

RESEARCH ARTICLE

Risk of Cancer Mortality according to the Metabolic Health Status and Degree of Obesity

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Abstract

Background: We investigated the risk of cancer mortality according to obesity status and metabolic health status using sampled cohort data from the National Health Insurance system. **Materials and Methods:** Data on body mass index and fasting blood glucose in the sampled cohort database (n=363,881) were used to estimate risk of cancer mortality. Data were analyzed using a Cox proportional hazard model (Model 1 was adjusted for age, sex, systolic blood pressure, diastolic blood pressure, total cholesterol level and urinary protein; Model 2 was adjusted for Model 1 plus smoking status, alcohol intake and physical activity). **Results:** According to the obesity status, the mean hazard ratios were 0.82 [95% confidence interval (CI), 0.75-0.89] and 0.79 (95% CI, 0.72-0.85) for the overweight and obese groups, respectively, compared with the normal weight group. According to the metabolic health status, the mean hazard ratio was 1.26 (95% CI, 1.14-1.40) for the metabolically unhealthy group compared with the metabolically healthy group. The interaction between obesity status and metabolic health status on the risk of cancer mortality was not statistically significant (p=0.31). **Conclusions:** We found that the risk of cancer mortality decreased according to the obesity status and increased according to the metabolic health status. Given the rise in the rate of metabolic dysfunction, the mortality from cancer is also likely to rise. Treatment strategies targeting metabolic dysfunction may lead to reductions in the risk of death from cancer.

Keywords: Cancer - metabolic dysfunction - mortality - obesity

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Introduction

Increasing rates of obesity and metabolic disturbance are becoming major public health problems in Korea (Wang et al., 2008; Finkelstein et al., 2012; Kang et al., 2014; Lee et al., 2014). Obesity is associated with numerous non-communicable diseases, such as type 2 diabetes mellitus, metabolic syndrome, cardiovascular diseases, and cancer. Notably, cancer is the leading cause of death and is associated with the largest disease burden in Korea (Lee et al., 2013; Jung et al., 2014). Many studies have suggested that obesity is related to all-cause mortality and cancer mortality (Calle et al., 2013; Flegal et al., 2013; Ozbek et al., 2013). Indeed, the risk of death from cancer increases with body mass index (BMI) (Jee et al., 2006; Lee et al., 2013). A previous report found that BMI was an independent predictor of the incidence and mortality of a variety of cancers including colon cancer (Moore et al., 2004; Renehan et al., 2008; Vucenik et al., 2012; Calle et al., 2013; Morrison et al., 2013). In addition, obesity-related cancers, such as colorectal, female reproductive, and postmenopausal breast cancer, were found to be associated with prolonged exposure to impaired fasting glucose (Parekh et al., 2013). Finally, Moore et al. (2014) reported that obesity and metabolic dysfunction act synergistically to increase the incidence risk of cancer (Moore et al., 2014). However, to our knowledge, nobody

has examined whether these synergistic interactions between obesity and metabolic dysfunction are consistent in the risk of cancer mortality.

Under the Korean National Health Insurance Act, the Korean National Health Insurance system is required to cover the country's entire population. This system has provided a medical health check-up program to facilitate the early detection of diseases since 1999. The participants of the health check-up program consist of employer-insured, self-employed-insured and their dependents. We used this valuable database to conduct a retrospective cohort study investigating the risk of cancer mortality according to obesity status and metabolic health status.

Materials and Methods

Study design and population

The National Health Insurance Corporation compiled a sample database that included information regarding medical insurance, hospitals, medical health check-ups and medical treatments from 2002 to 2010. The sample cohort consisted of approximately 1 million individuals. Of these, 424,712 participants who received the health check-up program from 2002 to 2008 were assessed for eligibility for this study. The identities of the participants were removed to maintain anonymity.

Of the 424,712 subjects, 409,402 (96.4%) met the

eligibility criteria, and 15,310 cases (3.6%) were excluded for the following reasons: 27 cases did not match to a death record or have dates of death, 448 died within 6 months of the health check-up, 14,574 were under 20 years of age, and 261 did not include a measurement for body mass index (BMI). Therefore, the total number of people who were eligible for the study was 409,402. We further excluded 45,521 participants who did not have covariate information. Finally, 363,881 participants were included in the analysis (Figure 1).

Data collection

The National Health Insurance-sampled cohort data included information provided by a questionnaire, anthropometric measurements and laboratory measurements, and the data also provided individual ages within a 5-year range (i.e., 20-24, 25-29, ..., 75-79, ≥ 80 years). Data on smoking status, alcohol intake and physical activity were collected by self-reported questionnaires. Questions about alcohol intake included the frequency of alcohol consumption and the usual amount that was consumed on a daily basis. Smoking status was categorized as never smoker, former smoker or current smoker. The participants were asked about their frequency of physical activity (0, 1-2, 3-4, ≥ 5 times/week). The BMI (kg/m^2) was calculated as weight (kg) divided by the square of the height (m). Systolic and diastolic blood pressures (mmHg) were measured. Blood samples were collected, and fasting blood glucose (mg/dL), total cholesterol level (mg/dL) and urinary protein were measured.

Certification of death from cancer

The National Health Insurance cohort data are linked to vital statistics from Statistics Korea (Statistics Korea, 2014). Therefore, we were able to follow up for mortality and cause of death for individuals who died prior to December 31, 2010. The underlying cause of death was coded according to the *International Classification of Diseases*, 10th edition (ICD-10; World Health Organization, 1994). Death from cancer was the primary end point for this study. To evaluate the risk of cancer mortality according to the metabolic health status and degree of obesity, we defined the cause of death from cancer according to the ICD-10 codes C00-C97 and D45-D47 (World Health Organization, 1994).

Definitions of obesity status and metabolic health status

BMI was categorized using the World Health Organization's classification for the Asian population (World Health Organization, 2000) as follows: $< 18.5 \text{ kg}/\text{m}^2$ (underweight), $18.5\text{-}22.9 \text{ kg}/\text{m}^2$ (normal weight), $23\text{-}24.9 \text{ kg}/\text{m}^2$ (overweight), and $\geq 25 \text{ kg}/\text{m}^2$ (obese). Those in the $< 18.5 \text{ kg}/\text{m}^2$ category ($n=15,598$) were included in the normal weight category for the analysis. Therefore, BMI values were categorized as normal weight ($< 23 \text{ kg}/\text{m}^2$), overweight ($23\text{-}24.9 \text{ kg}/\text{m}^2$), or obese ($\geq 25 \text{ kg}/\text{m}^2$). A metabolically unhealthy status was defined by abnormally elevated fasting blood glucose levels (i.e., fasting blood glucose $\geq 126 \text{ mg}/\text{dL}$; Moore et al., 2014)

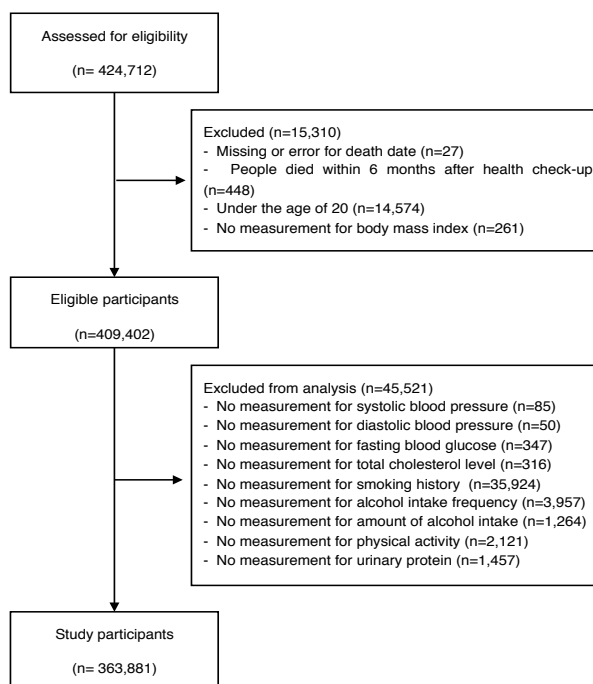


Figure 1. Flow-Chart for Study Participants Selection

Statistical analysis

Data were expressed as means \pm SD for continuous variables, and categorical data were expressed as numbers (percentages). An independent t-test was used to compare the differences between the metabolically healthy group and the metabolically unhealthy group. A one-way ANOVA was used to compare the baseline characteristics by the obesity status.

Because the date of examination was not included in the individual records, the date of the health check-up was assumed to be the year midpoint (July 1). All participants were followed up to the date of death or December 31, 2010 via the vital statistics provided by Statistics Korea. Cox proportional hazard model analyses were used to evaluate the risk of cancer mortality according to the obesity status and metabolic health status. Model 1 was adjusted for age, sex, systolic blood pressure, diastolic blood pressure, total cholesterol level and urinary protein. Model 2 was adjusted for Model 1 plus smoking status, alcohol intake and physical activity. We also investigated the interaction between obesity status and metabolic health status on the risk of cancer mortality using a likelihood ratio test comparing the main model (obesity status and metabolic health status) and the full model including the interaction term. $p < 0.05$ were considered statistically significant. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

Table 1 shows the baseline characteristics of the study participants. During an average of 6.07 person-years of follow-up, a total of 3,391 (0.9%) individuals died from cancer. Of the 363,881 participants, 112,133 (30.8%) were obese, 87,627 (24.1%) were overweight and 164,121 (45.1%) were of normal weight. Additionally, 342,442 (94.1%) were metabolically healthy, and 21,439

(5.9%) were metabolically unhealthy. The obese group showed higher BMI, fasting blood glucose, systolic blood pressure, diastolic blood pressure and total cholesterol values compared with the normal group. The metabolically unhealthy group showed higher BMI, fasting blood glucose, systolic blood pressure, diastolic blood pressure and total cholesterol values compared with the metabolically healthy group. The proportions of positive urinary protein results, current smoker and heavy alcohol drinker statuses were higher in the obese group and the metabolically unhealthy group compared with their counterparts.

Table 2 shows the HRs and 95% CIs for risk of cancer mortality according to the obesity status and metabolic health status. According to the obesity status, after adjusting for age, sex, systolic blood pressure, diastolic blood pressure, total cholesterol level, urinary protein,

smoking status, alcohol intake and physical activity, the adjusted HRs (95% CI) were 0.82 (0.75-0.89) and 0.79 (0.72-0.85) for the overweight and obese groups, respectively, compared with the normal weight group. In terms of the metabolic health status, after adjusting for age, sex, systolic blood pressure, diastolic blood pressure, total cholesterol level, urinary protein, smoking status, alcohol intake and physical activity, the adjusted HR (95% CI) was 1.26 (1.14-1.40) for the metabolically unhealthy group compared with the metabolically healthy group.

According to the obesity status, the metabolically unhealthy group had a significantly higher risk of cancer mortality compared with the metabolically healthy group after adjusting for age, sex, systolic blood pressure, diastolic blood pressure, total cholesterol level, urinary protein, smoking status, alcohol intake and physical activity (Table 3). In addition, the interaction between

Table 1. Baseline Characteristics of Study Participants according to the Obesity Status and Metabolically Healthy Status (n=363,881)

Variables	Overall	Obesity status			P-value	Metabolically healthy status		P-value
		Normal (BMI<23kg/m ²)	Overweight (BMI 23-24.9kg/m ²)	Obesity (BMI≥25kg/m ²)		Metabolically healthy (Glucose <126 mg/dL)	Metabolically unhealthy (Glucose ≥126 mg/dL)	
Total (%)	363,881 (100.0)	164,121 (100.0)	87,627 (100.0)	112,133 (100.0)		342,442 (100.0)	21,439 (100.0)	
Number of death from cancer (%)	3,391 (0.9)	1,671 (1.0)	794 (0.9)	926 (0.8)		2,947 (0.9)	444 (2.1)	
Person-year (average)	6.07	6.07	6.11	6.05		6.09	5.81	
Age group (years)								
20-44	205,997 (56.6)	105,724 (64.4)	45,186 (51.6)	55,087 (49.1)	<0.001	199,953 (58.4)	6,044 (28.2)	<0.001
45-64	126,091 (34.7)	44,048 (26.8)	34,903 (39.8)	47,140 (42.0)		114,739 (33.5)	11,353 (52.9)	
≥ 65	31,793 (8.7)	14,349 (8.8)	7,538 (8.6)	9,906 (8.8)		27,750 (8.1)	4,043 (18.9)	
Sex								
Men	186,825 (51.3)	73,134 (44.6)	48,985 (55.9)	64,706 (57.7)	<0.001	174,103 (50.8)	12,722 (59.3)	<0.001
Women	177,056 (48.7)	90,987 (55.4)	38,642 (44.1)	47,427 (42.3)		168,339 (49.2)	8,717 (40.7)	
BMI (kg/m ²)	23.6 ± 3.2	20.8 ± 1.6	24.0 ± 0.6	27.3 ± 2.2	<0.001	23.5 ± 3.2	24.8 ± 3.4	<0.001
Fasting blood glucose (mg/dL)	95.5 ± 28.8	92.4 ± 26.9	96.2 ± 29.2	99.5 ± 30.7	<0.001	90.5 ± 12.5	174.9 ± 70.2	<0.001
Systolic blood pressure (mmHg)	123.8 ± 17.0	119.3 ± 16.1	125.0 ± 16.5	129.3 ± 16.9	<0.001	123.2 ± 16.8	132.3 ± 18.5	<0.001
Diastolic blood pressure (mmHg)	77.4 ± 11.2	74.7 ± 10.6	78.1 ± 10.9	80.9 ± 11.1	<0.001	77.2 ± 11.1	81.4 ± 11.5	<0.001
Total cholesterol (mg/dL)	193.7 ± 37.9	185.0 ± 35.6	196.9 ± 37.3	203.8 ± 38.6	<0.001	192.9 ± 37.1	205.9 ± 47.2	<0.001
Urinary protein								
Negative (-)	357,384 (98.2)	161,714 (98.5)	86,120 (98.3)	109,550 (97.7)	<0.001	337,201(98.5)	20,183 (94.1)	<0.001
Positive (+)	6,497 (1.8)	2,407 (1.5)	1,507 (1.7)	2,583 (2.3)		5,241 (1.5)	1,256 (5.9)	
Smoking history								
Never smoker	245,976 (67.3)	114,273 (69.6)	57,941 (66.1)	77,762 (64.9)	<0.001	231,137 (67.5)	13,839 (64.6)	<0.001
Former smoker	15,211 (4.2)	5,263 (3.2)	4,177 (4.8)	5,771 (5.1)		14,226 (4.2)	985 (4.6)	
Current smoker	103,694 (28.5)	44,585 (27.2)	25,509 (29.1)	33,600 (30.0)		97,079 (28.3)	6,615 (30.8)	
Alcohol intake								
0 g/day	193,219 (53.1)	89,109 (54.3)	45,766 (52.2)	58,344 (52.0)	<0.001	181,154 (52.9)	12,065 (56.3)	<0.001
1-19g/day	135,312 (37.2)	61,922 (37.7)	32,842 (37.5)	40,548 (36.2)		129,100 (37.7)	6,212 (29.0)	
20-39g/day	18,990 (5.2)	7,161 (4.4)	4,876 (5.6)	6,953 (6.2)		17,446 (5.1)	1,544 (7.2)	
≥40g/day	16,360 (4.5)	5,929 (3.6)	4,143 (4.7)	6,288 (5.6)		14,742 (4.3)	1,618 (7.5)	
Physical activity								
0 times per week	210,059(57.7)	101,927 (62.1)	47,637 (54.4)	60,495 (53.9)	<0.001	197,978 (57.8)	12,081 (56.3)	<0.001
1-2 times per week	91,220 (25.1)	37,916 (23.1)	22,950 (26.2)	30,354 (27.1)		86,295 (25.2)	4,925 (23.0)	
3-4 times per week	33,800 (9.3)	13,569 (8.3)	9,034 (10.3)	11,197 (10.0)		31,853 (9.3)	1,947 (9.1)	
≥5 times per week	28,802 (7.9)	10,709 (6.5)	8,006 (9.1)	10,087 (9.0)		26,316 (7.7)	2,486 (11.6)	

Data are expressed as means±SD for the continuous variables and number (percentages) for the categorical variables; *p-value was tested using t-test or 1-way ANOVA for the continuous variables and chi-square test for the categorical variables.

Table 2. Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) for Risk of Death from Cancer according to the Obesity Status and Metabolically Healthy Status (n=363,881)

Variables	Number of death	Mortality rate per 100,000 person-year	Hazard ratios (95% CI)		
			Unadjusted model	Model1	Model2
Obesity status					
Normal (BMI<23kg/m ²)	1,671	167.7	1.0 (reference)	1.0 (reference)	1.0 (reference)
Overweight (BMI ≥23, <25kg/m ²)	794	148.1	0.88 (0.81-0.96)	0.78 (0.72-0.85)	0.82 (0.75-0.89)
Obesity (BMI≥25kg/m ²)	926	136.5	0.82 (0.75-0.88)	0.75 (0.69-0.82)	0.79 (0.72-0.85)
Metabolically healthy status					
Metabolically healthy (Glucose<126 mg/dL)	2,947	141.3	1.0 (reference)	1.0 (reference)	1.0 (reference)
Metabolically unhealthy (Glucose≥126 mg/dL)	444	356.4	2.55 (2.30-2.81)	1.27 (1.15-1.40)	1.26 (1.14-1.40)

*Model 1 was adjusted for age, sex, systolic blood pressure, diastolic blood pressure, total cholesterol level and urinary protein; Model 2 was adjusted for model 1 plus smoking status, alcohol intake, physical activity.

Table 3. Effects of Metabolically Unhealthy Status on the Risk of Cancer Mortality according to the Obesity Status (n=363,881)

Status		Cases/person-year	Mortality rate per 100,000 person-year	HR (95% CI)*	P for interaction†
Normal weight	Metabolically healthy	1,486/959,541.1	154.9	1.00 (reference)	0.31
	Metabolically unhealthy	185/36,796.8	502.8	1.29 (1.10-1.50)	
Overweight	Metabolically healthy	676/504,275.2	134.1	1.00 (reference)	
	Metabolically unhealthy	118/31,694.8	372.3	1.43 (1.17-1.75)	
Obesity	Metabolically healthy	785/621,820.6	126.2	1.00 (reference)	
	Metabolically unhealthy	141/56,090.5	251.4	1.21 (1.01-1.45)	

HR (95% CI)*=Hazard ratios (95% Confidence Interval); *Hazard ratios and their confidence intervals are estimated using Cox proportional model after adjusting for age, sex, systolic blood pressure, diastolic blood pressure, total cholesterol level, urinary protein, smoking status, alcohol intake and physical activity; †P for interaction was tested by likelihood ratio test comparing main model and full model with all covariates

obesity status and metabolic health status on the risk of cancer mortality was not statistically significant ($p=0.31$).

Discussion

We found that the risk of cancer mortality decreased with increasing obesity status. Conversely, a meta-analysis by McGee and the Nurses' Health Study that compared obese and normal weight subjects found that the risk of death from cancer was increased in overweight subjects (Calle et al., 1999; Calle et al., 2003; McGee et al., 2005). Additionally, the large, prospective, Cancer Prevention Study II reported 52% and 62% higher cancer mortality rates among obese males and females, respectively. The distribution of deaths according to the type of tumor differed between Korean and American populations. Further, the association between BMI and mortality is influenced by racial differences (Dahlberg et al., 2013). Nevertheless, a previous Korean study reported a slightly increased risk of death from cancer among overweight individuals (Jee et al., 2006). Mortality caused by some cancer types, such as colorectal, liver, and esophageal, increases with obesity, whereas other cancers, such as lung, show increased mortality in underweight subjects (Seidell et al., 1996; Dahlberg et al., 2013). We did not estimate the cancer mortality risk according to the type of cancer, and therefore did not distinguish cancers as obesity-related or-unrelated.

We found that the metabolically unhealthy group had a significantly higher risk of cancer mortality compared with the metabolically healthy group in all obesity status groups. These findings are in accordance with those of the Framingham study, which reported that subjects with elevated blood glucose levels had higher incidences of cancer (Moore et al., 2014). Although the mechanism behind the association between glucose metabolism and cancer is not well understood, diabetes mellitus is reported to be associated with an increased risk of different types of cancer, specifically, pancreatic, liver and endometrial (relative risk range, 2.0-2.5), and breast, colon and bladder cancers (relative risk range, 1.2-1.5) (Giovannucci et al., 2010).

It is hypothesized that the mechanism behind the glucose-cancer link is related to metabolic dysfunction and inflammation (Garcia-Jimenez et al., 2013). Glucose is an essential nutrient for actively proliferating cells, and tumor cells exhibit particularly rapid growth and proliferation rates. Therefore, it is reasonable to infer that

tumor cells require greater glucose uptake compared with normal cells to accelerate their proliferation. *In vivo* and animal studies have shown that hyperglycemia promotes tumor growth and proliferation (Nunez et al., 2006; Liu et al., 2011). Indeed, this is the basis for Positron Emission Tomography/Computed Tomography (PET/CT), which enables detection of potentially cancerous cells based on their greater uptake of glucose (Gambhir, 2002; Uzel et al., 2013). A prospective cohort study in Sweden also reported that abnormally elevated fasting glucose and postload glucose levels are associated with an increased risk of cancer incidence in females (Stattin et al., 2007).

This is the first study to use sampled cohort data from a national health insurance system to examine the effects of obesity and metabolic status on the risk of cancer mortality. It demonstrated that such sampled cohort data can be representative of the entire national health insurance system. Thus, the results of this study could provide an indication of cancer risk and mortality in the Korean population.

There are a number of limitations to this study. First, we used a simplistic measure of metabolic dysfunction (fasting blood glucose) and simple anthropometric measures of body fat (BMI) to assess metabolic health and obesity, respectively. More precise measures of body fat composition and metabolic health would be useful. However, any error introduced using these simple measures was most likely non-differential. Therefore, our results are likely underestimates of the true effects. Second, we defined the endpoint simply as death due to cancer. Future studies should assess the types of cancer to evaluate obesity-related cancers. Third, the date of the health check-up was assumed to be the year midpoint (July 1), because the date of examination was not included in the individual records. This assumption may cause a measurement bias. Finally, only participants of the health check-up programs of the National Health Insurance system were assessed for eligibility. Thus, we were not able to evaluate subjects who did not participate in the health check-up programs. In addition, most participants who received the health check-up program are likely to be healthier compared with non-participants. Therefore, our sampled cohort data may be biased by the healthy volunteer effect.

In conclusion, we found that the risk of cancer mortality decreased with increasing obesity status and increased with reduced metabolic health. Therefore, given that the rates of metabolic dysfunction are rising, it can be

expected that mortality due to cancer will also increase. It thus follows that treatment strategies targeting metabolic dysfunction may contribute to reducing the risk of death from cancers.

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