Original Article

J Prev Med Public Health 2016;49:143-152 • http://dx.doi.org/10.3961/jpmph.16.021

pISSN 1975-8375 eISSN 2233-4521

Journal of Preventive Medicine & Public Health

Metabolic Risk Profile and Cancer in Korean Men and Women

Seulki Ko[1], Seok-Jun Yoon[1], Dongwoo Kim[1], A-Rim Kim[2], Eun-Jung Kim[3]*, Hye-Young Seo[2]

[1]Department of Preventive Medicine, Korea University College of Medicine, Seoul; [2]Department of Public Health, Graduate School of Korea University, Seoul; [3]Department of Economics, Economic Research Institute, Korea University, Seoul, Korea

Objectives: Metabolic syndrome is a cluster of risk factors for type 2 diabetes mellitus and cardiovascular disease. Associations between metabolic syndrome and several types of cancer have recently been documented.

Methods: We analyzed the sample cohort data from the Korean National Health Insurance Service from 2002, with a follow-up period extending to 2013. The cohort data included 99 565 individuals who participated in the health examination program and whose data were therefore present in the cohort database. The metabolic risk profile of each participant was assessed based on obesity, high serum glucose and total cholesterol levels, and high blood pressure. The occurrence of cancer was identified using Korean National Health Insurance claims data. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models, adjusting for age group, smoking status, alcohol intake, and regular exercise.

Results: A total of 5937 cases of cancer occurred during a mean follow-up period of 10.4 years. In men with a high-risk metabolic profile, the risk of colon cancer was elevated (HR, 1.40; 95% CI, 1.14 to 1.71). In women, a high-risk metabolic profile was associated with a significantly increased risk of gallbladder and biliary tract cancer (HR, 2.05; 95% CI, 1.24 to 3.42). Non-significantly increased risks were observed in men for pharynx, larynx, rectum, and kidney cancer, and in women for colon, liver, breast, and ovarian cancer.

Conclusions: The findings of this study support the previously suggested association between metabolic syndrome and the risk of several cancers. A high-risk metabolic profile may be an important risk factor for colon cancer in Korean men and gallbladder and biliary tract cancer in Korean women.

Key words: Metabolic syndrome, Risk factors, Neoplasms, Cohort studies

INTRODUCTION

Metabolic syndrome is defined as a cluster of risk factor for type 2 diabetes mellitus and cardiovascular disease [1,2]. Its components are abdominal obesity, insulin resistance, dyslipidemia, and hypertension, and each factor is related with unhealthy life-styles [3]. Despite its obvious importance as a risk cluster of several diseases, the definition of metabolic syndrome has been the source of constant controversy. Many organizations—the World Health Organization, the European Group for the Study of Insulin Resistance, the National Cholesterol Education Program Adult Treatment Panel III (NCEP-AT-

Received: February 22, 2016 Accepted: April 5, 2016

Corresponding author: Seok-Jun Yoon, MD, PhD
73 Inchon-ro, Seongbuk-gu, Seoul 02841, Korea
Tel: +82-2-2286-1412, Fax: +82-2-927-7220
E-mail: yoonsj02@korea.ac.kr

*Current affiliation: Department of Nursing, Pyeongtaek University, Pyeongtaek, Korea

PIII), the American Association of Clinical Endocrinology, the International Diabetes Federation (IDF), and the American Heart Association/National Heart, Lung, and Blood Institute—have defined metabolic syndrome using fundamentally similar components, but with different parameters and cut-off points [4,5]. Although studies have employed different criteria to define metabolic syndrome when studying different populations, most studies have found that the prevalence of metabolic syndrome is increasing worldwide [6-8]. In Korea, the prevalence of metabolic syndrome markedly increased from 24.9% in 1998 to 31.3% in 2007 [7].

Interestingly, recent studies have shown associations between metabolic syndrome and the risk of several cancers, including liver, colorectal, bladder, and renal cancer in men [9-12], and endometrial, postmenopausal breast, pancreatic, and colorectal cancer in women [9,10,12,13]. Although the above findings were reported in meta-analyses, few studies have assessed Asian populations, and those that have done so have mostly been Japanese and Chinese studies [14,15]. In Korea, several studies have investigated associations of the risk of site-specific cancers with body mass index (BMI), fasting serum glucose levels, and total cholesterol levels [16-18], but it is hard to find a study explored relationships between an integrated measure of metabolic risk factors and diverse site-specific cancers. One study that used health examination data from a single hospital analyzed metabolic syndrome and total cancer-related mortality in Korean men and women [19], whereas previous studies have shown different levels of risk for site-specific types of cancer to be related with metabolic syndrome [9].

The aim of this study was to determine whether clusters of metabolic risk factors were related to several types of cancer in Korean men and women. We conducted a retrospective cohort study with approximately 100 000 participants from the Korean National Health Insurance Service (KNHIS) national sample cohort data. In this article, we report the associations of metabolic risk profiles and site-specific cancers among the Korean population.

METHODS

Study Population and Data Collection

We analyzed the KNHIS national sample cohort data originating from the National Health Information database established by the KNHIS in 2011. These cohort data were drawn from approximately 1 000 000 individuals, comprising 2.2% of the total Korean population, extracted by sampling from the 2002 records of the National Health Information database [20]. These data include insurance status, socioeconomic status, the utilization of health care services, and KNHIS biannual health examination data for eligible participants from 2002 to 2013.

A total of 113 641 individuals were included in the KNHIS national sample cohort and received a KNHIS health check-up in 2002. Individuals who had lost insurance since 2003 (n=122), were under 20 years of age at the end of 2002 (n=301), had already experienced cancer according to their responses to a self-reported questionnaire in the KNHIS health examination (n=359), and with missing information for anthropometric measurements, laboratory measurements, or a self-reported questionnaire (n=13 294) were excluded. Therefore, a total of 99 565 participants were eligible for this study. Finally, we excluded cancer cases diagnosed during the same year of the health check-up, and consequently the analysis of each site-specific cancer had a different total population number at the starting point of follow-up.

The KNHIS health check-up included anthropometric measurements, laboratory measurements, and a self-reported questionnaire. The standard procedures for this examination are specified in the Framework Act on National Health Examination. Systolic and diastolic blood pressure (mmHg), weight (kg), and height (m) were measured. BMI was calculated as weight divided by height squared (kg/m^2). Fasting glucose and total cholesterol levels (mg/dL) were determined using serum samples. Information about each participant's history of cancer, smoking status, alcohol intake, and exercise habits were collected by self-reported questionnaires. Participants were classified according to smoking status as never, former, or current smokers. Alcohol intake was calculated as alcohol consumed in an average day (g/d) by multiplying the frequency of alcohol consumption (times/mo) and the average drinking volume in one sitting, and categorized into five categories (0, <20, <40, <60, and ≥60 g/d). Whether participants engaged in regular exercise was evaluated in terms of the frequency of exercise (no activity, 1-2, and ≥3 times/wk).

Definitions of Metabolic Risk Profile

Most of the widely used definitions of metabolic syndrome include components reflecting obesity, abnormal serum glucose levels and lipid profiles, and high blood pressure [5]. According to these fundamental components, the criteria for

metabolic risk profile in this study were set using the available anthropometric and laboratory measurements from the KNHIS health check-up data, which were BMI, fasting plasma glucose level, serum total cholesterol level, and blood pressure.

The BMI was used for the component of obesity, and a BMI ≥25 kg/m^2 was regarded as obesity in both sexes in accordance with the recommendations of the International Obesity Task Force and the World Health Organization Regional Office for the Western Pacific Region [21]. The cut-off for a fasting plasma glucose level was ≥100 mg/dL, reflecting the 2003 definition of impaired fasting glucose tolerance by the American Diabetes Association [22]. We also included individuals who had a history of type 2 diabetes together with the subjects who had high fasting serum glucose levels, in order to create a category of participants with dysfunctions of glucose regulation. In many cases, the criteria for dyslipidemia are levels of triglycerides and high-density lipoprotein (HDL) cholesterol [5], but the KNHIS health check-up in 2002 did not collect full lipid profiles. Therefore we chose the serum total cholesterol level as a proxy indicator with a cut-off of ≥200 mg/dL as the borderline-high level. It was defined to be the same as the NCEP-ATPIII borderline-high category of triglycerides (≥150 mg/dL) [23]. Hypertension was defined as a history of hypertension or an elevated measured blood pressure (systolic pressure ≥130 mmHg or diastolic pressure ≥85 mmHg). We defined a high-risk metabolic profile as the presence of three or more of the above criteria.

Follow-up and Outcome Detection

We linked the general information of individuals who met the eligibility criteria from the KNHIS health check-up with each participant's claims data from 2002 to 2013 and checked their insurance status and death during the follow-up period. The endpoint of follow-up was the occurrence of site-specific cancer. Incident cases of cancer were detected using the principal diagnosis and the first additional diagnosis in the claims data. Incident cases were defined as those who had two or more claims in a year with site-specific cancer diagnoses according to the International Classification of Diseases, 10th revision. The event times of individuals who died before the end of follow-up were censored. The follow-up period was from the first day of 2003 until the end of 2013. We did not include the year 2002 in the follow-up period to minimize the likelihood of reverse causation. We did not have exact information regarding the date of each participant's health check-up; therefore, the follow-up time was calculated from the end of 2002.

Statistical Analysis

Basic characteristics are presented using descriptive analysis. Cox proportional hazards models were applied to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between high-risk metabolic profiles and the risk of site-specific cancers. All statistical analyses were stratified by gender. We presented a crude model and an adjusted model including age group, smoking status, alcohol intake, and regular exercise. We also categorized participants according to the number of metabolic risk factors present. Linear trends in HRs according to the number of metabolic risk factors were evaluated using the Wald test. The analysis of each site-specific cancer had a different total number of the population because we excluded cancer cases diagnosed during the same year of the health check-up in a site-specific manner.

We also compared subjects with and without each metabolic risk factor with regard to the cancers related with a high-risk metabolic profile. The first model estimated HRs and 95% CIs adjusted for age group, smoking status, alcohol intake, and regular exercise. The second and third models were additionally adjusted for other metabolic risk factors using categorical and continuous variables.

All statistical tests were two-sided and p-values <0.05 were considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics

This study was approved by the Korea University Ethical Review Board (no. KU-IRB-13-118-A-1). The authors could not identify any participant in the sample cohort data. KNHIS provided data with anonymous identification codes for the included individuals, and especially sensitive medical information of the patients was masked.

RESULTS

Of the 61 758 men and 37 807 women initially included in this cohort, 3680 cancer cases in men and 2257 cancer cases in women were observed over an average follow-up period of 10.4 years. The most prevalent sites of cancer were the stomach (n=781), lung (n=474), liver (n=468), and colon (n=431) in men and the thyroid (n=634), breast (n=359), stomach (n=280), and colon (n=206) in women. Overall, 43.4% of par-

Table 1. Baseline characteristics of study participants according to the presence or absence of a high-risk metabolic profile

Characteristics	Men (n=61 758)		Women (n=37 807)	
	With metabolic risk (n=12 618)	Without metabolic risk (n=49 140)	With metabolic risk (n=5371)	Without metabolic risk (n=32 436)
Age group				
20s	825 (6.5)	7271 (14.8)	115 (2.1)	8107 (25.0)
30s	3464 (27.5)	17 235 (35.1)	183 (3.4)	5786 (17.8)
40s	4008 (31.8)	13 610 (27.7)	1115 (20.8)	9318 (28.7)
50s	2684 (21.3)	6611 (13.5)	1787 (33.3)	4875 (15.0)
≥60s	1637 (13.0)	4413 (9.0)	2171 (40.4)	4350 (13.4)
Body mass index (kg/m^2)	26.3±2.6	23.2±2.7	26.5±3.1	22.2±2.9
Fasting plasma glucose (mg/dL)	111.9±43.8	91.2±25.8	112.6±46.2	88.5±22.9
Serum total cholesterol (mg/dL)	223.6±38.8	186.9±34.4	228.6±36.5	186.5±35.6
Systolic blood pressure (mmHg)	137.0±14.7	122.9±14.7	138.6±17.4	116.9±15.9
Diastolic blood pressure (mmHg)	86.9±10.2	78.0±10.3	85.0±11.1	73.6±10.6
Smoking status				
Never	4992 (39.6)	17 918 (36.5)	5212 (97.0)	31 502 (97.1)
Former	1117 (8.9)	3856 (7.8)	16 (0.3)	141 (0.4)
Current	6509 (51.6)	27 366 (55.7)	143 (2.7)	793 (2.4)
Alcohol intake (g/d)				
0	3114 (24.7)	12 802 (26.1)	4297 (80.0)	21 486 (66.2)
1-19	7220 (57.2)	29 984 (61.0)	1027 (19.1)	10 705 (33.0)
20-39	1565 (12.4)	4474 (9.1)	32 (0.6)	184 (0.6)
40-59	504 (4.0)	1359 (2.8)	11 (0.2)	50 (0.2)
≥60	215 (1.7)	521 (1.1)	4 (0.1)	11 (0.0)
Regular exercise (times/wk)				
0	5683 (45.0)	23 593 (48.0)	3823 (71.2)	23 066 (71.1)
1-2	4520 (35.8)	16 849 (34.3)	758 (14.1)	5490 (16.9)
≥3	2415 (19.1)	8698 (17.7)	790 (14.7)	3880 (12.0)

Values are presented as number (%) or mean±standard deviation.

ticipants had hypertension, 40.2 % had dyslipidemia, 29.9% were obese, and 26.0% had hyperglycemia. No components of the metabolic risk profile were present in 25 584 participants (25.7%), while 30 939 (31.1%) presented one metabolic risk profile component, 25 053 (25.2%) presented two components, 14 119 (14.2%) three components, and 3870 (3.9%) all four components.

The baseline characteristics of the study population by gender divided into those with a high-risk metabolic profile and others are shown in Table 1. Those with a high-risk metabolic profile were older, had a higher BMI, higher fasting plasma glucose, higher serum total cholesterol, and higher blood pressure, and were more likely to be current or former smokers, to consume large amounts of alcohol, and to exercise.

Table 2 shows HRs with 95% CIs for site-specific cancers according to the number of metabolic risk factors and presence of a high-risk metabolic profile. In men, the HR of colon cancer adjusted for age group, smoking status, alcohol intake, and regular exercise was 1.40 (95% CI, 1.14 to 1.71). Non-significantly increased risks were observed for pharynx, rectum, larynx, and kidney cancer. Esophageal cancer had a borderline significant inverse association with the presence of a high-risk metabolic profile (HR, 0.51; 95% CI, 0.25 to 1.04; $p=0.06$). With regard to the number of metabolic risk factors, only colon cancer showed a significant linear trend ($p<0.01$). Women with a high-risk metabolic profile presented a significantly increased risk of gallbladder and biliary tract cancer (HR, 2.05; 95% CI, 1.24 to 3.42) and a significant linear trend for an increasing number of metabolic risk factors ($p<0.05$). Brain cancer in women also showed a significant linear trend ($p<0.05$) and a relatively strong but statistically non-significant association with a high-risk metabolic profile (HR, 1.81; 95% CI, 0.88 to

Table 2. Hazard ratio and 95% confidence interval of site-specific cancer incidence by the number of metabolic risk factors and the presence of a high-risk metabolic profile in Korean during 10.4 years of follow-up in the Korean National Health Insurance Service national sample cohort data

Type of cancer (ICD-10 code)	Cases (n)	Person-years	No. of metabolic risk factors				*p* for trend	Presence of a high-risk metabolic profile[1]	
			1	2	3	4		Crude	Adjusted[2]
Men									
Pharynx (C10-C14)	37	645 641	0.85 (0.31, 2.32)	0.59 (0.20, 1.72)	1.21 (0.44, 3.36)	0.40 (0.05, 3.35)	0.89	1.88 (0.95, 3.74)	1.36 (0.68, 2.73)
Esophagus (C15)	57	645 554	0.64 (0.30, 1.36)	0.68 (0.32, 1.43)	0.36 (0.14, 0.94)	0.37 (0.08, 1.68)	0.05	0.73 (0.36, 1.50)	0.51 (0.25, 1.04)
Stomach (C16)	781	642 645	1.26 (0.99, 1.59)	1.20 (0.94, 1.52)	1.03 (0.79, 1.35)	1.27 (0.89, 1.80)	0.97	1.23 (1.05, 1.45)	0.91 (0.77, 1.08)
Colon (C18-C19)	431	644 188	1.12 (0.80, 1.57)	1.11 (0.79, 1.55)	1.53 (1.09, 2.16)	1.50 (0.96, 2.37)	0.005	1.95 (1.60, 2.38)	1.40 (1.14, 1.71)
Rectum (C20)	247	644 859	0.85 (0.56, 1.29)	0.97 (0.64, 1.45)	1.19 (0.78, 1.82)	0.91 (0.48, 1.73)	0.34	1.68 (1.28, 2.20)	1.22 (0.92, 1.60)
Liver (C22)	468	644 385	1.22 (0.91, 1.65)	1.13 (0.84, 1.53)	1.06 (0.76, 1.47)	1.10 (0.69, 1.76)	0.87	1.22 (0.99, 1.51)	0.93 (0.75, 1.16)
GB and biliary tract (C23-24)	109	645 559	0.99 (0.52, 1.90)	1.02 (0.54, 1.93)	1.08 (0.55, 2.13)	0.81 (0.29, 2.29)	1.00	1.49 (0.98, 2.27)	1.02 (0.67, 1.56)
Pancreas (C25)	122	645 559	1.31 (0.71, 2.42)	1.07 (0.57, 2.01)	1.36 (0.71, 2.60)	1.07 (0.41, 2.79)	0.77	1.51 (1.02, 2.25)	1.12 (0.75, 1.67)
Larynx (C32)	41	645 546	0.69 (0.25, 1.91)	0.78 (0.29, 2.09)	0.96 (0.35, 2.67)	1.06 (0.26, 4.29)	0.70	1.82 (0.94, 3.51)	1.26 (0.65, 2.45)
Lung (C33-C34)	474	644 959	1.29 (0.94, 1.77)	1.22 (0.89, 1.67)	1.21 (0.87, 1.70)	1.05 (0.64, 1.73)	0.83	1.32 (1.07, 1.62)	0.97 (0.79, 1.20)
Prostate (C61)	371	644 179	1.13 (0.78, 1.63)	1.20 (0.84, 1.73)	1.09 (0.74, 1.61)	1.45 (0.89, 2.36)	0.33	1.53 (1.22, 1.92)	1.02 (0.81, 1.28)
Kidney (C64)	87	645 357	1.45 (0.67, 3.11)	1.66 (0.78, 3.54)	1.87 (0.85, 4.13)	0.94 (0.25, 3.51)	0.33	1.49 (0.93, 2.39)	1.15 (0.71, 1.85)
Bladder (C67)	126	645 166	1.61 (0.84, 3.06)	1.59 (0.83, 3.03)	1.34 (0.66, 2.71)	1.31 (0.49, 3.52)	0.79	1.17 (0.77, 1.77)	0.89 (0.59, 1.35)
Brain (C70-C72)	53	645 595	2.08 (0.84, 5.12)	1.02 (0.37, 2.79)	1.78 (0.66, 4.81)	0.56 (0.07, 4.66)	0.75	1.27 (0.68, 2.38)	1.06 (0.56, 1.99)
Thyroid (C73)	276	644 841	1.02 (0.73, 1.42)	0.94 (0.67, 1.33)	0.89 (0.59, 1.34)	0.77 (0.39, 1.51)	0.34	0.91 (0.67, 1.23)	0.88 (0.65, 1.19)
Women									
Stomach (C16)	280	392 084	1.20 (0.84, 1.72)	1.03 (0.70, 1.51)	0.84 (0.54, 1.31)	1.39 (0.81, 2.38)	0.78	1.73 (1.30, 2.29)	0.89 (0.67, 1.19)
Colon (C18-C19)	206	392 480	1.08 (0.69, 1.68)	1.01 (0.63, 1.60)	1.25 (0.77, 2.04)	1.33 (0.70, 2.53)	0.30	2.50 (1.85, 3.38)	1.23 (0.90, 1.68)
Rectum (C20)	124	392 746	1.22 (0.69, 2.14)	1.22 (0.68, 2.18)	1.16 (0.60, 2.21)	0.96 (0.37, 2.50)	0.95	1.86 (1.22, 2.81)	0.94 (0.61, 1.45)
Liver (C22)	120	392 880	0.86 (0.49, 1.53)	0.96 (0.54, 1.71)	1.14 (0.61, 2.11)	0.95 (0.39, 2.32)	0.62	2.40 (1.61, 3.57)	1.18 (0.78, 1.77)
GB and biliary tract (C23-C24)	62	393 210	1.08 (0.41, 2.85)	0.91 (0.34, 2.42)	1.93 (0.75, 4.93)	2.37 (0.80, 7.02)	0.02	5.01 (3.04, 8.26)	2.05 (1.24, 3.42)
Pancreas (C25)	54	393 216	0.69 (0.30, 1.58)	0.64 (0.28, 1.48)	0.77 (0.32, 1.86)	0.62 (0.17, 2.33)	0.57	2.34 (1.29, 4.24)	1.03 (0.56, 1.88)
Lung (C33-C34)	150	392 861	1.19 (0.71, 1.99)	0.76 (0.44, 1.32)	0.87 (0.49, 1.57)	0.93 (0.43, 2.01)	0.28	2.14 (1.48, 3.08)	0.93 (0.64, 1.35)
Breast (C50)	359	391 533	0.75 (0.58, 0.99)	0.75 (0.55, 1.02)	1.07 (0.76, 1.52)	0.87 (0.46, 1.64)	0.76	1.30 (0.99, 1.70)	1.27 (0.95, 1.69)
Cervix (C53)	94	392 660	0.86 (0.49, 1.54)	1.66 (0.94, 2.95)	1.54 (0.75, 3.14)	0.81 (0.19, 3.56)	0.17	1.25 (0.73, 2.13)	1.16 (0.66, 2.06)
Uterus (C54)	52	393 066	1.53 (0.69, 3.37)	1.24 (0.51, 3.03)	1.82 (0.70, 4.71)	1.26 (0.26, 6.06)	0.44	1.82 (0.96, 3.48)	1.31 (0.66, 2.58)
Ovary (C56)	82	392 851	0.68 (0.37, 1.23)	1.31 (0.72, 2.39)	1.17 (0.53, 2.57)	0.44 (0.06, 3.38)	0.72	0.94 (0.50, 1.77)	1.03 (0.53, 2.03)
Brain (C70-C72)	40	393 198	3.05 (0.97, 9.60)	3.24 (0.95, 10.97)	5.70 (1.63, 19.92)	1.80 (0.19, 17.24)	0.04	2.61 (1.33, 5.12)	1.81 (0.88, 3.73)
Thyroid (C73)	634	390 524	1.08 (0.88, 1.32)	1.21 (0.97, 1.52)	0.95 (0.69, 1.29)	1.56 (1.01, 2.41)	0.21	0.91 (0.73, 1.15)	0.97 (0.76, 1.23)

ICD, International Classification of Disease; GB, gallbladder.

[1]Components of metabolic risk profile were defined using the following criteria: (i) obesity, defined as a body mass index ≥25 kg/m^2; (ii) dysfunction of glucose regulation, defined as a fasting glucose level ≥100 mg/dL or a history of type 2 diabetes; (iii) dyslipidemia, defined as a serum total cholesterol level ≥200 mg/dL; (iv) hypertension, defined as blood pressure ≥130/85 mmHg or a history of hypertension.

[2]The Cox proportional hazards model was adjusted for age group, smoking status, alcohol intake, and regular exercise.

Table 3. Hazard ratio and 95% confidence interval of high-risk metabolic profile-related cancers by the presence of each metabolic risk factor

Metabolic risk factor	Model[1]	Model[2]	Model[3]
Colon cancer in men			
Obesity	1.11 (0.91, 1.36)	1.06 (0.86, 1.29)	1.07 (0.87, 1.30)
Hyperglycemia	1.12 (0.92, 1.36)	1.08 (0.89, 1.32)	1.07 (0.88, 1.31)
Dyslipidemia	1.09 (0.90, 1.32)	1.06 (0.87, 1.28)	1.04 (0.86, 1.26)
Hypertension	1.40 (1.14, 1.71)	1.37 (1.12, 1.69)	1.35 (1.10, 1.66)
Gallbladder and biliary cancer in women			
Obesity	1.67 (1.01, 2.75)	1.59 (0.96, 2.65)	1.66 (1.00, 2.77)
Hyperglycemia	1.76 (1.06, 2.91)	1.68 (1.01, 2.80)	1.61 (0.97, 2.70)
Dyslipidemia	1.14 (0.68, 1.90)	1.06 (0.64, 1.78)	1.11 (0.66, 1.86)
Hypertension	1.10 (0.65, 1.86)	0.98 (0.57, 1.66)	0.95 (0.56, 1.63)

[1]Hazard ratios were estimated from the Cox proportional hazards model adjusted for age group, smoking status, alcohol intake, and regular exercise.
[2]Additionally adjusted for other metabolic risk factors by categorical variables.
[3]Additionally adjusted for other metabolic risk factors by continuous variables.

3.73). Colon, liver, breast, and ovarian cancer also had HRs greater than one, but did not show statistically significant associations.

We determined the effect of each metabolic risk factor on high-risk metabolic profile-related cancers. There was no single metabolic factor overwhelming the effect of full metabolic risk profile for colon cancer in men and gallbladder and biliary cancer in women with this study population. Surprisingly, hypertension in men was the sole metabolic risk factor significantly associated with colon cancer (HR, 1.35; 95% CI, 1.10 to 1.66 in model 3, adjusted for other metabolic risk factors using continuous variables). For gallbladder and biliary cancer in women, obesity and hyperglycemia were the factors associated with cancer risk more than other factors, but these associations were weaker than those observed for the full metabolic risk profile within this study (Table 3).

DISCUSSION

This analysis of the KNHIS national sample cohort demonstrated that the presence of a high-risk metabolic profile significantly increased the risk of colon cancer in men and gallbladder and biliary tract cancer in women. Both types of cancer also exhibited a gradient increase in risk with the number of metabolic risk factors. The finding of an increased site-specific cancer risk related with a high-risk metabolic profile is generally consistent with recent studies [9,12,24]. A meta-analysis of the association of colon cancer and metabolic syndrome found a significantly increased risk in men and women (men: relative risk [RR], 1.36; 95% CI, 1.02 to 1.79; women: RR, 1.41; 95% CI, 1.04 to 1.92) [12]. In fact, in our study, the risk of colon cancer in women with a high-risk metabolic profile was not significant, and a Japanese cohort study did not present an appreciably increased risk associated with metabolic syndrome [14]. We were not able to find a cohort study with a Korean population that assessed the association between metabolic syndrome and colon cancer, but several case-control studies have reported significant associations between colorectal adenomas and metabolic syndrome, especially in men [25,26]. The relationship of gallbladder and/or biliary tract cancer with metabolic syndrome has been scarcely studied, although a collaborative study of Metabolic Syndrome and Cancer (Me-can) project showed that an elevated risk of gallbladder cancer was associated with the metabolic syndrome z-score (RR, 1.37; 95% CI, 1.07 to 1.73) [24]. No study of a Korean population has evaluated clusters of metabolic risk factors in association with gallbladder and biliary tract cancer, but an association between obesity defined by BMI and gallbladder cancer was presented by Jee et al. [16].

According to a meta-analysis of metabolic syndrome and the risk of different types of cancer, liver, colorectal, and bladder cancers in men were related to the presence of metabolic syndrome [9]. Our study did not demonstrate a significant association for liver and bladder cancers in men or any other high-risk metabolic profile-related cancers in women. Most meta-analyses of the relationship between metabolic syndrome and cancer risk include few results from Asian populations, and therefore this discrepancy may offer the chance to

consider racial differences in the association between metabolic syndrome and the risk of several site-specific cancers.

The most common form of liver cancer is hepatocellular carcinoma, for which hepatitis B or C infection is the major risk factor. Therefore, additional adjustment for hepatitis B or C infection should be conducted to evaluate the risk of liver cancer more precisely.

For women, elevated risk for endometrial, pancreatic, postmenopausal breast, and colorectal cancers were associated with metabolic syndrome in the 2012 study carried out by Esposito et al. [9]. In our study, the initially enrolled population included fewer women than men and the incident cancer cases were not sufficient to perform an analysis for several site-specific cancers, especially pancreatic (n=54) and uterine (n=52) cancers. A meta-analysis likewise did not show an association between metabolic syndrome and breast cancer in all women (RR, 1.14; 95% CI, 0.98 to 1.32), but the risk was elevated in postmenopausal women with metabolic syndrome (RR, 1.56; 95% CI, 1.08 to 2.24) [9,27]. Another study with a multicenter Italian cohort found an increased breast cancer risk in all women with metabolic syndrome (HR, 1.52; 95% CI, 1.14 to 2.02) and in postmenopausal women with metabolic syndrome (HR, 1.80; 95% CI, 1.22 to 2.65) [28]. Our cohort data did not provide information about menopausal status; therefore, we could not conduct a subgroup analysis, although a non-significant association was found in a simply separated group consisting of women over 50 years of age (HR, 1.28; 95% CI, 0.86 to 1.88).

The biological plausibility of the relation between metabolic syndrome and risk of cancers has been studied in reference to insulin and insulin-like growth factor systems, estrogen, and inflammatory response-related hormones and factors [29]. In particular, for colon cancer, Giovannucci [30] highlighted hyperinsulinemia as a main component among the metabolic risk factors because it mechanistically enhanced concentrations of insulin-like growth factor-1. Mendonca et al. [29] reviewed the mechanisms linked to the pathophysiology of metabolic syndrome and colorectal cancer and pointed out that both obesity and colorectal cancer are related with a chronic subclinical inflammatory condition, dyslipidemia results in elevated bile salts that have a carcinogenic effect on colon cells, and hyperglycemia can provide an energy source for cancer cells because neoplastic cells mainly use glucose. Hypertension is less commonly considered to be a risk factor for colon cancer or adenomas, and recent studies have presented conflicting results [30]. According to our findings, hypertension was the single metabolic factor that significantly increased the risk of colon cancer. To our knowledge, no study has been conducted to evaluate the relationship between hypertension and colon cancer in Korean men, although one Taiwanese cross-sectional study found that patients who had adenomas of the rectosigmoid colon had higher blood pressure than the polyp-free group [31]. According to another Korean population study evaluating isolated metabolic risk factors, individuals who had a BMI $\geq$30 kg/m^2 or a serum total cholesterol $\geq$240 mg/dL had an elevated risk of colon cancer [16,18]. The cut-off points of BMI or serum total cholesterol used in previous studies might be relatively high for this study population, and we therefore need to conduct further studies to confirm the associations of isolated metabolic risk factors and cancer with properly categorized BMI or total cholesterol levels for the same study populations.

The association of metabolic syndrome with gallbladder and/or biliary tract cancer is poorly understood [15,24]. Shebl et al. [15] pointed out that chronic inflammation is considered to be the main biological mechanism relating metabolic syndrome and biliary tract cancer. Interestingly, gallstone disease appears to be associated with metabolic syndrome [32], and both biliary tract cancer and stone formation are related to pathogenesis-linked inflammation and insulin resistance [15]. Our findings from the analysis of isolated metabolic risk factors support those pieces of experimental evidence. Although the statistical significance was slightly different across our models, obese women (BMI $\geq$25 kg/m^2) or women who had dysfunctions of glucose regulation presented elevated risks of gallbladder and biliary tract cancer. Analogously to a previous study of total cholesterol levels in women with gallbladder cancer [18], dyslipidemia did not significantly increase the risk of gallbladder and biliary tract cancer in our study. In the case of gallbladder and biliary tract cancer, the relatively lower incidence rate means that we need more site-specific cancer cases to clarify the effect of each metabolic risk factor and cluster thereof on developing cancers.

The main strength of our study is that examined the risk of each site-specific cancer according to an integrated metabolic risk profile using Korean national cohort data. Several previous studies have separately investigated each component of metabolic syndrome as a risk factor for different types of cancer [16-18] or the relationship between clusters of metabolic risk factors and total cancer-related mortality in the Korean popu-

lation [19]. In this study, we demonstrated the relationship between metabolic risk profiles and colon cancer in Korean men and gallbladder and biliary tract cancer in Korean women.

This study has several limitations. First, instead of commonly used definitions of metabolic syndrome such as the NCEP-ATPIII or IDF definitions, we introduced proxy indicators (i.e., total serum cholesterol level as a proxy indicator for high triglyceride and/or low HDL cholesterol levels and BMI for waist circumference). The working definitions applied in our study might be a concern when comparing our findings with those of other studies, but previous studies have shown consistent association trends with different definitions of metabolic syndrome [9,14]. Furthermore, half of the studies included in a recent meta-analysis of metabolic syndrome and cancer risk had atypical definitions [9] and a representative pooled cohort, the Me-can project, also introduced proxy indicators due to the absence of available data fulfilling the typical criteria of metabolic syndrome [33]. Notwithstanding the limitation imposed by using working definitions, we strictly defined a high-risk metabolic profile as meeting any three or more criteria among four risk factors; as a result, the proportion of individuals who had a high-risk metabolic profile in our study was lower than the prevalence of metabolic syndrome in the Korean population. Further studies using more standard definitions of metabolic syndrome are needed to confirm our findings and ensure comparability.

Second, the KNHIS national sample cohort is linked to claims data and we detected cancer cases using working definition with the claims data, although this kind of setting has already been debated [34]. In our findings, this issue was related with the potential overestimation of incident cases of site-specific cancers. The mean difference between the crude incidence rates in Korean cancer statistics [35] and those within this study was 10.6 per 100 000 men and 12.7 per 100 000 women, although the differences varied considerably among the types of cancer. On one hand, the identification of incidence cases using claims data is sometimes considered inaccurate, but on the other hand, diagnosis codes for cancer may have become more accurate than other disease codes after a special coinsurance rate was applied for cancer patients in Korea in 2005 [36]. Furthermore, we excluded individuals who developed cancer before we started follow-up based on responses in their past medical history self-questionnaires included in the health check-up, meaning that it is possible that we did not exclude all prevalent cancer cases. If we could deal with personal privacy related with Personal Information Protection Act properly, linkage of the Korean Central Cancer Registry with claims data or applying of Expanding Benefit Coverage-related codes to claims data would be helpful in establishing the exact number of incident cases.

Additionally, although we included well-known confounders in this analysis, residual confounding for each site-specific cancer could not be considered because this study had a retrospective cohort design. Since 2009, the KNHIS health check-up database has provided additional information, including waist circumference, serum triglyceride levels, HDL cholesterol levels, and low density lipoprotein cholesterol levels, as well as detailed lifestyle questionnaires [37]. We needed to ensure a sufficiently long follow-up period to detect enough incident cases of each site-specific cancer, and we therefore used KNHIS health check-up data from 2002. Subsequent studies should investigate the associations between metabolic syndrome and site-specific cancers according to the generally accepted definition of metabolic syndrome and performing detailed adjustments using additional variables that reflect the characteristics of each cancer type.

In summary, this study demonstrated that individuals with a high-risk metabolic profile had a significantly elevated risk of colon cancer in men and gallbladder and biliary tract cancer in women. Our analysis may support the presence of different patterns of association between metabolic risk and several site-specific cancers in Korean men and women. These results, if confirmed, will provide additional data about the risk pattern of metabolic syndrome-related cancers in Asian populations and, from a public health perspective, evidence of associations between metabolic syndrome and certain types of cancer may encourage public health interventions for healthy lifestyle.

ACKNOWLEDGEMENTS

This study was supported by a grant from the National R&D Program for Cancer Control, Ministry of Health and Welfare, Korea (grant no. 1320310).

CONFLICT OF INTEREST

The authors have no conflicts of interest associated with the material presented in this paper.

ORCID

Seulki Ko *http://orcid.org/0000-0003-0346-2035*
Seok-Jun Yoon *http://orcid.org/0000-0003-3297-0071*
Dongwoo Kim *http://orcid.org/0000-0001-7731-4081*

REFERENCES

1. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15(7):539-553.
2. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120(16):1640-1645.
3. Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, et al. The metabolic syndrome. Endocr Rev 2008;29 (7):777-822.
4. Cameron AJ, Shaw JE, Zimmet PZ. The metabolic syndrome: prevalence in worldwide populations. Endocrinol Metab Clin North Am 2004;33(2):351-375.
5. Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. BMC Med 2011;9:48.
6. Mozumdar A, Liguori G. Persistent increase of prevalence of metabolic syndrome among U.S. adults: NHANES III to NHANES 1999-2006. Diabetes Care 2011;34(1):216-219.
7. Lim S, Shin H, Song JH, Kwak SH, Kang SM, Yoon JW, et al. Increasing prevalence of metabolic syndrome in Korea: the Korean National Health and Nutrition Examination Survey for 1998-2007. Diabetes Care 2011;34(6):1323-1328.
8. Misra A, Khurana L. Obesity and the metabolic syndrome in developing countries. J Clin Endocrinol Metab 2008;93(11 Suppl 1):S9-S30.
9. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes Care 2012;35(11):2402-2411.
10. Stocks T, Bjørge T, Ulmer H, Manjer J, Häggström C, Nagel G, et al. Metabolic risk score and cancer risk: pooled analysis of seven cohorts. Int J Epidemiol 2015;44(4):1353-1363.
11. Jinjuvadia R, Patel S, Liangpunsakul S. The association between metabolic syndrome and hepatocellular carcinoma: systemic review and meta-analysis. J Clin Gastroenterol 2014; 48(2):172-177.
12. Esposito K, Chiodini P, Capuano A, Bellastella G, Maiorino MI, Rafaniello C, et al. Colorectal cancer association with metabolic syndrome and its components: a systematic review with meta-analysis. Endocrine 2013;44(3):634-647.
13. Bjørge T, Lukanova A, Jonsson H, Tretli S, Ulmer H, Manjer J, et al. Metabolic syndrome and breast cancer in the Me-Can (metabolic syndrome and cancer) project. Cancer Epidemiol Biomarkers Prev 2010;19(7):1737-1745.
14. Osaki Y, Taniguchi S, Tahara A, Okamoto M, Kishimoto T. Metabolic syndrome and incidence of liver and breast cancers in Japan. Cancer Epidemiol 2012;36(2):141-147.
15. Shebl FM, Andreotti G, Meyer TE, Gao YT, Rashid A, Yu K, et al. Metabolic syndrome and insulin resistance in relation to biliary tract cancer and stone risks: a population-based study in Shanghai, China. Br J Cancer 2011;105(9):1424-1429.
16. Jee SH, Yun JE, Park EJ, Cho ER, Park IS, Sull JW, et al. Body mass index and cancer risk in Korean men and women. Int J Cancer 2008;123(8):1892-1896.
17. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. JAMA 2005;293(2):194-202.
18. Kitahara CM, Berrington de González A, Freedman ND, Huxley R, Mok Y, Jee SH, et al. Total cholesterol and cancer risk in a large prospective study in Korea. J Clin Oncol 2011;29(12): 1592-1598.
19. Lee JS, Cho SI, Park HS. Metabolic syndrome and cancer-related mortality among Korean men and women. Ann Oncol 2010;21(3):640-645.
20. Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort profile: the National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. Int J Epidemiol 2016. doi: http://dx.doi.org/10.1093/ije/dyv319.
21. World Health Organization Western Pacific Region. The Asian-Pacific perspective: redefining obesity and its treatment; 2000 [cited 2016 May 11]. Available from: http://www.wpro.who.int/nutrition/documents/docs/Redefiningobesity.pdf.
22. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, et al. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003;26(11):3160-3167.
23. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cho-

lesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106(25):3143-3421.

24. Borena W, Edlinger M, Bjørge T, Häggström C, Lindkvist B, Nagel G, et al. A prospective study on metabolic risk factors and gallbladder cancer in the metabolic syndrome and cancer (Me-Can) collaborative study. PLoS One 2014;9(2):e89368.
25. Kim BC, Shin A, Hong CW, Sohn DK, Han KS, Ryu KH, et al. Association of colorectal adenoma with components of metabolic syndrome. Cancer Causes Control 2012;23(5):727-735.
26. Lee GE, Park HS, Yun KE, Jun SH, Kim HK, Cho SI, et al. Association between BMI and metabolic syndrome and adenomatous colonic polyps in Korean men. Obesity (Silver Spring) 2008;16(6):1434-1439.
27. Esposito K, Chiodini P, Capuano A, Bellastella G, Maiorino MI, Rafaniello C, et al. Metabolic syndrome and postmenopausal breast cancer: systematic review and meta-analysis. Menopause 2013;20(12):1301-1309.
28. Agnoli C, Grioni S, Sieri S, Sacerdote C, Ricceri F, Tumino R, et al. Metabolic syndrome and breast cancer risk: a case-cohort study nested in a multicentre Italian cohort. PLoS One 2015;10(6):e0128891.
29. Mendonça FM, de Sousa FR, Barbosa AL, Martins SC, Araújo RL, Soares R, et al. Metabolic syndrome and risk of cancer: which link? Metabolism 2015;64(2):182-189.
30. Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. Am J Clin Nutr 2007;86(3):s836-s842.
31. Wang YY, Lin SY, Lai WA, Liu PH, Sheu WH. Association between adenomas of rectosigmoid colon and metabolic syndrome features in a Chinese population. J Gastroenterol Hepatol 2005;20(9):1410-1415.
32. Chen LY, Qiao QH, Zhang SC, Chen YH, Chao GQ, Fang LZ. Metabolic syndrome and gallstone disease. World J Gastroenterol 2012;18(31):4215-4220.
33. Stocks T, Borena W, Strohmaier S, Bjørge T, Manjer J, Engeland A, et al. Cohort profile: the metabolic syndrome and cancer project (Me-Can). Int J Epidemiol 2010;39(3):660-667.
34. Song SO, Jung CH, Song YD, Park CY, Kwon HS, Cha BS, et al. Background and data configuration process of a nationwide population-based study using the Korean National Health Insurance System. Diabetes Metab J 2014;38(5):395-403.
35. Jung KW, Won YJ, Kong HJ, Oh CM, Cho H, Lee DH, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2012. Cancer Res Treat 2015;47(2):127-141.
36. Seo HJ, Oh IH, Yoon SJ. A comparison of the cancer incidence rates between the national cancer registry and insurance claims data in Korea. Asian Pac J Cancer Prev 2012;13(12):6163-6168.
37. National Health Insurance Data Sharing Service. DB detail and payment of fee [cited 2016 Mar 21]. Available from: https://nhiss.nhis.or.kr/bd/ab/bdaba006cv.do# (Korean).