Metabolic Syndrome and Risk of Colorectal Cancer: Results of Propensity Score-based Analyses in a Community-based Cohort Study

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Abstract

Background: This study aimed to determine the effects of metabolic syndrome (MetS) on colorectal cancer (CRC) using propensity score (PS) methods.

Methods: The study subjects were 2,417 men and 4,568 women from the Korean National Cancer Center (KNCC) Community Cohort enrolled between 2003 and 2010 who were followed up by 2016 (median follow-up time, 10.4 years). Modified criteria for MetS, adopted body mass index ≥ 25 kg/m² instead of waist circumference (≥ 90 cm for men and ≥ 80 cm for women for Asian) was applied. Hazard risks (HRs) and 95% confidence intervals (CIs) using unadjusted and multiple Cox's hazard regression models, PS matching analysis, regression models adjusted by the PS or stratified into five strata according to PS, and PS weighting methods were calculated.

Results: There were 57 and 54 incident colorectal cases for men and women, respectively (median follow-up time was 4.8 years for men and 5.5 years for women). In women, MetS and abnormally high triglyceride (TG) levels were associated with CRC risk (HR for MetS, 2.12 [95% CI, 1.22-3.68] using the multiple Cox's hazard regression and 2.19 [95% CI, 1.10-4.33] using the PS matching analysis; HR for abnormal TG levels, 2.06 [95% CI, 1.20-3.55] using the multiple Cox's hazard regression and 2.08 [95% CI, 1.07-4.02] using the PS matching analysis). In men, MetS and TG levels did not show significant associations with the risk of CRC (HR for MetS, 1.04 [95% CI, 0.54-1.99] using the multiple Cox's hazard regression and 0.93 [95% CI, 0.42-2.03] using the PS matching analysis; HR for abnormal TG levels, 0.84 [95% CI, 0.47-1.50] using the multiple Cox's hazard regression and 1.11 [95% CI, 0.55-2.21] using the PS matching analysis).

Conclusions: Our study might provide additional evidence that deteriorated metabolic profiles increase the risk of CRC in women rather than men. Thus, it may have an important role in effective population-level interventions for deteriorated metabolic profiles at an early stage.

Background

Colorectal cancer (CRC) is the third most common cancer in both sexes worldwide (1,360,602 cases, 9.7% of the total cancer burden). According to GLOBOCAN 2018, the ranking of the estimated age-standardized rates of CRC incidence for both sexes at all cancer sites were observed to be similarly high ranked in most countries, ranking fourth in the United States, third in Europe, second in Japan, and third in the Republic of Korea [1].

Worldwide, over a billion people are known to be affected with metabolic syndrome (MetS). The MetS prevalence is increasing in low socio-economic countries as well as high socio-economic countries. In even young adults, the prevalence ranges from 5 to 7% worldwide, although it increases with age. MetS is a complex disorder characterized by a cluster of moderate levels of metabolic, anthropometric, and hemodynamic abnormalities, accepted as a modifiable risk factor CRC, although the mechanism linking MetS and CRC has not been clearly elucidated [2, 3]. Recent systematic reviews and meta-analyses have conclusively reported that MetS is associated with an approximately 1.3-fold increased risk of CRC in both sexes, although the risk in women was slightly higher than that in men [2, 4]. A few studies have been conducted in the Republic of Korea among national health insurance subscribers or subjects who underwent colonoscopy for a health examination in a hospital. However, these studies reported inconsistent results [5-7]. So far, there are limited evidences on the association between MetS and CRC, especially for the Asian population. Furthermore, the findings of previous observational studies have pointed inevitably lower causality than randomized controlled trials due to selection biases. In order to overcome this weakness of observational studies, propensity score (PS)-based methods were proposed to attenuate selection biases by balancing many covariates [8, 9]. Studies using these methods have been increasingly published in a wide range of fields, including some observational studies on MetS [10, 11].

In this context, this study investigated the impact of MetS on CRC incidence by conducting PS-based analyses considering age, alcohol consumption, smoking, high animal fat intake, obesity, a lack of dietary fiber intake, and a lack of physical activity etc. that have been identified as modifiable risk factors for CRC [12-19], in a community-based prospective cohort in the Republic of Korea.

Methods

Data source and study population

The Korean National Cancer Center (KNCC) Community Cohort, as a community-based prospective cohort, was conducted by the KNCC and included 16,304 men and women who resided in Changwon-si, Chuncheon-si, Chungju-si, Sancheong-gun, and Haman-gun in the Republic of Korea [20]. All participants were aged over 30 years, with an average age when cohort entry as follows; 58.6 ± 12.4 years for men (N=6302) and 57.7 ± 13.3 for women (N=10002). The questionnaire survey was conducted by well-trained interviewers and included the following demographic information: age, sex, home region, education level, occupational history, marriage status, average household income, alcohol consumption, smoking status, physical activity, dietary intake, history of cancer, and exposure to pesticides. Additionally, the results of anthropometric measurements and clinical laboratory examinations were included. All study participants are followed through linkage to the

Korean Central Cancer Registry for cancer incidence and mortality by 2016. This cohort was linked to mortality data of Statistics Korea for all participants by 2016.

6,985 participants (2,417 men and 4,568 women) were eligible for the analysis after excluding 9,319 participants who had history of cancer before entry, did not participate in the nutrition survey, developed cancers other than CRC, and had missing data for MetS, alcohol consumption, smoking, physical activity, diet, and education (Figure 1). The study was approved by the KNCC Institutional Review Board (IRB No. NCC2016-0300). All participants had provided written informed consent.

Definition of CRC and MetS

The outcome of this study was CRC incidence; the type of cancer was coded as C18, C19, and C20 according to the International Classification of Diseases 10th edition (ICD-10).

In this study, modified definition of MetS was applied. Since there is no information of waist circumference (WC) in this study, WC >90 cm for men and >80 cm for women were substituted by body mass index (BMI) ≥ 25 kg/m² referring to previous studies [21, 22], and the other four components of MetS were applied from National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) definition ; hypertension (systolic blood pressure [SBP] ≥ 130 mmHg and diastolic blood pressure [DBP] ≥ 85 mmHg), low high-density lipoprotein (HDL) cholesterol level (<40 mg/dL for men and <50 mg/dL for women), high triglyceride (TG) level (≥ 150 mg/dL), and abnormal fasting blood sugar (FBS) level (≥ 110 mg/dL) [23]

Statistical analyses

Descriptive analyses between subjects who developed CRC and those who did not were performed for continuous parameters using the Mann-Whitney U test and for categorical parameters using the Chi-square test and Fisher's exact test.

Follow-up started at enrollment until a colorectal cancer diagnosis or censoring. Censoring occurred at date of death, or end of follow-up (December 31, 2016).

To elucidate associations between MetS and risk of CRC in both sexes and an association between abnormal TG levels and CRC in women, hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated by the following statistical analyses using Cox's hazard regression models: unadjusted and multiple regression, PS matching analysis, regression adjustment with the PS, and PS weighting methods. An overview of the pros and cons of covariate adjustment and various propensity score methods has been presented in detail by Elze et al [24] (see supplementary method 1). In these analyses, we included the following covariates known as the known risk factors of CRC [2, 12-19, 25, 26]: age, alcohol consumption (non-drinkers, moderate drinkers [<24 g/day], heavy drinkers [≥ 24 g/day]), smoking status (non-smokers, moderate smokers [<20 pack-year], heavy smokers [≥ 20 pack-year]), moderate-intensity physical activity (days/week), frequency of fruit or vegetable intake (days/week), frequency of intake of beef or pork (days/month), education level (illiterate, middle school or less, high school, and college or more), and study area (Changwon-si, Chuncheon-si, Chungju-si, Sancheong-gun, and Haman-gun).

To perform PS-based methods, we needed first to calculate the PS. The PS is the probability that an individual would have MetS or abnormal TG levels based on personal demographic and lifestyle information, and it was obtained from the fit of a Cox's hazard regression model adjusted with all the covariates mentioned above.

To evaluate the balance in baseline characteristics in the dataset used for different regression models, we calculated the standardized mean differences, and values less than 0.1 were considered negligible differences. First, we applied a 1:1 case-control matching to the PS technique, which is the eighth digit to first digit greedy matching method [27]. method may result in a drop-out of unmatched cases for the best matching. detail on subjects in the matching analyses for MetS, abnormal TG levels, hypertension, obesity, abnormal high-density lipoprotein cholesterol levels, and abnormal fasting blood sugar levels was shown in supplementary method 2. Second, we performed weighted Cox's hazard regression models that were considered for an adjusted MetS effect after stratifying into 5 strata according to the quintiles of the estimated PS [28]. Additionally, a Cox's hazard regression model that used the PS as a covariate (a continuous variable and a categorical variable by quintiles) was a simple PS method similar to traditional regression analysis. Lastly, there are two major PS weighting methods referred to as standardization methods that depend on the establishment of a standard population. One is the inverse probability-of-treatment weighted (IPTW) model [29]. It considers the overall study participants as the standard population, and it uses weights of (1/PS) for those with MetS and [1/(1-PS)] for those without MetS. The other is the standardized mortality ratio weighted (SMRW) model. It regards those without MetS as the standard population and applies weights of 1 for those with MetS and [PS/(1-PS)] for those without MetS.

Statistical analyses were carried out using SAS software, version 9.3 (SAS Institute, Cary, NC, USA) and R version 3.4.3 using the 'tableone' package [30] and were two-sided, with a significance level of $p < 0.05$.

Results

In total, 2,417 men and 4,568 women were included in this study (Figure 1). Table 1 shows the baseline characteristics of the study population. Among the study subjects, there were 57 men and 54 women newly diagnosed CRC after the entry of this cohort and their median follow-up years were 4.76 (IQR, 2.91-7.79) for men and 5.55 (IQR, 3.06-7.53) for women, respectively. The mean age of the study subjects was approximately 60 years old (data not shown), which is older than the general Korean population. CRC cases were significantly older than non-cancer controls. In men, alcohol consumption was higher in CRC cases, i.e., there was a high percentage of non-drinkers in non-cancer controls. On the other hand, CRC cases for women took in more beef or pork per week than non-cancer controls. In this study, 524 men (21.7%) and 1,297 (28.4%) women had at least three components of MetS at the entry of a cohort.

Table 1. Baseline Characteristics of Study Participants

Characteristics	Men			Women		
	Colorectal cancer		P-value	Colorectal cancer		P-value
	No (N=2,360)	Yes (N=57)		No (N=4,514)	Yes (N=54)	
Follow-up (years, Median (IQR))	10.43 (8.5-12.48)	4.76 (2.91-7.79)	<0.001	10.44 (9.48-12.88)	5.55 (3.06-7.53)	<0.001
Age (years, Mean±SD)	59.66±10.93	64.18±8.67	0.002	59.95±11.2	64.72±9.19	0.001
Physical activity (days/week, Mean±SD)	3.97±2.86	4.26±2.7	0.754	2.99±2.96	3.2±3.02	0.60
Intake of fruits or vegetables (days/week, Mean±SD)	5.43±1.44	5.19±1.57	0.28	5.51±1.46	5.04±1.8	0.073
Intake of beef or pork (days/week, Mean±SD)	2.55±1.4	2.44±1.49	0.732	1.75±1.33	1.31±1.33	0.012
Alcohol consumption [N(%)]						
Non-drinkers	640 (27.12)	7 (12.28)	0.03	3,598 (79.71)	45 (83.33)	0.796
Moderate drinkers (<24 g/day)	797 (33.77)	26 (45.61)		797 (17.66)	8 (14.81)	
Heavy drinkers (≥24 g/day)	923 (39.11)	24 (42.11)		119 (2.64)	1 (1.85)	
Smoking status [N(%)]						
Non-smokers	483 (20.47)	12 (21.05)	0.952	4,186 (92.73)	52 (96.3)	0.894
Moderate smokers (<20 pack-year)	669 (28.35)	17 (29.82)		263 (5.83)	2 (3.7)	
Heavy smokers (≥20 pack-year)	1,208 (51.19)	28 (49.12)		65 (1.44)	0 (0)	
Education level [N(%)]						
Illiterate	222 (9.41)	6 (10.53)	0.448	1,445 (32.01)	24 (44.44)	0.24
Middle school or less	1,443 (61.14)	39 (68.42)		2,505 (55.49)	26 (48.15)	
High school	484 (20.51)	10 (17.54)		438 (9.7)	3 (5.56)	
College or more	211 (8.94)	2 (3.51)		126 (2.79)	1 (1.85)	
Residential area [N(%)]						
Sancheong-gun	1,270 (53.81)	23 (40.35)	0.209	2,380 (52.72)	21 (38.89)	0.072
Changwon-si	485 (20.55)	16 (28.07)		867 (19.21)	13 (24.07)	
Chooncheon-si	167 (7.08)	7 (12.28)		438 (9.7)	3 (5.56)	
Choongjoo-si	281 (11.91)	8 (14.04)		558 (12.36)	11 (20.37)	
Haman-gun	157 (6.65)	3 (5.26)		271 (6)	6 (11.11)	
Metabolic syndrome [N(%)]						
No (No. of components of MetS <3)	1,848 (78.31)	45 (78.95)	0.907	3,243 (71.84)	28 (51.85)	0.001
Yes (No. of components of MetS ≥3)	512 (21.69)	12 (21.05)		1,271 (28.16)	26 (48.15)	
Blood pressure [N(%)]						
SBP <130 mmHg and DBP <85 mmHg	996 (42.2)	21 (36.84)	0.418	2,017 (44.68)	19 (35.19)	0.163
SBP ≥130 mmHg or DBP ≥85 mmHg	1,364 (57.8)	36 (63.16)		2,497 (55.32)	35 (64.81)	
BMI [N(%)]						
<25 kg/m ²	1,667 (70.64)	40 (70.18)	0.94	2,840 (62.92)	33 (61.11)	0.785
≥25 kg/m ²	693 (29.36)	17 (29.82)		1,674 (37.08)	21 (38.89)	
HDL cholesterol [N(%)]						
≥40 mg/dL for men, ≥50 mg/dL for women	1,913 (81.06)	54 (94.74)	0.009	2,309 (51.15)	26 (48.15)	0.661
<40 mg/dL for men, <50 mg/dL for women	447 (18.94)	3 (5.26)		2,205 (48.85)	28 (51.85)	
Triglyceride level [N(%)]						
<150 mg/dL	1,552 (65.76)	40 (70.18)	0.488	3,148 (69.74)	27 (50)	0.002
≥150 mg/dL	808 (34.24)	17 (29.82)		1,366 (30.26)	27 (50)	
FBS [N(%)]						
<110 mg/dL	2,047 (86.74)	46 (80.7)	0.186	4,042 (89.54)	49 (90.74)	0.775
≥110 mg/dL	313 (13.26)	11 (19.3)		472 (10.46)	5 (9.26)	

IQR, interquartile range; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HDL, high-density lipoproteins; FBS, fasting blood sugar.

Tables 2, 3 and Figure S1~S4 show participants' characteristics according to the presence of MetS and abnormal TG levels as well as the degree of imbalance among covariates. A statistically negligible difference in covariates was found in the following datasets: the matched, stratified, and IPTW datasets for MetS and abnormal TG levels in men; the matched, and IPTW datasets for MetS in women; the matched, stratified and IPTW datasets for increased TG level in women.

Table 2. Comparison of baseline characteristics according to metabolic syndrome and abnormal triglyceride (TG) levels and differences in baseline characteristics with different propensity score-based methods in men

Characteristics	Metabolic syndrome (N)		Standardized mean differences ^{a)} (N)					Abnormal TG levels (N)		Standardized mean differences ^{a)} (N)				
	No (1,893)	Yes (524)	Crude (2,417)	Matched (1,038)	Strata5 (2,402)	IPTW (2,417)	SMRW (2,417)	No (1,592)	Yes (825)	Crude (2,417)	Matched (1,038)	Strata5 (2,402)	IPTW (2,417)	SMRW (2,417)
Age [years, Mean (SD)]	60.31 (11.03)	57.80 (10.17)	0.237	0.032	<0.001	0.029	0.385	60.58 (11.18)	58.19 (10.15)	0.224	0.006	0.021	0.007	0.308
Physical activity [days/week, Mean (SD)]	4.09 (2.84)	3.59 (2.88)	0.175	0.019	0.019	0.019	0.267	4.01 (2.85)	3.92 (2.88)	0.243	0.037	0.020	0.018	0.331
Intake of fruits or vegetables [days/week, Mean (SD)]	5.47 (1.42)	5.24 (1.48)	0.164	0.041	0.011	0.002	0.253	5.46 (1.42)	5.36 (1.48)	0.123	0.024	0.029	0.013	0.164
Intake of beef or pork [days/week, Mean (SD)]	2.52 (1.42)	2.62 (1.31)	0.073	0.052	0.003	0.005	0.127	2.51 (1.40)	2.62 (1.38)	0.030	0.013	0.020	0.010	0.034
Alcohol consumption [N(%)]														
Non-drinkers	525 (27.7)	122 (23.3)	0.105	0.029	0.007	0.031	0.182	469 (29.46)	178 (21.58)	0.071	0.013	0.008	0.004	0.091
Moderate drinkers (<24 g/day)	640 (33.8)	183 (34.9)						560 (35.18)	263 (31.88)					
Heavy drinkers (≥24 g/day)	728 (38.5)	219 (41.8)						563 (35.36)	384 (46.55)					
Smoking status [N(%)]														
Non-smokers	381 (20.1)	114 (21.8)	0.092	0.042	0.008	0.031	0.161	338 (21.23)	157 (19.03)	0.078	0.038	0.004	0.012	0.113
Moderate smokers (<20 pack-year)	554 (29.3)	132 (25.2)						473 (29.71)	213 (25.82)					
Heavy smokers (≥20 pack-year)	958 (50.6)	278 (53.1)						781 (49.06)	455 (55.15)					
Education level [N(%)]														
Illiterate	194 (10.2)	34 (6.5)	0.211	0.049	0.016	0.029	0.337	165 (10.36)	63 (7.64)	0.118	0.017	0.011	0.014	0.168
Middle school or less	1180 (62.3)	302 (57.6)						978 (61.43)	504 (61.09)					
High school	359 (19.0)	135 (25.8)						307 (19.28)	187 (22.67)					
College or more	160 (8.5)	53 (10.1)						142 (8.92)	71 (8.61)					
Residential area [N(%)]														
Sancheong-gun	1046 (55.3)	247 (47.1)	0.312	0.027	0.068	0.011	0.448	867 (54.46)	426 (51.64)	0.141	0.030	0.005	0.012	0.185
Changwon-si	410 (21.7)	91 (17.4)						340 (21.36)	161 (19.52)					
Chooncheon-si	130 (6.9)	44 (8.4)						109 (6.85)	65 (7.88)					
Choongjoo-si	185 (9.8)	104 (19.8)						167 (10.49)	122 (14.79)					
Haman-gun	122 (6.4)	38 (7.3)						109 (6.85)	51 (6.18)					

SD, standard deviation; Crude, whole dataset; Matched, 1:1 matched dataset; Strata5, dataset stratified with 5 strata; IPTW, inverse probability-of-treatment weighted dataset; SMRW, standardized mortality ratio weighted dataset. ^{a)}The values highlighted in bold are significant imbalances according to metabolic syndrome (standardized mean differences > 0.1).

Table 3. Comparison of baseline characteristics according to metabolic syndrome and abnormal triglyceride (TG) levels and differences in baseline characteristics with different propensity score-based methods in women

Characteristics	Metabolic syndrome (N)		Standardized mean differences ^{a)} (N)					Abnormal TG levels (N)		Standardized mean differences ^{a)} (N)				
	No (3,271)	Yes (1,397)	Crude (4,568)	Matched (2,580)	Strata5 (4,558)	IPTW (4,568)	SMRW (4,568)	No (3,175)	Yes (1,393)	Crude (4,568)	Matched (2,786)	Strata5 (4,554)	IPTW (4,568)	SMRW (4,568)
Age [years, Mean (SD)]	59.38 (11.72)	61.59 (9.54)	0.206	0.016	0.039	0.036	0.428	59.09 (11.74)	62.10 (9.47)	0.282	0.008	0.021	0.021	0.472
Physical activity [days/week, Mean (SD)]	3.13 (2.96)	2.65 (2.92)	0.164	0.02	0.001	0.006	0.199	3.08 (2.96)	2.78 (2.94)	0.102	0.042	0.017	0.003	0.121
Intake of fruits or vegetables [days/week, Mean (SD)]	5.55 (1.43)	5.37 (1.53)	0.127	0.004	0.002	0.004	0.173	5.51 (1.45)	5.48 (1.50)	0.021	0.011	0.011	0.008	0.028
Intake of beef or pork [days/week, Mean (SD)]	1.77 (1.34)	1.67 (1.31)	0.071	0.029	0.029	0.007	0.166	1.81 (1.34)	1.60 (1.31)	0.158	0.021	0.006	0.005	0.263
Alcohol consumption [N(%)]														
Non-drinkers	2560 (78.3)	1083 (83.5)	0.137	0.027	0.011	0.007	0.255	2473 (77.9)	1170 (84.0)	0.156	0.017	0.008	0.009	0.261
Moderate drinkers (<24 g/day)	615 (18.8)	190 (14.6)						612 (19.3)	193 (13.9)					
Heavy drinkers (≥24 g/day)	96 (	24 (						90 (	30 (					
	2.9)	1.9)						2.8)	2.2)					
Smoking status [N(%)]														
Non-smokers	3028 (92.6)	1210 (93.3)	0.034	0.016	0.011	0.008	0.056	2958 (93.2)	1280 (91.9)	0.059	0.037	0.016	0.004	0.084
Moderate smokers (<20 pack-year)	197 (	68 (						178 (	87 (					
	6.0)	5.2)						5.6)	6.2)					
Heavy smokers (≥20 pack-year)	46 (	19 (						39 (	26 (					
	1.4)	1.5)						1.2)	1.9)					
Education level [N(%)]														
Illiterate	1040 (31.8)	429 (33.1)	0.263	0.056	0.111	0.023	0.534	993 (31.3)	476 (34.2)	0.246	0.034	0.052	0.012	0.441
Middle school or less	1757 (53.7)	774 (59.7)						1716 (54.0)	815 (58.5)					
High school	356 (10.9)	85 (						354 (11.1)	87 (					
		6.6)							6.2)					
College or more	118 (	9 (						112 (	15 (					
	3.6)	0.7)						3.5)	1.1)					
Residential area [N(%)]														
Sancheong-gun	1830 (55.9)	571 (44.0)	0.348	0.018	0.078	0.01	0.459	1724 (54.3)	677 (48.6)	0.159	0.031	0.057	0.007	0.214
Changwon-si	653 (20.0)	227 (17.5)						619 (19.5)	261 (18.7)					
Chooncheon-si	304 (	137 (10.6)						291 (	150 (10.8)					
	9.3)							9.2)						
Choongjoo-si	311 (	258 (19.9)						351 (11.1)	218 (15.6)					
	9.5)													
Haman-gun	173 (	104 (						190 (	87 (					
	5.3)	8.0)						6.0)	6.2)					

SD, standard deviation; Crude, whole dataset; Matched, 1:1 matched dataset; Strata5, dataset stratified with 5 strata; IPTW, inverse probability-of-treatment weighted dataset; SMRW, standardized mortality ratio weighted dataset. ^{a)}The values highlighted in bold are significant imbalances according to metabolic syndrome (standardized mean differences > 0.1).

Table 4 showed the associations of MetS and abnormal TG levels on CRC risk according to various analytical methods. In women, unadjusted and adjusted HRs between abnormal MetS and CRC risk were 2.33 (95% CI: 1.37, 3.97) and 2.12 (95% CI: 1.22, 3.68), respectively. The HR from the PS 1:1 matching analysis was 2.19 (95% CI: 1.10, 4.33) and that from the IPTW analysis was 2.03 (95% CI: 1.40, 2.95). Besides, unadjusted and adjusted HRs between abnormal TG levels and CRC were 2.27 (95% CI: 1.33, 3.87) and 2.06 (95% CI: 1.20, 3.55), respectively. The HRs from the PS 1:1 matched, stratified, and IPTW datasets were 2.08 (95% CI: 1.07, 4.02), 2.26 (95% CI: 1.32, 3.84), and 1.98 (95% CI: 1.36, 2.89), respectively. On the other hand, in men, all associations between MetS and abnormal TG levels and CRC risk were not significant.

Additionally, associations between 4 metabolic components except abnormal TG levels (i.e., hypertension, obesity, abnormal high-density lipoprotein cholesterol levels, and abnormal fasting blood sugar levels) and CRC risk are summarized in Table S1. In women, All HRs between

4 metabolic components (hypertension, obesity, abnormal high-density lipoprotein cholesterol levels, and abnormal fasting blood sugar levels) and CRC risk according to were not consistently significant by various analyses. On the other hand, in men, only abnormal high-density lipoprotein cholesterol levels had a significant inverse association with CRC risk.

Besides, when associations between metabolic syndrome and the incidence of (a) colon cancer and (b) rectum cancer were evaluated, in women, there was an association between metabolic syndrome and rectum cancer (Table S2). The HRs from the PS 1:1 matched and IPTW datasets were 3.67 (95% CI: 1.03, 13.17) and 3.29 (95% CI: 1.29, 8.36), respectively, which were the only HRs estimated from datasets with balanced covariates (the degree of imbalance among covariates was not shown).

Table 4. Association between (a) Metabolic Syndrome, (b) Triglyceride Level and Colorectal Cancer risk

Methods	Total				Men				Women			
	Cases (N)	Controls (N)	HR (95% CI)	P-value	Cases (N)	Controls (N)	HR (95% CI)	P-value	Cases (N)	Controls (N)	HR (95% CI)	P-value
(a) Metabolic syndrome												
General Cox's hazard regression												
Unadjusted	111	6,874	1.46 (0.99, 2.16)	0.060	57	2,360	0.94 (0.50, 1.78)	0.856	54	4,514	2.33 (1.37, 3.97)	0.002
Multivariable ^{a)}	111	6,874	1.55 (1.04, 2.33)	0.033	57	2,360	1.04 (0.54, 1.99)	0.908	54	4,514	2.12 (1.22, 3.68)	0.008
PS-based Cox's hazard regression												
Matched for PS	67	3,573	1.32 (0.81, 2.13)	0.266	25	1,013	0.93 (0.42, 2.03)	0.847	38	2,542	2.19 (1.10, 4.33)	0.025
Stratification into 5 strata by PS	111	6,862	1.48 (1.00, 2.19)	0.050	57	2,345	1.06 (0.56, 2.02)	0.859	53	4,505	2.23 (1.32, 3.77)	0.003
Regression adjusted with PS												
as a continuous term	111	6,874	1.45 (0.97, 2.16)	0.071	57	2,360	1.05 (0.55, 2.01)	0.878	54	4,514	2.03 (1.17, 3.53)	0.012
as a quintile term	111	6,874	1.48 (0.99, 2.22)	0.054	57	2,360	1.02 (0.54, 1.95)	0.947	54	4,514	2.07 (1.20, 3.58)	0.009
Weighted models												
IPTW model	111	6,874	1.43 (1.11, 1.85)	0.007	57	2,360	1.06 (0.73, 1.52)	0.772	54	4,514	2.03 (1.40, 2.95)	<0.001
SMRW model	111	6,874	1.44 (1.04, 2.01)	0.031	57	2,360	0.92 (0.52, 1.64)	0.780	54	4,514	2.48 (1.63, 3.75)	<0.001
(b) Triglyceride level												
General Cox's hazard regression												
Unadjusted	111	6874	1.39 (0.95, 2.03)	0.090	57	2,360	0.79 (0.45, 1.39)	0.416	54	4,514	2.27 (1.33, 3.87)	0.003
Multivariable ^{a)}	111	6874	1.33 (0.91, 1.95)	0.145	57	2,360	0.84 (0.47, 1.5)	0.557	54	4,514	2.06 (1.2, 3.55)	0.009
PS-based Cox's hazard regression												
Matched for PS	76	4360	1.36 (0.86, 2.14)	0.191	32	1,606	1.11 (0.55, 2.21)	0.777	40	2,746	2.08 (1.07, 4.02)	0.031
Stratification into 5 strata by PS	111	6866	1.3 (0.89, 1.9)	0.168	57	2,354	0.82 (0.47, 1.45)	0.498	53	4,501	2.26 (1.32, 3.84)	0.003
Regression adjusted with PS												
as a continuous term	111	6874	1.28 (0.87, 1.88)	0.210	57	2,360	0.85 (0.48, 1.51)	0.570	54	4,514	2.02 (1.18, 3.48)	0.011
as a quintile term	111	6874	1.28 (0.87, 1.88)	0.202	57	2,360	0.82 (0.46, 1.46)	0.504	54	4,514	2.03 (1.18, 3.50)	0.010
Weighted models												
IPTW model	111	6874	1.28 (0.99, 1.66)	0.063	57	2,360	0.85 (0.58, 1.23)	0.380	54	4,514	1.98 (1.36, 2.89)	<0.001
SMRW model	111	6874	1.44 (1.05, 1.97)	0.025	57	2,360	0.79 (0.48, 1.30)	0.350	54	4,514	2.42 (1.6, 3.66)	<0.001

HR, hazard ratio; CI, confidence interval; PS, propensity score; IPTW, inverse probability-of-treatment weighted; SMRW, standardized mortality ratio weighted. ^{a)}Adjusted by age, sex (in case of total) education, smoking status, alcohol consumption, physical activity, frequency of intake of fruits or vegetables, frequency of intake of red meats, and residential area.

Discussion

To the best of our knowledge, our study is the first cohort study using PS-based methods to examine the effect of MetS on CRC incidence for both sexes in the Asian population. In this community-based cohort study in the Republic of Korea, we found an increased risk of CRC in women associated with MetS and abnormal TG level in both traditional Cox's hazard regression and PS methods. In women, both MetS and

abnormal TG level were associated with an approximately 2.0-fold to 2.5-fold and increased risk of CRC. However, we showed that there was no significant association between MetS and abnormal TG level and CRC risk in men no matter which analytic methods we performed.

As previously known, there are its pros and cons according to PS methods, which may lead to poor performance with few outcome events (stratification), drop-out of unmatched cases for the best matching (PS matching), and imprecise estimates of treatment effect (IPTW) etc. [24]. The meaningful findings of this study are consistent and have similar strengths of associations regardless of PS-based methods, although various methodologies were applied in statistical analysis. Thus, this study provides the strong evidence on relationship between MetS and abnormal TG level and CRC risk. However, it seems that previous research findings were inconsistent: A meta-analysis reported that there was a significant association between MetS and CRC in both sexes in cohort studies across populations including the United States, European, Asian, and other populations (RR for men, 1.25 [95% CI, 1.19, 1.32]; RR for women, 1.34, [95% CI, 1.09, 1.64]) [2]. In another meta-analysis, the results in cohort studies across populations showed that men with MetS had a significantly elevated risk on CRC, but women with MetS did not [4]. However, in the United States, a cohort study that examined for postmenopausal women showed a similar risk level to ours (HR, 2.15; 95% CI, 1.30, 3.53) [31]; the subsequent study recruited more participants but reported non-significant lower risks (HR, 1.16; 95% CI, 0.95-1.41) [32].

To discuss the association between MetS and CRC for the Asian population, two previous meta-analyses reported results using a couple of cohort studies for the Asian population: One showed that there was no association in cohort studies (RR for men, 1.10 [95% CI, 0.80, 1.51]; RR for women, 1.02, [95% CI, 0.76, 1.36]) [2]. Another also found that RRs for men and women were non-significant (RR for men, 1.23 [95% CI, 0.80, 1.88]; RR for women, 1.12, [95% CI, 0.86, 1.48]) [4]. In the case of the Republic of Korea, there were prior cohort studies about this association. Of these two studies using colon or colorectal adenoma risks as outcomes, one reported no association, but the other showed an association (adjusted HR, 1.28; 95% CI, 1.09-1.51) [6, 7]. The subjects of these cohort studies underwent colonoscopy for a health examination in a large hospital and could, therefore, be generally regarded as individuals who are interested in the prevention of future disease and the pursuit of a healthy lifestyle. Two studies using the National Health Insurance Service–National Sample Cohort to represent the Korean population reported somewhat conflicting results: One found only a significantly increased risk of colon cancer, not rectum cancer, for men with MetS (HR, 1.40 [95% CI, 1.14, 1.71]) , but did not find significant colon or rectum cancer risks for women [5]; the other found that MetS was associated with the development of CRC in both sexes (HR for men, 1.41 [95% CI, 1.37, 1.44]; HR for women, 1.23 [95% CI, 1.20, 1.27]) [33]. Our finding seems to be slightly different from previous studies above, as we have estimated using PS-based methods and study subjects of our study were just community residents. Thus, we expect that this study might contribute to providing additional evidence that there is the association between MetS and an elevated risk of CRC in the Asian population and future large cohort studies using PS-based methods could provide more definitive evidence.

In addition, our study showed that abnormal TG levels were associated with CRC risk in women. However, a previous review and meta-analysis reported that TG was not related to the risk of CRC [4]. Cohort studies in the United States and Japan also arrived at similar conclusions [31, 34]. In the Republic of Korea, previous cohort studies showed the HRs of colorectal adenoma to be 1.19 (95% CI, 1.03, 1.37) and 0.76 (95% CI, 0.45, 1.27) [6, 7] and the HR of CRC to be 1.15 (95% CI, 1.07, 1.23) [33]. Future studies are recommended as it remains controversial whether the risk of CRC or colorectal adenoma is elevated when individuals' levels of TG are 150 mg/dL or higher.

As is well known, MetS is widely known as a risk factor for CRC, but the biological mechanism underlying this association remains to be clarified. Insulin resistance, systemic inflammation, and oxidative stress, and higher leptin levels have been suggested as potential mechanisms that may explain the association between MetS and CRC [3]. Insulin increases cell proliferation and reduces apoptosis, which may lead to tumor development. Insulin also induces the overstimulation of receptors of insulin-like growth factor-1 and 2 (IGF-1 and IGF-2), a key promoter of tumor development. Besides, deteriorated metabolic status influences elevated levels of inflammatory cytokines such as interleukin 6 (IL-6), tumor necrosis factor alpha (TNF- α), C-reactive protein (CRP), and leptin hormone, which may be implicated in insulin resistance and tumor development. Further studies are required to elucidate the mechanism underlying the effect of each component of MetS on CRC.

The strengths of this study include its prospective nature (i.e., cohort design), the strong causality between MetS and CRC by using PS-based methods. The selection biases that are present in most observational studies may lead to a lack of causality in this study. To improve the causality between MetS and CRC incidence, we performed PS-based analyses in a community-based cohort. A major advantage of using PS-based methods in observational studies can minimize selection biases by balancing nonrandomized individuals' data to reach the level of causality determined by randomized controlled trials. Recently, there have been some well-designed studies that have revealed associations between MetS and non-communicable diseases, including cancers, using PS-based analyses [35, 36].

There were several limitations to this study. First, we could not observe the following confounders: the history of MetS before cohort entry, individuals' stressful events, menopause, the consumption of carbohydrate and starchy foods, etc. In addition, there is the possibility of information bias due to the use of a self-reported questionnaire. Second, we measured MetS only at the entry of this cohort study, so we could

not estimate the risk of CRC due to changes in MetS over time. Third, we used BMI as a measure of abdominal obesity of MetS due to the absence of WC data, although BMI and WC have slightly difference in the pathological meaning of MetS. Lastly, this study had limited statistical power due to the relatively small study sample. We found association between MetS and rectum cancer in women. However, due to few rectum cancer cases, HRs by general regression methods and PS-based methods were significant but these CIs were quite wide. Thus, studies with larger sample sizes are needed to improve the statistical validation of the findings.

Conclusion

In conclusion, this study may provide additional evidence that deteriorated metabolic profiles increase the risk of CRC in women. We highlight the importance of effective population-level interventions for deteriorated metabolic profiles at the early stages.

List Of Abbreviations

BMI: body mass index, CI: confidence interval, CRC: colorectal cancer, DBP: diastolic blood pressure, FBS: fasting blood sugar, HDL: high-density lipoprotein, HR: hazard risk, IPTW: inverse probability-of-treatment weighted, MetS: metabolic syndrome, PS: propensity score, SBP: systolic blood pressure, SMRW: standardized mortality ratio weighted, TG: triglyceride, WC: waist circumference

Declarations

Ethics approval and consent to participate

The study was approved by the KNCC Institutional Review Board (IRB No. NCC2016-0300). All participants had provided written informed consent.

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare no potential conflicts of interest.

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Authors' contributions

*All authors have read and approved the manuscript.

EYP contributed to conceptualization and methodology of this study and helped in writing the manuscript. JK drafted the manuscript and performed the statistical analysis. EP and BK contributed to the statistical analysis and interpretation of the results. MKL involved in the design and coordination of the study. JKO involved in data collection in the field and questionnaire design.

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Figures

Figure 1

Flow Diagram of the Derivation of the Study Population.

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