RESEARCH ARTICLE

Joint Effects of Low Body Mass Index and Alcohol Consumption on Developing Esophageal Squamous Cell Cancer: a Korean Nationwide Population-Based Cohort Study

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Abstract

Objective: In Korea, 95% of esophageal cancer (EC) was the squamous cell-type. We sought to determine the combined risk of alcohol consumption on developing esophageal squamous cell carcinoma (ESCC) in pre-diagnostic underweight subjects using Korean national data. **Methods:** We analyzed the clinical data from a total of 264,084 individuals aged 40 years or older, who received healthcare checkups arranged by the national insurance program, between 2003 and 2008 in Korea. Cox proportional hazards regression was used after adjusting confounding factors. **Result:** Newly diagnosed 278 EC was identified using the claims data during a median follow-up duration of 7.9 years. It was determined that underweight and obesity-compared with normal weight-were significantly associated with 73% increased risk and 30% decreased risk of EC, respectively. Weight gain reduced the risk of EC. Alcohol consumption increased risk for EC in a dose-dependent manner. Heavy alcohol consumption in individuals with underweight increased the risk of developing EC dramatically. **Conclusion:** Underweight was a risk factor for ESCC and alcohol consumption raised the risk synergistically with low BMI. Achieving normal range of BMI could reduce the risk of ESCC.

Keywords: Esophageal cancer- body mass index- underweight- alcohol- smoking

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Introduction

Esophageal cancer (EC) is the tenth most common cancer and the sixth leading cause of cancer-related deaths worldwide (Globocan, 2016); Because EC is characterized by rapid growth and early metastasis, most of cases reported have been advanced at diagnosis. Despite the remarkable progress made in cancer management, the 5-year overall survival rate EC is only 20% in China. Therefore, understanding and preventing the risk factors for EC are important. Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) are the two most common histopathological cell types which vary significantly in geographical distribution (Hongo et al., 2009). While EAC is the more common in Western countries (Bollschweiler et al., 2001), ESCC still remains to be the dominant type of EC worldwide, particular in East Asia including Korea (Son et al., 2001), China (Corley and Buffler, 2001), Japan (Shibata et al., 2008), and Taiwan(Chang et al., 2002). The ratio of EAC among esophageal malignancies was as low as 1– 4% in Korea, Taiwan and Japan (Son et al., 2001; Chang et al., 2002; Shibata et al., 2008).

Different histologic type of EC has shown different risk factors. While EAC is considered to be an obesity-related disease (Enzinger and Mayer, 2003), there is a limited amount of literature evaluating the relationship between BMI and squamous cell type-EC. This is at part attributable to that most studies confirming this association have been performed in Western societies, where overweight or obese population is much higher than in Asian countries(World Health Organization, 2000; Kim et al., 2010; Yang et al., 2016) and where EAC is more common (Bollschweiler et al., 2001; Shiwaku et al., 2004). Although smoking increases risk for both EAC and ESCC (Stoner et al, 2001; Enzinger and Mayer, 2003), there is a controversy about the effect of alcohol consumption and developing of EC. It has been reported that alcohol intake above 170 g per week significantly increases the risk of ESCC, but not EAC (Pandeya et al, 2009). However, the effect of alcohol cosumption on carcinogensis of EC in underweight subjects have not been evaluated.

Because there has been a lack of large cohort studies which evaluate ESCC, we explored the risk factor of ESCC focusing on a joint effect pre-diagnostic low BMI and alcohol consumption on incidence of ESCC using Korean population-based national cohort data in which 95% of EC was the squamous cell-type (Son et al., 2001).

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In addition, we sought to identify whether weight change can modify the risk of developing EC.

Materials and Methods

Data source and study population

We used the database from the National Health Insurance Corporation (NHIC). The dynamic retrospective cohort data were extracted from the sample. It consisted of a random sample of 852,643 individuals, equivalent to approximately 2% of the Korean population, and contained claims and mortality data. NHIC is the single, national insurer managed by the Korean government, where 97% of the Korean population is subscribed (Lee et al., 2016). This database can be purchased to all Korean researchers with the approval by the official review committee.

Among the 852,643 individuals from the database, we evaluated the medical records of 264,330 Korean residents aged 40 years or older, who had undergone a biennial evaluation provided by NHIC, between the years 2003 and 2008. The medical examinations that took place between 2003 and 2008 included measurements of blood pressure, height, and weight, as well as laboratory tests results, including serum fasting glucose and cholesterol, creatinine, liver enzymes, and urinalysis. Past medical history and health-related behaviors, such as smoking, alcohol consumption, and physical activity, were collected using a standardized, self-reporting questionnaire. Quality control procedures for laboratory tests were performed in accordance with the Korean Association of Laboratory Quality Control. This study was exempt from review by the Institutional Review Board of Seoul National University Bundang Hospital (X-1608/360-904), in accordance with the Declaration of Helsinki as revised in Brazil 2013.

Outcome

The primary endpoint of this study was newly diagnosed EC, which was defined using the International Classification of Diseases, 10th revision (ICD-10) codes (C150-155, C158 and C159). For a full diagnosis, a diagnosis during hospitalization or two more diagnoses at the outpatient clinics were required. To avoid confounding effects by preexisting diseases, individuals with any diagnosis of EC during the preceding year were excluded.

Covariates

Subjects were categorized into four groups according to BMI, in compliance with the recommendations for Asians by the World Health Organization: The underweight group (< 18.5 kg/m^2); the normal group (18.5–22.9 kg/m^2); the overweight group (23.0–24.9 kg/m^2); and the obese group (≥ 25.0 kg/m^2) (Yang et al., 2016; Kim et al., 2010; World Health Organization, 2000; Pandeya et al., 2009). The presence of diabetes was defined when any of the follows was detected; the following criteria; (1) any claim per year for the prescription of antidiabetic medication under ICD–10 codes E10–14, or (2) fasting glucose level ≥7 mmol/L(Yang et al.,2016). Hypertension was defined when (1) at least one claim per year for the prescription of antihypertensive agent under ICD-10 codes I10–I15, or (2) systolic/diastolic blood pressure ≥140/90 mmHg was proven(Yang et al.,2016). The presence of dyslipidemia was defined according to the presence of at least (1) claim per year for the prescription of antihyperlipidemic agent under ICD-10 codes E78, or (2) total cholesterol ≥ 6.21 mmol/L (Yang et al.,2016). Participants were categorized as never/ex or current smokers according to their smoking status 1 year prior to the diagnosis. Other known risk factors that were included in this analysis were yearly income (lower quintile of income), unit of alcohol consumption per drink (complete or near abstinence, < 3, 6, 9 or 12 standard drinks of 10 g alcohol units per drink), frequency of alcohol consumption (never or near abstinence, 2-3 times/month, 1-2 times/week, 3-4 times/week, ≥ 5times/week), physical activity (low, moderate, or high level) based on the frequency and intensity of activity per week, and residency area (urban or rural) at baseline.

Statistics

The data are expressed as the means (SD), geometric means (95% CI), or percentages. The characteristics of the four groups according to their BMI and occurrence of EC were compared using one-way analysis of variance or Chi-squared tests. We used univariate or age- and sex-adjusted Cox proportional hazards regression models. Variables with a p-value of less than 0.20 in age- and sex-adjusted analyses were selected for multivariate analyses. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R programming version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria, http://www. R project. org). A two-sided p-value of less than 0.05 was considered statistically significant.

Results

Demographic characteristics

Among the 264,330 individuals, 91 patients who had been diagnosed with EC by 2002 were excluded. After excluding another 155 patients for missing data, a total of 264,084 persons were included for the final analysis. After a median follow-up period of 7.9 years, 278 individuals (0.11 % of total population) developed EC. The median time to EC development was 3.82 years (1.33 /10,000 person-year). Among the total of 264,084 study subjects, 2.6% (n = 6,784) were classified as underweight, 36.7% (n = 96,867) as normal, 26.6% (n = 70,350) as overweight, and 34.1% (n = 90,083) as obese (Table 1). The underweight group was generally older and included more females. This group also included more individuals who were less physically active, smoked more frequently, consumed alcohol less frequently, had lower income levels, lower blood pressure/fasting glucose levels, and lower serum total cholesterol, and they were mostly residents of rural areas.

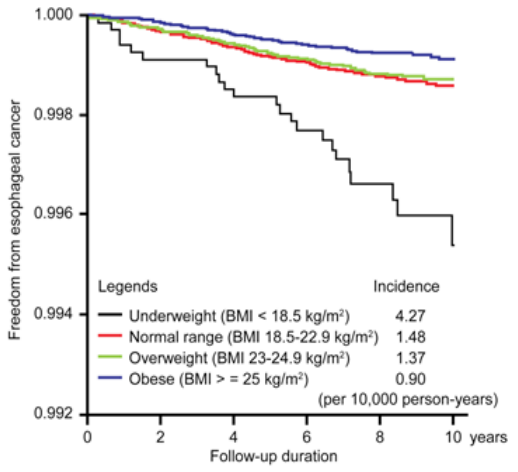
Risk factors associated with the development of esophageal cancer

Figure 1 shows the Kaplan-Meier survival curves

Table 1. Baseline Characteristics of the Study Population

Variables	Underweight < 18.5 Kg/m² n = 6,784	Normal 18.5-22.9 Kg/m² n = 96,867	Overweight 23-24.9 Kg/m² n = 70,350	Obesity ≥ 25 Kg/m² n = 90,083	P for trend
Age (y, mean±SD)	57.6 ± 13.7	53.0 ± 11.1	53.2 ± 10.3	53.7 ± 10.2	0.013
Age (≥ 65year)	2,298 (33.9)	16,935 (17.5)	10,769(15.3)	14,541(16.1)	< 0.001
Sex (male)	3,215 (47.4)	43,185 (44.6)	35,746(50.8)	46,099(51.2)	< 0.001
Height (cm)	160.2 ± 9.1	160.7 ± 8.6	161.4±8.8	161.2 ± 9.2	< 0.001
Body weight (kg)	45.1 ± 5.7	55.2 ± 6.7	62.7 ± 7.0	70.9 ± 9.2	< 0. 001
Body mass index (kg/m²)	17.5 ± 0.9	21.3 ± 1.2	24.0 ± 0.6	27.2 ± 2.0	< 0.001
Systolic blood pressure (mmHg)	120.4 ± 18.7	122.4 ± 17.3	126.3 ± 17.1	130.4 ± 17.3	< 0.001
Diastolic blood pressure (mmHg)	74.6 ± 11.3	76.2 ± 11.0	78.7 ± 11	81.3 ± 11.2	< 0.001
Glucose	96.0 ± 34.4	96.0 ± 29.4	98.4 ± 29.2	101.9 ± 31.4	< 0.001
Total cholesterol	183.7 ± 35.1	192.3 ± 36.3	199.6 ± 37.3	205.0 ± 38.6	< 0.001
Current smoker	1,929 (28.4)	22,653 (23.4)	15,544 (22.1)	19,338 (21.5)	0.03
Current alcohol intake	2,203 (32.5)	36,472 (37.7)	28,805 (41.0)	36,662 (40.7)	< 0.001
Exercise None	4,739 (70.3)	55,804 (58.0)	36,980 (52.9)	47,938 (53.6)	< 0.001
1-4times/week	1,559 (23.1)	31,572 (32.8)	25,392 (36.4)	32,028 (35.8)	
≥5times/week	447 (6.6)	8,843 (9.2)	7,481 (10.7)	9,455 (10.6)	
Lower quintile of yearly income	1,287 (19.0)	15,934 (16.5)	10,560 (15.0)	13,945 (15.5)	< 0.001
Residence area (rural)	3,959 (58.4)	52,519 (54.2)	37,994 (54.0)	50,322 (55.9)	< 0.001
Comorbidity					
Diabetes	552 (8.14)	7,595 (7.84)	7,238 (10.3)	12,797 (14.2)	< 0.001
Hypertension	1,719 (25.3)	26,703 (27.6)	25,781 (36.7)	43,894 (48.7)	< 0.001
Dyslipidemia	520 (7.7)	12,324 (12.7)	12,783 (18.2)	21,820 (24.3)	< 0.001
Developing esophageal cancer	23 (0.34)	114 (0.12)	77 (0.11)	64 (0.07)	< 0.001
Duration (year)	7.9 ± 1.7	7.9 ± 1.7	8.0 ± 1.7	7.9 ± 1.8	0.001

of freedom from EC for up to 10 years in accordance with different BMI ranges. The annual incidence rate of EC was 1.5 per 10,000 person-years for the normal range group, 1.4 for the overweight group, 0.9 for the



Patient number at risk

Underweight	6784	6778	6774	5869	4083	1643
Normal range	96867	96837	96806	83422	58127	23728
Overweight	70350	70331	70309	60767	42790	17885
Obese	90083	90070	90049	77135	53194	22053

Figure 1. Kaplan-Meier Survival Curves of Freedom from Esophageal Cancer for Up to 10 Years according to the World Health Organization Classification of BMI. BMI denotes body mass index. Incidence shows annual incidence rates per 1000 person-years

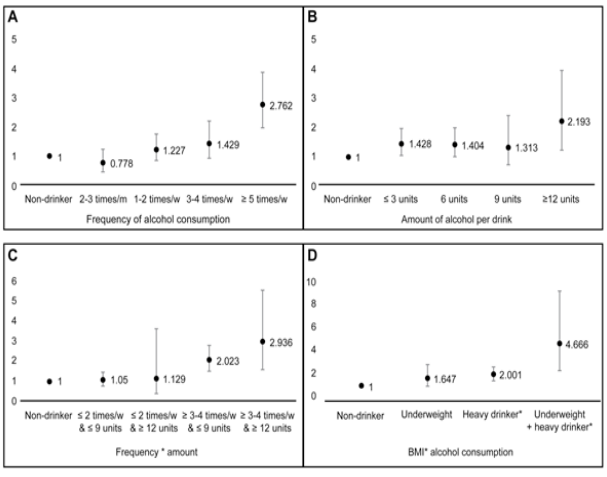


Figure 2. Alcohol Consumption and Risk for Developing Esophageal Cancer. There is an increased risk of esophageal cancer (A) with an increased amount of alcohol consumption; (B) with an increased frequency of alcohol consumption; (C) There was an increased risk of esophageal cancer with an increased frequency or amount of alcohol consumption; (D) Increased risk of esophageal cancer was more prominent in those with underweight and heavy alcohol use than subjects with one risk factor.

Table 2. Univariate and Age/Sex Adjusted Analyses for the Risk of Esophageal Cancer

Variables	Events (n)		Unadjusted		Age/sex-adjusted		Multivariable†	
		IR*	HR	95% CI	HR	95% CI	HR	95% CI
Age <65yrs	90	0.6	1 (ref)		1 (ref)		1.49	**1.42-1.57‡**
≥65yrs	188	3.11	5.16	**4.02-6.64**	1.56	**1.01-2.42**		
Women	49	0.46	1 (ref)		1 (ref)		1 ref)	
Men	229	2.23	5.6	**4.11-7.63**	4.89	**3.59-6.66**	3.92	**2.79-5.52**
Non/ex-smoking	168	1.38	1 (ref)		1 (ref)		1 ref)	
Current smoker	110	2.3	2.23	**1.75-2.83**	1.62	**1.25-2.09**	1.31	**1.00-1.73**
Exercise None	169	1.46	1 (ref)		1 (ref)			
1-4times/week	79	1.1	0.76	0.56-0.99	0.91	0.69-1.20		
≥5times/week	29	1.39	0.95	0.34-1.41	0.77	0.52-1.15		
Non-drinker	127	1	1 (ref)		1 (ref)		1 (ref)	
Drinker	151	1.82	1.82	**1.44-2.31**	1.55	**1.20-2.00**	1.29	**1.17-1.42**
BMI < 18 kg/m^2	23	4.27	2.88	**1.84-4.51**	1.76	**1.12-2.76**	1.73	**1.10-2.71**
BMI 18-23 kg/m^2	114	1.48	1 (ref)		1 (ref)		1(ref)	
BMI 23-25 kg/m^2	77	1.37	0.93	0.69-1.24	0.97	0.72-1.29	1	0.75-1.34
BMI ≥ 25 kg/m^2	64	0.9	0.61	**0.45-0.82**	0.67	**0.49-0.91**	0.7	**0.51-0.95**
Non-diabetes	236	1.26	1 (ref)		1 (ref)			
Diabetes	42	1.9	1.51	**1.09-3.00**	0.95	0.68-1.32		
Normal BP	136	1.04	1 (ref)		1 (ref)			
Hypertension	142	1.8	1.74	**1.37-2.20**	0.98	0.77-1.25		
Non-dyslipidemia	169	1.58	1 (ref)		1 (ref)			
Dyslipidemia	20	1.47	0.91	0.57-1.44	0.93	0.58-1.48		
Yearly income (others)	225	1.27	1 (ref)		1 (ref)			
Lower quintile yearly income	53	1.59	1.25	0.93-1.69	1.17	0.87-1.58		
Urban residence	113	1.2	1 (ref)		1 (ref)			
Rural residence	165	1.43	1.2	0.94-1.52	1.02	0.80-1.30		

HR, denotes hazard ratios; CI, confidence intervals; BMI, body mass index; BP, blood pressure; ref, reference; IR, Incidence rate; *1,000 persons-year) ;†, Adjusted by age, sex, alcohol consumption, BMI and smoking; ‡, increasing 5 years old; Bold indicates statistical significance.

obese group, and 4.3 for the underweight group. The univariate and age-/sex-adjusted risk factors for EC are listed in Table 2. Age, male sex, smoking more than 5 times/week, and alcohol consumption were all associated with increased risk of developing EC. Diabetes and hypertension were also positively associated with EC; however, dyslipidemia, low economic status, and rural residency had no effect on the risk of EC. BMI of less than 18.5 Kg/m^2 was a risk factor for EC, while BMI of greater than 25.0 Kg/m^2 was a protective factor.

After adjusting for age (older than 65 years) and sex (male sex), factors like old age , male sex, smoking more than 5 times/week, alcohol consumption, and BMI of less than 18.5 Kg/m^2 were still associated with increased risk for EC (Table 2). BMI of greater than 25 Kg/m^2 was associated with preventive effect of EC (HR, 0.67; 95% CI, 0.49-0.91).

The risk of developing EC rises sharply after age 55 in the general population (For those in the age range of 60-64 years, the incidence rate was 2.28 per 10,000 person-years The incidence of EC in each age range is illustrated in Supplementary Figure 1.

A multivariable analysis was performed after controlling for smoking, alcohol consumption, age, sex, and BMI (Table 2). BMI of less than 18.5 kg/m^2, increased age, male sex, current alcohol consumption, and current smoking were all independent risk factors for developing EC.

Amount of alcohol consumption and BMI on developing esophageal cancer

Analyses were performed according to the amount and frequency of alcohol consumption. There was an increased risk of EC with an increased frequency or amount of alcohol consumption (Figure 2). Those who consumed alcohol daily showed a 2.8-fold increase in the risk of EC compared with never drinkers (Figure 2A). Those who consumed more than 12 units of alcohol had a 2.2-fold increase in the risk of EC compared with never drinkers (Figure 2 B). When both frequency and amount of consumed alcohol were considered simultaneously, those who drank more than 12 units of alcohol, with a frequency of more than 3 times a week, showed a 2.9-fold increase in the risk of EC compared with never drinkers or compared with those who consumed less than 2 times a week and less than 9 units (Figure 2C). This dose-dependent relationship was more prominent in those with BMI of less than 18.5 Kg/m^2. Those who were underweight and consumed more

Table 3. Incidence of Esophageal Cancer According to Change of Weight at 2 Or 4 Years Follow-Up Compared to the Baseline

	Subjects (n)	Event	Duration (person-year)	Incidence rate (per10,000)
at 2 year health check-up†				
BMI ≥18.5 Kg/m^2→BMI ≥18.5 Kg/m^2	140,406	97	1,129,669	0.86
BMI ≥18.5 Kg/m^2→BMI <18.5 Kg/m^2	1,383	4	11,021	3.63
BMI <18.5 Kg/m^2→BMI ≥18.5 Kg/m^2	1,242	0	10,068	0.00
BMI <18.5 Kg/m^2→BMI <18.5 Kg/m^2	2,042	8	16,558	4.83
at 4 year health check-up†				
BMI ≥18.5 Kg/m^2→BMI ≥18.5 Kg/m^2	139,982	62	1,123,777	0.55
BMI ≥18.5 Kg/m^2→BMI <18.5 Kg/m^2	1,499	2	11,921	1.68
BMI <18.5 Kg/m^2→BMI ≥18.5 Kg/m^2	1,409	2	11,478	1.74
BMI <18.5 Kg/m^2→BMI <18.5 Kg/m^2	1,782	4	14,472	2.76

BMI, body mass index; †, Compared to the enrollment

than 12 units of alcohol, with a frequency of greater than 5 times a week, showed a 4.7-fold increase in the risk of EC compared with those who had none of these conditions (Figure 2D).

Effect of weight change on developing esophageal cancer

Among the study population, 145,073 persons had undergone at least one biennial evaluation. In order to evaluate the effect of weight change on developing esophageal cancer, participants were subclassified to four groups according to the weight change during follow-up interval period (Table 3). Individuals whose BMI had been less than 18.5 Kg/m^2 at baseline but became greater 18.5 Kg/m^2 at the 2 year follow-up showed a lower incidence of EC than those who remained underweight. Non-underweight subjects at baseline who became underweight at the 2 year follow-up showed a higher incidence of EC than those who remained non-underweight. This result was same at the 4-year follow up (Table 3).

Effect of underweight on developing esophageal cancer according to smoking status

Tabaco use has often been regarded as a confounding factor of underweight for ESCC (Gallus et al, 2001; Steffen et al., 2009). In the analyses stratified by smoking status (Supplementary Table 1), increased age, male sex, and current alcohol consumption were associated with increased risk of developing EC. Among the non-smokers, underweight increased the risk of EC by up to 1.88-fold compared with those in the normal weight range. Among the current smokers, underweight was not significantly associated with the development of EC when the 18.0-22.9 Kg/m^2 was a reference. However, it is clear that low BMI, regardless of smoking status, was associated with increased risk of EC (all p for trend < 0.05).

Discussion

We found that individuals with a BMI of less than 18.5 kg/m^2 had a 73% increase in the risk of developing EC in Korea compared with normal-weight subjects (BMI: 18.5 to 22.9 kg/m^2), while individuals with a BMI of greater than 25 kg/m^2 had a 30% decrease in the risk of developing EC. We further determined that alcohol intake was associated with increased risk of EC in a dose-dependent manner. There is a synergistic interaction for the risk of EC between heavy alcohol consumption and underweight. Since 95% of EC in Korea were ESCC (Son et al., 2001), ECs in the study were assumed to be ESCC.

Obesity has been associated with the development EAC (Nilsson et al., 2003); because individuals with high BMI are more likely to experience gastro-esophageal reflux, they are more likely to develop Barrett's esophagus, which is a premalignant condition of EAC (Solaymani-Dodaran et al., 2004). While most studies have evaluated the association between overweight or obesitiy and cancer, the impact of underweight on cancer susceptibility has been relatively ignored. In terms with EC, researchers have evaluated mostly smoking tobacco, alcohol drinking and poor diet (low fresh fruit and vegetable intake) as risk factors for EC rather than BMI.

Smith et al., (2008) has reported the evidence for low BMI or leanness as a factor associated with an increased risk of ESCC in Western and Asian populations. However, because only three Asian cohort studies were included and estimated median BMI of Asian population was lower than that of West, more study on the association between BMI and EC for Asian are required. Poor diet leading to micronutrient deficiencies or malnutrition reflected in low BMI has been implicated as one of the underlying mechanisms explaining higher risk of ESCC (Tran et al., 2005; Umar et al., 2008). Low BMI can be a good indicator of long-term malnutrition, but specific micronutrients, which may affect the development of EC, need to be discovered.

While other studies on the inverse association between BMI and ESCC risk have paid attention to the possible confounding effects of smoking (Gallus et al, 2001; Reeves et al., 2007; Smith et al., 2008; Steffen et al.,2009;), we stratified the amount of alcohol consumption to assess its possible impact on increased risk of ESCC. The synergistic effect of heavy drinking and underweight on the vulnerability of EC was for the first time demonstrated in this present study. The carcinogenicity of alcoholic beverages in relation to ESCC may most likely be due to both ethanol itself and acetaldehyde, which the latter is a known as a carcinogen derived from ethanol metabolism

(Johnson et al., 2015). The effects of this may further be amplified by undernutrition, which is usually associated with insufficiency of micronutrients from improper maintenance of anti-oxidants and immune functions (Venesky et al, 2012; Szuroczki et al., 2012; Lelijveld et al., 2016). There is evidence of protective effects from diets that are rich in fruits, vegetables, and whole-grain cereals on both ESCC and EAC (Thompson et al., 2009; Li et al., 2014; Liu et al., 2013).

Rather than focusing on BMI at early adulthood, assessing BMI at several years prior to diagnosis may be more relevant where carcinogenic mechanisms are concerned. Moreover, in the present study, the preventive effect of weight gain on development of EC was evaluated by categorizing subjects according to change of BMI between baseline and at 2 and 4 year health check-up. Even though the sample size was small, weight loss was associated with developing of ESCC and weight gain was associated with reduced risk of ESCC.

Our finding that BMI is inversely associated with the risk of EC-mostly ESCC-when restricted to non-smokers is in accordance with the results from two large studies (Tran et al., 2005; Reeves et al., 2007; Smith et al., 2008; Umar et al., 2008). Although current smoking status did not significantly contribute to the inverse relationship betweeen underweight and EC development, we observed that there was a higher prevalence of EC among those with lower BMI among smokers. The statistical power may have been insufficient due to the small sample size. The range of BMI, 18.5 $Kg/m^2 \leq$ BMI $<$ 23.0 Kg/m^2, may have been sub-optimal for good health (Whitlock et al, 2009). Indeed, BMI $\geq$ 25.0 Kg/m^2 was associated with reduced risk of EC in the present study. However, because overweight and obesity can contribute to develop metabolic diseases, this result needs cautious interpretation.

One of the limitations of this study is that the data we used did not include specific histological type of EC. However, most ECs in the present study would be ESCC according to previous data (Son et al., 2001). East Asia showed very low ratio of EAC among esophageal cancers (Son et al., 2001; Corley and Buffler, 2001; Shibata et al., 2008; Chang et al., 2002), and an increase in EAC has not yet been observed in Asia, despite a recent increase in prevalence of gastroesophageal reflux disease (Hongo et al., 2009). It was not possible to collect the exact information regarding the TNM stage or symptoms at the time of diagnosis. However, the present study is a cohort study with 7.9 years of follow-up period, not a cross-sectional study. Since the median time to the development of EC was almost 4 years in the present study, it was not reasonable to assume that the low BMI at the time of enrollment was attributable solely to dysphasia or advanced disease, itself. The median survival time, following radiation therapy or combined chemotherapy plus radiotherapy, is generally less than 1.5 years (al-Sarraf et al., 1997).

Nonetheless, the present study is a large-scale, nationwide cohort study, which may offset the aforementioned limitation. Moreover, this is one of the rare studies demonstrating the combined effect of alcohol consumption on ESCC in underweight. We also demonstrated the possible prevention effect of weight gain against ESCC.

In conclusion, our study shows that underweight is an independent risk factor for EC in Koreans, which is predominantly ESCC, along with increased age, male sex, alcohol consumption, and smoking status. Heavy drinkers with a BMI of less than 18.5 Kg/m^2 are at far greater risk of developing ESCC compared with their counterparts. According to our results, more exhaustive examination during the endoscopy is required for male, underweight subjects who consume alcohol. It is also important for individuals with low BMI to avoid excessive alcohol consumption and to maintain healthy body weight.

Competing financial interests

The authors declare that they have no conflict of interest.

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Author Contributions YJC analyzed data and drafted the article. DHL designed this study and edited the manuscript. KDH performed data handling and statistical analysis. HY, CMS and YSP provided statistical support and analyzed questionnaire. NK provided advice on the study design. All authors have read and approved the manuscript.

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