCS scoring system and overweight			
G1: overweight and high risk (n=36)	23 (64%)	6.49 (2.87-14.67)	<0.01
G2: overweight and average risk (n=156)	62 (40%)	2.42 (1.39-4.21)	<0.01
G3: normal weight and high risk (n=34)	11 (32%)	1.75 (0.75-4.10)	0.19
G4: normal weight and average risk (n=112)	24 (21%)	reference	--

APCS score, Asia-Pacific Colorectal Screening score

overweight (G1), 156 subjects (46%) were categorized as average-risk group with overweight (G2), 34 subjects (10%) were categorized as high-risk group with normal weight (G3), and 112 subjects (33%) were categorized as average-risk group with normal weight (G4). The detection rates of CRN for G1, G2, G3 and G4 were 64%, 40%, 32% and 21%, respectively ( $p < 0.01$ ). One CRC was found in G1 and one CRC was found in G2. None of CRC was detected in G3 and G4. The significant differences in the detection rates of advanced CRN among 4 groups was observed ( $p < 0.01$ ) (Figure 1). For the risk of CRN detection, the OR for G1 was 6.49 (95% CI, 2.87-14.67), 2.42 for G2 (1.39-4.21) and 1.75 for G3 (0.75-4.10) as compared with G4 (Table 4).

## Discussion

In this study, we demonstrated that apart from the traditional CRC risk factors, overweight is the additional risk factor for CRN detection in asymptomatic subjects. In other words, the synergistic effect of combining overweight with the APCS score for predicting the CRN detection was observed. In subjects with high-risk, the relative risk for detecting CRN were twice as likely as subjects with average-risk. Likewise, in subjects with overweight, the risk for detecting CRN increased to 2.5-fold as compared to subjects with normal weight. Synergistically, high-risk subjects with overweight had approximately 6.5-fold increased risk for detecting CRN as compared to average-risk subjects with normal weight.

APCS scoring system is helpful to predict individual harboring CRN in Asian population. In this study, the result is concordant with our earlier reports showing an approximately 1.5-fold higher prevalence of colorectal adenoma in the high-risk subjects as compared to that of in the average-risk subjects (Aniwan et al., 2015; Aniwan et al., 2017). The development of APCS scoring system included several important variables including age, sex, smoking, family history of CRC, alcohol and diabetes. However, there were some limitations in the APCS score, other potential clinical factors regarding component of metabolic syndrome (i.e. body mass index, hypertension, and hyperlipidemia) were not included during the initial development of the APCS score (Yeoh et al., 2011). In this study, BMI and metabolic syndrome were combined with individual parameter of APCS score and later assessed. Moreover, the separate analysis on the risk stratified by APCS was also performed. A recent study from Hong Kong developed a modified APCS score in Chinese population by adding BMI  $\geq 23$  kg/m<sup>2</sup> as 1 point and deducting 1 point from age and family history criteria (Sung et al., 2018). The new model showed that the modified high-risk subjects had 2-fold increased risk for CRN and 2.5-fold increased risk for advanced CRN as compared with the modified low-risk subjects (Sung et al., 2018). However this modified APCS score requires further validation by comparing with the original APCS score.

The objective of using risk stratified approach for CRC screening is to minimize the burden of colonoscopy and maximize the detection rate of CRN. Accordingly, the approach strategy is based on the prevalence of CRN

and the number of requiring colonoscopy to detect CRN. Theoretically, selecting subjects with higher risk for CRN to undergo for colonoscopy helps to reduce the number of colonoscopy needed to detect one CRN, whereas the lower risk subjects should undergo for a colonoscopy only after being screened by a less expensive test with higher predictive value. Herein, our results showed that the prevalence of CRN were 36% in all screened subjects, 49% in the high-risk subjects, and 64% in the high-risk subjects with overweight, respectively. The number needed for colonoscopy (NNC) to detect one CRN in all screened subjects was 2.8 whereas the NNC to detect one CRN in subjects with high APCS score was 2, which corresponded to 29% reduction rate of colonoscopy. Incorporating BMI with the APCS score, the NNC to detect one CRN in high-risk subjects with overweight was even lower (1.6), and resulted to 43% reduction in NNC.

With regard to the association between BMI and the risk of CRN, our results are in line with previous studies and meta-analyses (Okabayashi et al., 2012; Omata et al., 2013). Okabayashi et al., (2012) demonstrated a significant association between an increased BMI and CRN. The prevalence of colorectal adenoma in subjects with overweight defined as BMI of 25-30 kg/m<sup>2</sup> was 21% higher than those of in subjects with BMI  $< 25$  kg/m<sup>2</sup> while the prevalence of colorectal adenoma in obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) was 32% higher when compared to those with BMI  $< 25$  kg/m<sup>2</sup>. It is noted that in our study, we defined overweight as BMI  $\geq 23$  kg/m<sup>2</sup>. Because Thais have low rates of overweight/obesity defined by the standard definition for Asian population according to WHO. In 2003, by using this definition, one-third of Thai population had overweight and less than 10% with obesity whereas two-third of United States population had overweight and more than 20% with obesity (WHO, 2004). However, the prevalence of CRN at the cutoff level of BMI 23 kg/m<sup>2</sup> in our study still held true by showing the higher prevalence than those with lower BMI. An additional support from Chinese population confirmed that the prevalence of CRN and advanced CRN were comparable between using the cutoff level of BMI  $\geq 23$  kg/m<sup>2</sup> (35% and 6.5%) and the cutoff level of BMI  $\geq 25$  kg/m<sup>2</sup> (38% and 7%), respectively (Sung et al., 2018). In addition, This study showed that using the cutoff level of BMI  $\geq 23$  kg/m<sup>2</sup> had enough power to detect more advanced CRN (OR, 1.5; 95% CI, 1.1-2.1) similar to using the higher cutoff BMI  $\geq 25$  kg/m<sup>2</sup> (OR, 1.4; 1.1-1.9) (Sung et al., 2018). Another study from Korea supports that there was no difference between using the cutoff level of BMI 23 kg/m<sup>2</sup> and BMI 25 kg/m<sup>2</sup> on the risk of CRC (Shin et al., 2017). The authors showed that when compared to those with BMI at 18.5-23 kg/m<sup>2</sup>, the relative risk of CRC increased to 17% equally in those with BMI 23-25 kg/m<sup>2</sup> and those with BMI 25-30 kg/m<sup>2</sup> (Shin et al., 2017).

A previous meta-analysis study from worldwide populations demonstrated there was a modest association between metabolic syndrome and the risk of CRC; 33% increased risk of CRC for men and 41% increased risk of CRC for women (Esposito et al., 2013). However, subgroup analysis by race showed no increased risk of CRC in Asian populations with metabolic syndrome

(Esposito et al., 2013). Their results were similar to our findings. We found that subjects with metabolic syndrome had 22% increase in the risk for detecting CRN as compared to those without metabolic syndrome, unfortunately this was not significant statistically. Perhaps metabolic syndrome has a lower impact to predict the risk for CRN as compared to the BMI factor, especially in Asian populations. However, we did not perform a separate analysis by metabolic syndrome component such as abdominal girth, triglyceride and fasting plasma sugar levels. Because there was a relatively small number of CRN among metabolic syndrome component in this study. Therefore no conclusion regarding to these components could be drawn.

A key strength of this study is that all asymptomatic subjects were prospectively enrolled. Data on body weight, height, component of metabolic syndrome were measured rather than using patient-reported. However, there are certain limitations in this study. First, all subjects were enrolled from the CRC screening clinic. Therefore, we cannot avoid self-referral bias. This could be the explanation that we had more than half of our screened subjects were female (62%) and being an overweight (57%). Possibly, women often are interested in health-related information and subjects being overweight are the population that already caught medical attention for their metabolic syndrome. Second, our CRC screening subjects were recruited either from those who presented for opportunistic colonoscopy or from those with positive fecal immunochemical test (FIT). This could explain the high prevalence of CRC was observed in our population. The selection bias would limit the generalizability of our results. By prediction, colonoscopy in subjects with FIT positive would have a higher prevalence of CRN than that of from those without prior FIT screening (Aniwan et al., 2015). However, the overall prevalence of CRN in our study was 36% and this was not higher than the previous report in opportunistic colonoscopies (Aniwan et al., 2015). Third, we used different cutoff level of BMI. This might possibly restrict the generalizability to the countries with higher percentage of obese population. However, in the Asia-Pacific region, the lower cutoff level of BMI could be more practical and appropriate to combine with the Asian risk score. Lastly, our results showed higher prevalence of CRN in overweighted high-risk population as compared with normal weight high-risk population but was not statistically significant which may probably caused by the relatively small number of CRN in our subgroups. In conclusion, this study illustrates that in addition to APCS scoring system, overweight is an independent risk factor for detecting CRN. A combination of overweight and the APCS score is useful for improving the prediction for CRN and may prioritize patients for colonoscopy in a country with limited resource. However, the slightly lower BMI cutoff for determining overweight used in our study may be applicable only to the countries with low prevalence of obese population.

#### Abbreviations

APCS: Asia-Pacific Colorectal Screening  
BMI: body mass index

CI: confidence interval  
CRC: colorectal cancer  
CRN: colorectal neoplasia  
FIT: fecal immunochemical test  
HDL: high-density lipoproteins  
OR: odds ratio

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#### Conflicts of interests

None of the authors have any relevant conflicts of interests.

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