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Original Article

Cumulative obesity exposure increases the risk of kidney cancer: a longitudinal nationwide cohort study

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Abstract: Obesity is one of the most important prognostic factors of kidney cancer. However, little is known regarding the cumulative impacts of obesity on kidney cancer risk. We aimed to analyze the dose- and time-dependent impact of obesity on kidney cancer risk using the Korean National Health Insurance System database. This longitudinal nationwide cohort study used data from the Korean National Health Insurance System database between 2012 and 2013. In total, 3,102,240 participants who received annual health examination more than four times consecutively were included in the final analysis. The primary endpoint was newly diagnosed kidney cancer according to the dose- and time-dependent impact of obesity. Dose-dependent impact was measured using body mass index (BMI) and waist circumference (WC), and time-dependent impact was measured using general and abdominal cumulative obesity exposure (gCOE and aCOE). COE was defined as the number of years since obesity diagnosis during the exposure period. We identified 1,831 participants with newly diagnosed kidney cancer (median follow-up: 4.3 years). The hazard ratios (HRs) for kidney cancer increased significantly alongside BMI and WC. The HRs for kidney cancer increased significantly in the higher gCOE groups (*P* for trend <0.001) as follows: 1 (1.33, 95% confidence intervals: 1.10-1.60), 2 (1.33, 1.08-1.63), 3 (1.55, 1.30-1.85), and 4 (1.82, 1.64-2.03) years. Similar trends were observed for aCOE (*P* for trend <0.001) as follows: 1 (1.42, 1.23-1.64), 2 (1.71, 1.46-2.02), 3 (1.76, 1.48-2.08), and 4 (2.11, 1.84-2.42) years. Risks of kidney cancer related to COE were much more pronounced in participants with the following characteristics: younger than 65 years old, male gender, diabetes, hypertension, and dyslipidemia. Longer COE was associated with an increased risk of kidney cancer in the Korean population. Participants with prolonged obesity and metabolic syndrome need active surveillance for kidney cancer.

Keywords: Kidney cancer, cumulative obesity exposure, obesity duration

Introduction

Obesity has become a burdensome social and medical problem in almost all countries, reaching pandemic levels in several [1, 2]. According to a systematic analysis of the Global Burden of Disease Study 2013, the proportion of adults with a body mass index (BMI) of 25 kg/m^2 or greater increased worldwide from 28.8% to 36.9% in men, and from 29.8% to 38.0% in women between 1980 and 2013 [2].

Many studies have reported the adverse effects of obesity on cardiovascular diseases, diabetes mellitus (DM), musculoskeletal diseases, and several cancers [3, 4]. There is abundant evidence that obesity is a modifiable lifestyle risk factor for several cancers. The International Agency for Research on Cancer Working Group has concluded that excess adiposity is associated with an increased risk for 13 cancer types, with obese individuals being approximately 1.8 times more likely to develop kidney cancer [5]. A recent umbrella review of 204 meta-analyses has supported the conclusions of previous studies indicating that an increase in BMI is associated with a higher risk of developing esophageal cancer, colon cancer in men, rectal cancer in men, biliary tract cancer, pancreatic cancer, endometrial cancer in premenopausal

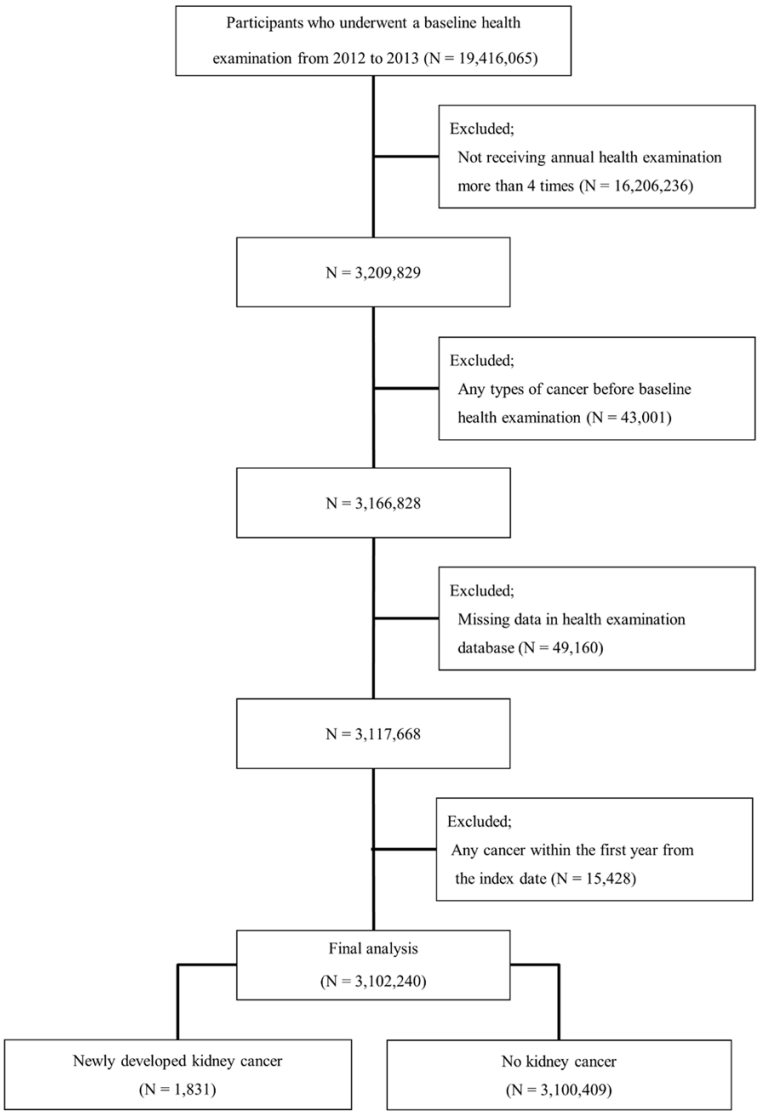

Figure 1. Flowchart of participant inclusion.

women, kidney cancer, and multiple myeloma [6].

Most studies have explored the association between obesity and the risk of kidney cancer with cross-sectional exposure information on obesity measured at one point in time [7-11]. A longitudinal study by the Women's Health Initiative has reported that a longer duration of obesity is associated with an increased risk of developing several forms of cancer, including kidney cancer in postmenopausal women [12]. However, little is known regarding the time-dependent association of the cumulative impacts of obesity on kidney cancer risk. In this study, we analyzed the dose- and time-dependent impact of general and abdominal obesity on the risk of newly developed kidney cancer using data from the Korean National Health Insurance System (NHIS) database, which covers nearly the entire South Korean population.

Materials and methods

Data acquisition

The NHIS provides mandatory health insurance that covers all forms of health services, and contains a broad range of information, including principal diagnoses classified by the International Classification of Disease, 10th revision (ICD-10). Details of the NHIS database have been described elsewhere [13, 14]. The NHIS also provides health examination data, consisting of anthropometric measurements, laboratory tests, and standardized self-reported questionnaires for all insured Koreans. After approval by the Institutional Review Board, we extracted the data from the NHIS database. We followed the recommendations of the REporting of studies Conducted using Observational Routinely collected health Data statement [15].

Study population

From the NHIS database, participants over 20 years old who had undergone a health examination between 2012 and 2013 were included (n=19,416,065). Participants who did not receive more than four consecutive health examination were excluded (n=16,206,236). Participants with any type of cancer diagnosed before baseline health examination (n=43,001), missing data (n=49,160), or diagnosis of any type of cancer within the first year from the index date (n=15,428) were excluded. In total, 3,102,240 participants were included in the final analysis (**Figure 1**). The primary endpoint was newly diagnosed kidney cancer, which was defined as described in C64 of the ICD-10.

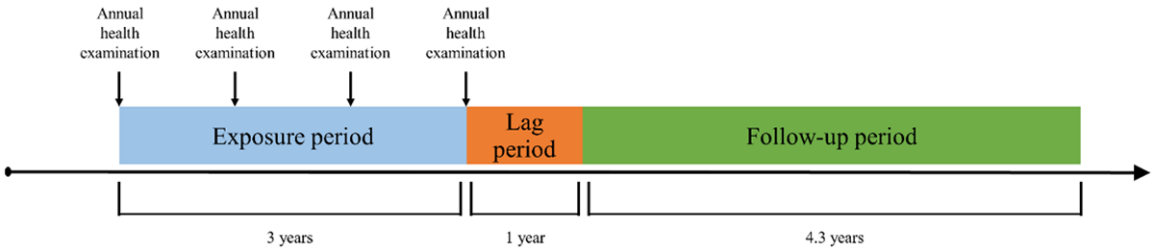

Figure 2. Schematic diagram for a timeline of participants.

BMI and WC categories

The height, body weight, and waist circumference (WC) were measured, and BMI was calculated by dividing the participants' weight by the square of their height. General obesity was defined as BMI≥25 kg/m^2 [16], and participants were categorized into five BMI groups as follows: <18.5 kg/m^2, 18.5-22.9 kg/m^2, 23.0-24.9 kg/m^2, 25.0-29.9 kg/m^2, and ≥30.0 kg/m^2. Abdominal obesity was defined as WC≥90 cm for men and ≥85 cm for women [17], and participants were categorized into six WC groups as follows: <80.0 cm, 80.0-84.9 cm, 85.0-89.9 cm, 90.0-94.9 cm, 95.0-99.9 cm, and ≥100.0 cm in men; and <75.0 cm, 75.0-79.9 cm, 80.0-84.9 cm, 85.0-89.9 cm, 90.0-94.9 cm, and ≥95.0 cm in women.

Definition of cumulative obesity exposure

It was not possible to track the lifetime BMI and WC changes in the participants of the general cohort. Thus, we introduced the concept of cumulative obesity exposure (COE) to analyze the time-dependent impact of obesity on kidney cancer risk [18, 19]. Consecutive annual health examination data were available for all participants. Using that data, COE was defined as the number of years obesity was clinically confirmed according to the above criteria during the exposure period. We only included participants who received four or more consecutive annual health examination; thus, the general COE (gCOE) and abdominal COE (aCOE) ranged from 0 to 4 years (**Figure 2**).

Covariate assessment

Laboratory tests, including serum fasting glucose and total cholesterol, and standardized self-reported questionnaires were collected. Standardized self-reported questionnaires were analyzed for past medical history, income level, smoking status, alcohol consumption, and regular physical activity. Income levels were dichotomized at the lowest quartile. Participants who were currently smoking and who had smoked 100 or more cigarettes during their lifetime were defined as current smokers. Participants who drank ≥30 g of alcohol per day according to the questionnaire were defined as heavy alcohol drinkers [8]. Regular physical activity was defined as strenuous exercise for at least 20 minutes at least once a week or moderate exercise for at least 30 minutes at least once a week [8].

Hypertension was defined according to the presence of at least one claim per year under ICD-10 codes I10-I13, and I15 as well as at least one claim per year for the prescription of an antihypertensive agent or systolic/diastolic blood pressure (BP) ≥140/90 mmHg. DM was defined by at least one claim per year for the prescription of antidiabetic medication under ICD-10 codes E10-14 or fasting glucose level ≥126 mg/dL. Dyslipidemia was defined as serum total cholesterol level ≥240 mg/dL or at least one claim per year for the prescription of a lipid-lowering medication under the E78 ICD-10 code.

Statistical analysis

Statistical analysis was performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA). The baseline characteristics of the study population were analyzed according to gCOE or aCOE. Comparison of demographic data was performed using analysis of variance (ANOVA) for continuous variables and the Chi-square test for categorical variables.

Incidence rates of kidney cancer were calculated per 1,000 person-years. The association of severity and duration of obesity with kidney cancer was assessed using multivariate Cox

proportional hazard regression analysis. Multivariate Cox proportional hazard regression analyses were performed to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) of kidney cancer according to the severities of general and abdominal obesity with the following adjustments: Model 1, adjusted for age and gender; Model 2, additionally adjusted for smoking status, alcohol consumption, regular activity, and income; and Model 3, additionally adjusted for DM. The same analysis was performed according to gCOE and aCOE: Model 1, adjusted for age and gender; Model 2, additionally adjusted for smoking status, alcohol consumption, DM, and BMI; and Models 3 and 4, additionally adjusted for BMI or WC. All statistical tests were two-tailed and the significance level was set at *P*-values less than 0.05.

Results

Baseline characteristics

Baseline characteristics according to gCOE and aCOE are described in **Table 1**. According to gCOE and aCOE, there were significant differences in almost all baseline characteristics. As gCOE and aCOE increased, the proportion of male participants and mean age increased. Cardiometabolic parameters, such as systolic and diastolic BP, serum fasting glucose and total cholesterol level, significantly increased alongside gCOE and aCOE. The prevalence of comorbidities, such as DM, hypertension, and dyslipidemia also increased alongside gCOE and aCOE.

Risk of kidney cancer according to obesity

During the median follow-up of 4.3 (4.1-4.6) years, 1,831 participants were diagnosed with kidney cancer (**Figure 1**). **Table 2** shows the HRs of kidney cancer according to the severity of general and abdominal obesity. A markedly increased incidence rate of kidney cancer was observed in higher BMI and WC categories. After adjusting for confounding variables (Model 3), underweight participants (<18.5 kg/m^2 of BMI) had a decreased HR for kidney cancer (0.53, 95% CI: 0.32-0.88) compared to those with normal BMI (18.5-22.9 kg/m^2). The HRs for kidney cancer increased significantly alongside BMI groups (*P* for trend <0.001) as follows: 23.0-24.9 kg/m^2 (HR: 1.32, 95% CI: 1.17-1.51), 25.0-29.9 kg/m^2 (HR: 1.76, 95% CI: 1.57-1.98), and ≥30 kg/m^2 (HR: 2.35, 95% CI: 1.90-2.93). Similar results were found in the WC categories. The HRs for kidney cancer increased significantly in higher WC categories (*P* for trend <0.001), and WC≥95 cm (in men) and ≥90 cm (in women) were associated with an increased risk of kidney cancer.

Risk of kidney cancer according to cumulative obesity exposure

Table 3 and **Figure 3** present the HRs of kidney cancer according to gCOE and aCOE. Significantly increased incidence rate of kidney cancer were observed in high gCOE and aCOE groups. After adjusting for all confounding variables (Model 2), the HRs for kidney cancer increased significantly alongside gCOE groups (*P* for trend <0.001) as follows: 1 year (HR: 1.33, 95% CI: 1.10-1.60), 2 years (HR: 1.33, 95% CI: 1.08-1.63), 3 years (HR: 1.55, 95% CI: 1.30-1.85), and 4 years (HR: 1.82, 95% CI: 1.64-2.03). These associations persisted even after further mutual adjustment for BMI and WC (Models 3 and 4). Similar trends were observed for aCOE. The HRs for kidney cancer increased significantly with increasing WC (Model 2, *P* for trend <0.001) as follows: 1 year (HR: 1.42, 95% CI: 1.23-1.64), 2 years (HR: 1.71, 95% CI: 1.46-2.02), 3 years (HR: 1.76, 95% CI: 1.48-2.08), and 4 years (HR: 2.11, 95% CI: 1.84-2.42). These associations were also present in Models 3 and 4, which adjusted for BMI or WC.

Risk of kidney cancer in clinically relevant subgroups

We also conducted a subgroup analysis after dichotomizing participants according to several variables (**Table 4**). The association between gCOE and kidney cancer risk was stronger in younger participants that older participants. Further, the risk of kidney cancer according to gCOE was more prominent in male participants and participants with DM or hypertension. In male participants and participants with DM or hypertension, kidney cancer risk was affected by an increase in gCOE. However, it was not affected in female participants and participants without DM and hypertension.

The association between aCOE and kidney cancer risk was more prominent in younger participants than older participants as well as in participants with hypertension compared to that in participants without hypertension. In addition,

Table 1. Demographics according to general and abdominal cumulative obesity exposure

	General cumulative obesity exposure (years)						Abdominal cumulative obesity exposure (years)					
	0	1	2	3	4	*p*-value	0	1	2	3	4	*p*-value
No. of patients	1,820,190	203,588	158,951	188,384	731,127	-	2,227,527	315,207	182,172	157,224	220,110	-
Age (years)[a]	43.2±10.9	44.0±10.8	44.0±10.7	44.3±10.6	44.5±10.1	<0.001	42.9±10.5	45.1±10.9	45.7±11.0	45.9±11.0	45.7±10.9	<0.001
Gender[b]						<0.001						<0.001
Male	1,192,146 (65.5)	156,190 (76.7)	126,438 (79.6)	152,356 (80.9)	617,830 (84.5)		1,541,173 (69.2)	236,372 (75.0)	146,528 (80.4)	130,944 (83.3)	189,943 (86.3)	
Female	628,044 (34.5)	47,398 (23.3	32,513 (20.5)	36,028 (19.1)	113,297 (15.5)		686,354 (30.8)	78,835 (25.0)	35,644 (19.6)	26,280 (16.7)	30,167 (13.7)	
Height (cm)[a]	166.8±8.4	167.9±8.4	168.4±8.3	168.5±8.3	169.1±8.1	<0.001	166.8±8.2	168.3±8.5	169.4±8.4	170.1±8.3	171.3±8.2	<0.001
Weight (kg)[a]	61.0±8.6	69.5±7.7	71.5±7.7	73.3±8.0	80.1±9.9	<0.001	63.2±9.5	72.2±9.2	76.3±8.9	79.8±9.2	86.2±10.8	<0.001
BMI (kg/m^2)[a]	21.8±1.9	24.6±1.2	25.2±1.1	25.8±1.3	28.0±2.2	<0.001	22.6±2.4	25.4±2.1	26.6±2.0	27.5±2.2	29.4±2.7	<0.001
WC (cm)[a]	76.2±7.0	82.5±5.8	83.9±5.5	85.3±5.6	90.0±6.8	<0.001	77.2±6.8	85.7±5.7	88.7±4.8	91.3±4.9	96.3±5.5	<0.001
sBP (mmHg)[a]	118.9±13.2	122.7±12.9	123.5±12.8	124.3±12.8	126.9±13.0	<0.001	119.9±13.2	123.8±13.2	125.6±13.1	126.9±13.1	128.9±13.3	<0.001
dBP (mmHg)[a]	74.8±9.2	77.2±9.1	77.8±9.1	78.3±9.1	80.1±9.4	<0.001	75.5±9.2	78.0±9.4	79.2±9.3	80.0±9.4	81.4±9.6	<0.001
Smoking status[b]						<0.001						<0.001
None	945,534 (52.0)	88,800 (43.6)	66,013 (41.5)	76,245 (40.5)	271,676 (37.2)		1,102,521 (49.5)	139,185 (44.2)	72,169 (39.6)	58,756 (37.4)	75,637 (34.4)	
Ex-smoker	325,317 (17.9)	47,616 (23.4)	38,916 (24.5)	46,703 (24.8)	183,727 (25.1)		427,773 (19.2)	73,392 (23.3)	45,371 (24.9)	39,894 (25.4)	55,849 (25.4)	
Current-smoker	549,339 (30.2)	67,172 (33.0)	54,022 (34.0)	65,436 (34.7)	275,724 (37.7)		697,233 (31.3)	102,630 (32.6)	64,632 (35.5)	58,574 (37.3)	88,624 (40.3)	
Alcohol consumption[b]	107,130 (5.9)	15,719 (7.2)	13,062 (8.2)	16,309 (8.7)	74,566 (10.2)	<0.001	141,892 (6.4)	25,760 (8.2)	17,333 (9.5)	16,249 (10.3)	25,552 (11.6)	<0.001
Regular exercise[b]	1,160,031 (63.7)	135,873 (66.7)	107,965 (67.9)	128,362 (68.1)	502,578 (68.7)	<0.001	1,459,590 (65.5)	206,410 (65.5)	120,456 (66.1)	103,930 (66.1)	144,423 (65.6)	<0.001
Income (the lowest quartile)[b]	352,329 (11.4)	41,239 (1.3)	31,990 (1.0)	38,910 (1.3)	143,562 (4.6)	<0.001	419,677 (18.8)	69,301 (22.0)	40,224 (22.1)	33,901 (21.6)	44,927 (20.4)	<0.001
Diabetes mellitus[b]	84,446 (4.6)	14,380 (7.1)	12,287 (7.7)	16,439 (8.7)	85,102 (11.6)	<0.001	106,750 (4.8)	27,390 (8.7)	19,700 (10.8)	20,616 (13.1)	38,198 (17.4)	<0.001
Hypertension[b]	247,504 (13.6)	42,135 (20.7)	35,939 (22.6)	47,409 (25.2)	244,831 (33.5)	<0.001	329,014 (14.8)	80,752 (25.6)	56,222 (30.9)	55,870 (35.5)	95,960 (43.6)	<0.001
Dyslipidemia[b]	227,528 (12.5)	38,395 (18.9)	31,608 (19.9)	40,469 (21.5)	187,771 (25.7)	<0.001	301,653 (13.5)	69,977 (22.2)	45,140 (24.8)	42,368 (27.0)	66,633 (30.3)	<0.001
Stroke[b]	3,480 (0.2)	575 (0.4)	466 (0.4)	558 (0.4)	2,210 (0.4)	<0.001	4,203 (0.2)	970 (0.4)	660 (0.5)	595 (0.5)	861 (0.5)	<0.001
Myocardial infarction[b]	11,287 (0.8)	1,872 (1.2)	1,554 (1.3)	1,992 (1.4)	8,685 (1.5)	<0.001	13,808 (0.8)	3,387 (1.4)	2,315 (1.7)	2,282 (1.9)	3,598 (2.1)	<0.001
Fasting glucose (mg/dL)[a]	94.1±18.2	97.1±20.6	97.9±21.8	98.9±22.7	101.8±25.1	<0.001	94.6±18.3	98.7±22.3	100.8±24.2	102.6±26.2	106.0±29.8	<0.001
Total cholesterol (mg/dL)[a]	190.9±33.8	197.7±35.5	198.6±35.4	199.5±35.7	202.3±36.3	<0.001	192.5±34.2	199.9±36.2	201.1±36.3	201.8±36.8	202.5±37.2	<0.001

[a]Values are presented as mean ± standard deviation. [b]Values are presented as number (percentage). BMI, body mass index; WC, waist circumference; sBP, systolic blood pressure; dBP, diastolic blood pressure.

Table 2. Hazard ratios of kidney cancer according to the severity of general and abdominal obesity

	Event	Person-years	Incidence rate[a]	HR (95% CI)		
				Model 1[b]	Model 2[c]	Model 3[d]
Body mass index (kg/m^2)						
<18.5	15	425,400	0.04	0.54 (0.32, 0.90)	0.53 (0.32, 0.88)	0.53 (0.32, 0.88)
18.5-22.9	460	4,937,318	0.09	1 (ref.)	1 (ref.)	1 (ref.)
23.0-24.9	492	3,341,510	0.15	1.32 (1.16, 1.50)	1.33 (1.17, 1.51)	1.32 (1.17, 1.51)
25.0-29.9	763	3,909,014	0.20	1.76 (1.56, 1.97)	1.78 (1.58, 2.00)	1.76 (1.57, 1.98)
≥30.0	101	485,173	0.21	2.38 (1.92, 2.96)	2.40 (1.93, 2.98)	2.35 (1.90, 2.93)
P for trend				<0.001	<0.001	<0.001
Waist circumference (cm)						
M<80.0, F<75.0	378	4,886,421	0.08	0.64 (0.56, 0.74)	0.64 (0.56, 0.74)	0.65 (0.56, 0.74)
M 80.0-84.9, F 75.0-79.9	469	3,333,313	0.14	0.89 (0.78, 1.01)	0.89 (0.78, 1.01)	0.89 (0.78, 1.02)
M 85.0-89.9, F 80.0-84.9	442	2,599,328	0.17	1 (ref.)	1 (ref.)	1 (ref.)
M 90.0-94.9, F 85.0-89.9	328	1,397,569	0.23	1.35 (1.17, 1.56)	1.35 (1.17, 1.56)	1.34 (1.17, 1.55)
M 95.0-99.9, F 90.0-94.9	136	574,980	0.24	1.42 (1.17, 1.71)	1.41 (1.17, 1.71)	1.40 (1.16, 1.70)
M≥100.0, F≥95.0	78	306,806	0.25	1.73 (1.36, 2.20)	1.72 (1.35, 2.19)	1.70 (1.34, 2.17)
P for trend				<0.001	<0.001	<0.001

[a]Incidence per 1,000 person-years. [b]Model 1 was adjusted for age and gender. [c]Model 2 was adjusted for age, gender, smoking status, alcohol consumption, regular activity, and income. [d]Model 3 was adjusted for age, gender, smoking status, alcohol consumption, regular activity, income, and diabetes mellitus. HR, hazard ratio; CI, confidence interval.

Table 3. Hazard ratios of kidney cancer according to general and abdominal cumulative obesity exposure

	Event	Person-years	Incidence rate[a]	HR (95% CI)			
				Model 1[b]	Model 2[c]	Model 3[d]	Model 4[e]
gCOE							
0	790	7,694,731	0.10	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
1	128	859,018	0.15	1.32 (1.10, 1.60)	1.33 (1.10, 1.60)	1.14 (0.94, 1.38)	1.17 (0.97, 1.42)
2	101	670,424	0.15	1.33 (1.08, 1.63)	1.33 (1.08, 1.63)	1.10 (0.89, 1.37)	1.14 (0.92, 1.41)
3	143	794,082	0.18	1.55 (1.30, 1.85)	1.55 (1.30, 1.85)	1.24 (1.02, 1.51)	1.29 (1.07, 1.55)
4	669	3,080,161	0.22	1.84 (1.66, 2.04)	1.82 (1.64, 2.03)	1.27 (1.06, 1.52)	1.36 (1.18, 1.56)
P for trend				<0.001	<0.001	<0.001	<0.001
aCOE							
0	1,000	9,422,947	0.11	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
1	233	1,327,286	0.18	1.43 (1.24, 1.65)	1.42 (1.23, 1.64)	1.24 (1.07, 1.45)	1.21 (1.04, 1.42)
2	172	765,553	0.22	1.73 (1.47, 2.03)	1.71 (1.46, 2.02)	1.42 (1.19, 1.70)	1.39 (1.15, 1.66)
3	157	660,178	0.24	1.78 (1.50, 2.11)	1.76 (1.48, 2.08)	1.39 (1.15, 1.68)	1.35 (1.10, 1.65)
4	269	922,452	0.29	2.16 (1.89, 2.47)	2.11 (1.84, 2.42)	1.51 (1.26, 1.82)	1.46 (1.19, 1.79)
P for trend				<0.001	<0.001	<0.001	<0.001

[a]Incidence per 1,000 person-years. [b]Model 1 was adjusted for age and gender. [c]Model 2 was adjusted for age, gender, smoking status, alcohol consumption, and DM. [d]Model 3 was adjusted for age, gender, smoking status, alcohol consumption, DM, and BMI. [e]Model 4 was adjusted for age, gender, smoking status, alcohol consumption, DM, and WC. HR, hazard ratio; CI, confidence interval; BMI, body mass index; WC, waist circumference; gCOE, general cumulative obesity exposure; aCOE, abdominal cumulative obesity exposure.

the risk of kidney cancer according to aCOE was more prominent in male participants and in participants with DM or dyslipidemia.

Discussion

Many previous studies have reported the association between general or abdominal obesity and kidney cancer risk. To the best of our knowledge, however, this is the first study to evaluate COE against the risk of kidney cancer using large-scale cohort data covering nearly an entire national population. We found that longer durations of general or abdominal obesity were significantly associated with an increased incidence of kidney cancer. This result

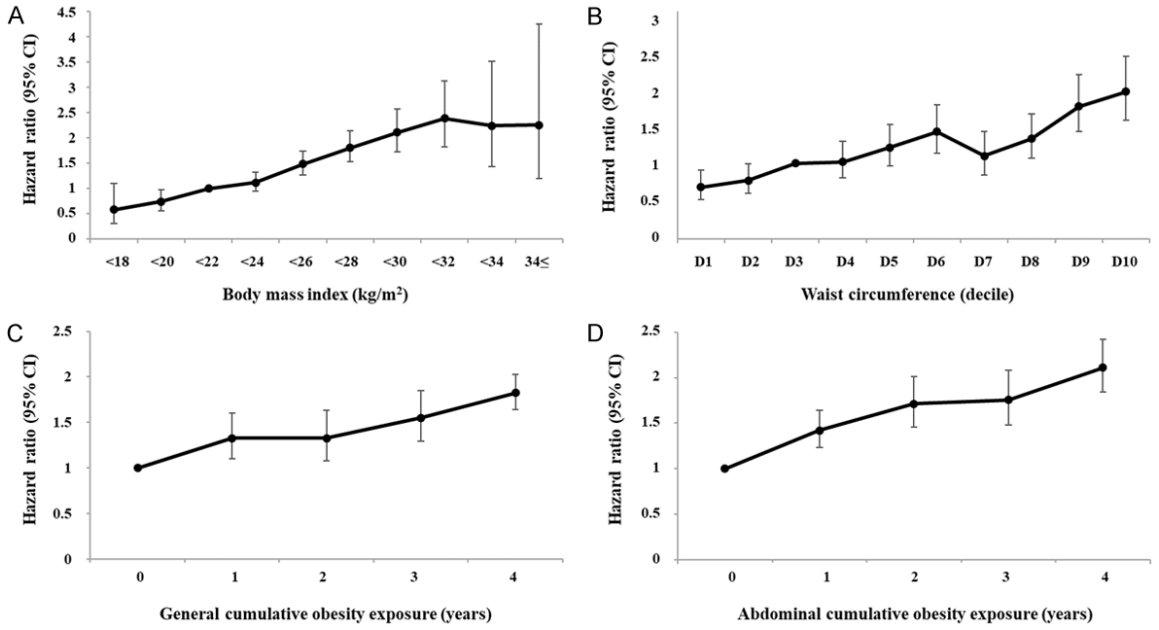

Figure 3. Hazard ratios of kidney cancer stratified by BMI, WC, gCOE, and aCOE. A. Risk of kidney cancer according to ten BMI ranges. B. Risk of kidney cancer according to decile of WC. C. Risk of kidney cancer according to gCOE. D. Risk of kidney cancer according to aCOE.

was similar to the results of previous studies on several diseases, demonstrating that the duration an individual is obese is associated with an increased risk of developing type 2 DM [20, 21], hypertension [22], cardiovascular disease [23], and several types of cancer [12]. We also found that the increased risk of kidney cancer related to COE was significantly augmented among participants with the following characteristics: younger than 65 years old, male gender, DM, hypertension, and dyslipidemia.

In many chronic diseases, obesity duration and baseline obesity are important risk factors. The Epidemiological Health Investigation of Teenagers in Porto, Portugal has reported that cumulative exposure to higher BMI for a period of 11 adolescent years is relevant to adulthood insulin resistance [21]. Another large-scale cohort study, the US National Longitudinal Study of Adolescent Health, has reported that persistent obesity from adolescence to young adulthood is associated with increased risk of DM in both men (odds ratio [OR] 2.27) and women (OR 2.08) [20]. Similar results have been reported for patients with hypertension and other cardiovascular diseases [22, 23]. However, little is known about the association between obesity duration and the risk of kidney cancer. A longitudinal study of the Women's Health Initiative has analyzed the impact of adulthood obesity duration and the risk of several types of cancer in US women [12]; a longer duration of obesity is significantly associated with an increased incidence of all obesity-related cancers, with the strongest association being with kidney cancer. Although it was the only study that had investigated the association between obesity duration and cancer, it was limited by several shortcomings. The study included only women, although the prevalence of kidney cancer is significantly higher in men. Height and weight for BMI calculation were collected in various ways, including retrospective self-reports. Our study overcame these limitations and included a near population-wide cohort.

One of the interesting details of the present study is that the impact of obesity duration on subsequent kidney cancer risk was more prominent in participants with metabolic syndromes, such as DM, hypertension, and dyslipidemia. Participants having such diseases had a higher risk for kidney cancer alongside gCOE and aCOE. Our results that obesity duration and such diseases increased the risk of kidney cancer suggest that these variables act to increa-

Table 4. Hazard ratios of kidney cancer according to general and abdominal cumulative obesity exposure in clinically relevant subgroups

	gCOE[a]			aCOE[b]		
	0	1-3	4	0	1-3	4
Age						
<65 years	1 (ref.)	1.14 (0.98, 1.33)	1.30 (1.08, 1.57)	1 (ref.)	1.34 (1.17, 1.54)	1.50 (1.21, 1.86)
≥65 years	1 (ref.)	1.39 (0.91, 2.13)	0.98 (0.55, 1.77)	1 (ref.)	0.92 (0.61, 1.37)	1.02 (0.56, 1.87)
Gender						
Male	1 (ref.)	1.12 (0.96, 1.30)	1.22 (1.01, 1.47)	1 (ref.)	1.27 (1.11, 1.46)	1.41 (1.04, 1.74)
Female	1 (ref.)	1.54 (1.03, 2.32)	1.50 (0.87, 2.58)	1 (ref.)	1.33 (0.90, 1.95)	1.32 (0.68, 2.56)
Smoking						
None or Ex-smoker	1 (ref.)	1.21 (1.01, 1.45)	1.21 (0.96, 1.51)	1 (ref.)	1.25 (1.06, 1.48)	1.34 (1.04, 1.74)
Current smoker	1 (ref.)	1.08 (0.85, 1.37)	1.36 (1.02, 1.80)	1 (ref.)	1.35 (1.09, 1.68)	1.57 (1.14, 2.17)
Alcohol consumption						
No	1 (ref.)	1.16 (1.00, 1.34)	1.25 (1.04, 1.50)	1 (ref.)	1.28 (1.12, 1.47)	1.39 (1.12, 1.72)
Yes	1 (ref.)	1.20 (0.75, 1.92)	1.38 (0.79, 2.41)	1 (ref.)	1.32 (0.86, 2.02)	1.86 (1.00, 3.46)
Regular physical activity						
No	1 (ref.)	1.07 (0.84, 1.37)	1.27 (0.94, 1.71)	1 (ref.)	1.19 (0.95, 1.49)	1.36 (0.97, 1.90)
Yes	1 (ref.)	1.21 (1.01, 1.44)	1.26 (1.01, 1.57)	1 (ref.)	1.34 (1.14, 1.57)	1.47 (1.14, 1.89)
Diabetes mellitus						
No	1 (ref.)	1.17 (1.00, 1.36)	1.21 (1.00, 1.46)	1 (ref.)	1.27 (1.10, 1.46)	1.38 (1.11, 1.72)
Yes	1 (ref.)	1.06 (0.70, 1.61)	1.63 (1.02, 2.60)	1 (ref.)	1.42 (1.00, 2.04)	1.76 (1.05, 2.97)
Hypertension						
No	1 (ref.)	1.13 (0.94, 1.36)	1.11 (0.88, 1.41)	1 (ref.)	1.37 (1.16, 1.63)	1.25 (0.93, 1.67)
Yes	1 (ref.)	1.15 (0.92, 1.44)	1.39 (1.07, 1.82)	1 (ref.)	1.12 (0.92, 1.37)	1.49 (1.11, 1.99)
Dyslipidemia						
No	1 (ref.)	1.13 (0.95, 1.34)	1.24 (1.01, 1.53)	1 (ref.)	1.27 (1.09, 1.48)	1.30 (1.02, 1.66)
Yes	1 (ref.)	1.21 (0.93, 1.59)	1.30 (0.93, 1.81)	1 (ref.)	1.32 (1.03, 1.70)	1.79 (1.24, 2.58)

HR, hazard ratio; CI, confidence interval; gCOE, general cumulative obesity exposure; aCOE, abdominal cumulative obesity exposure. [a]HRs (95% CIs) were obtained using multivariable Cox proportional hazard regression analysis after adjusting for age, gender, smoking status, alcohol consumption, regular physical activity, DM, and BMI. [b]HRs (95% CIs) were obtained using multivariable Cox proportional hazard regression analysis after adjusting for age, gender, smoking status, alcohol consumption, regular physical activity, DM, and WC.

se kidney cancer risk through distinct mechanisms. The well-known mechanisms linking DM, hypertension, and dyslipidemia to cancer are as follows: (1) abnormal insulin/insulin-like growth factor signaling, (2) chronic low grade inflammation, (3) increased oxidative stress responsible for DNA damage, (4) disrupted sex hormone biosynthesis pathway, and (5) increased synthesis of angiogenic growth factors, among others [24-26]. Other than these mechanisms, obesity affects the risk of kidney cancer by altering adipokine production, imparting microenvironmental changes, and disrupting intestinal microbiome [27-29]. It can be assumed that the risk of kidney cancer increases as different mechanisms of metabolic syndrome and obesity works complimentarily and stimuli from obesity accumulate over time.

We should consider some limitations in interpreting our results. Because no information regarding the histologic subtypes and staging of kidney cancer was included, the impact of obesity duration on the prognosis of kidney cancer could not be assessed. Total obesity duration may be underestimated or overestimated because we could not include any potential obesity duration prior to the start of this study. Moreover, we did not consider the impact of fluctuating obesity during the entire BMI or WC spectrum. We only analyzed the BMI and WC data from four time points, and it was not possible to analyze whether obesity reversal might attenuate the obesity-mediated risk of kidney cancer. However, the major strength of our study was the large sample size encompassing the entire South Korean population, allowing us to make comprehensive adjustments for confounding variables and to perform clinically relevant subgroup analyses. Although the present analysis did not reflect the severity of lifelong obesity, 3 years of popula-

tion-wide health data enabled medically worthwhile analysis of the pattern of obesity and its relationship with kidney cancer.

The novel result of our study is that a longer duration of obesity was significantly associated with an increased incidence of kidney cancer. Additionally, participants with the following characteristics were more susceptible to these associations: younger than 65 years old; male gender; and metabolic syndromes, such as DM, hypertension, or dyslipidemia. These findings suggested that physicians should consider more aggressive screening for the early detection of kidney cancer and more diligent lifestyle interventions to decrease the risk of kidney cancer in these participants.

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Disclosure of conflict of interest

None.

Abbreviations

BMI, Body mass index; DM, Diabetes mellitus; NHIS, National Health Insurance System; ICD-10, International Classification of Disease, 10th revision; WC, Waist circumference; COE, Cumulative obesity exposure; gCOE, General cumulative obesity exposure; aCOE, Abdominal cumulative obesity exposure; BP, Blood pressure; HRs, Hazard ratios; Cis, Confidence intervals.

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