Journal of Cancer Survivorship (2023) 17:1522–1532
https://doi.org/10.1007/s11764-022-01174-3

U-shaped association between body mass index and health-related quality of life impairment in Korean cancer survivors: a nationwide representative cross-sectional survey

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Received: 25 October 2021 / Accepted: 17 January 2022 / Published online: 28 January 2022

Abstract

Purpose Although obesity is an important risk factor for cancer incidence, the effect of body mass index (BMI) on health-related quality of life (HRQoL) after cancer treatment remains unknown. This population-based cross-sectional study assessed different levels of BMI as an important factor associated with impaired HRQoL in long-term cancer survivors.

Methods The study enrolled 1104 cancer survivors from the fourth to seventh Korea National Health and Nutrition Examination Surveys (KNHANES 2007–2018) who were alive at least 5 years after their cancer diagnoses. The BMI was classified into four categories: < 20 (underweight), 20–22.9 (healthy weight), 23–24.9 (overweight), and ≥ 25 kg/m^2 (obese). Impaired HRQoL was defined as the lowest quartile of European Quality of Life 5-Dimensions (EQ-5D) questionnaire scores.

Results Cancer survivors who were underweight or obese were more likely to report health problems on each dimension of the EQ-5D compared to the other BMI groups. In multivariate logistic regression analysis, the two extreme BMI categories were significantly associated with impaired HRQoL (BMI < 20 kg/m^2: odds ratio [OR] = 1.73, 95% confidence interval [CI] = 1.08–2.86; BMI ≥ 25 kg/m^2: OR = 2.14, 95% CI = 1.41–3.25; *P* trend = 0.049), especially in the gastrointestinal cancer group (*P* heterogeneity = 0.007). Moreover, the association between underweight/obese and impaired HRQoL showed a significant sex difference (*P* heterogeneity = 0.019).

Conclusions The results of this study suggest that deviations from normal BMI, such as being underweight or obese, are negatively associated with HRQoL in long-term cancer survivors; to some extent, this may depend on cancer type and sex.
Implications for Cancer Survivors.
Reaching or maintaining a healthy weight should be emphasized for cancer survivors as a long-term goal even after cancer treatment.

Keywords Cancer survivor · Health-related quality of life · EQ-5D · Body mass index · Obesity · Underweight

Introduction

Although cancer remains one of the leading causes of death worldwide, cancer survival rates continue to increase due to early detection and improved treatment [1–3]. There are differences in survival among cancer types, but overall survival trends are generally increasing, even for more lethal cancers [3]. The 5-year survival rates for breast cancer are 90.2% and 89.5% in the USA and Australia, respectively, while countries in Northeast Asia have the highest 5-year survival rates for gastrointestinal (GI) cancers (South Korea: colon cancer 71.8%, rectum cancer 71.1%, stomach cancer 68.9%; Japan: esophageal cancer 36.0%; and Taiwan: liver cancer, 27.9%) [3]. In South Korea, the 5-year relative survival rate for all patients diagnosed with cancer between 2014 and

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2018 was 70.3%, which was a factor in the high number of cancer survivors (> 2 million; 3.9% of the Korean population) at the end of 2018 [4].

For many people, cancer is a chronic disease that requires ongoing care to minimize and manage the long-term effects of treatment and comorbidities [5]. The goals of cancer treatment are to cure the cancer, prolong survival, and provide the highest possible quality of life (QoL) during and after treatment [6]. In oncology, QoL is an important endpoint beyond cancer recurrence and survival that shifts the focus from how long cancer patients survive to how "well" they survive [7]. QoL is now recognized as an important variable when predicting the long-term prognosis [8].

Growing evidence of the roles of lifestyle factors in cancer survivorship highlights that adherence to a healthy diet, sufficient physical activity, and a healthy weight may influence overall QoL, as well as disease-specific and overall health outcomes [9–12]. Among other variables, obesity is a well-established risk factor for many cancers and chronic diseases, and an important determinant of health [13–15]. Indeed, at the time of their initial diagnosis, many cancer survivors were overweight or obese, which was associated with a worse prognosis after diagnosis; this may be characterized by poorer overall health and QoL, as well as comorbidities, cancer recurrence, and cancer-related mortality [12, 16–18]. Previous studies of cancer survivors have found that a higher body mass index (BMI) is associated with a poorer QoL and lower physical functioning [19–24], while in obese cancer survivors weight loss is associated with better physical function [25].

However, many of these studies were conducted on specific cancer groups, such as patients with breast, prostate, and colorectal cancer. In addition, they focused on Western populations, which tend to have relatively high BMIs. Evidence of an association between obesity and QoL in Asian cancer survivors remains insufficient, especially for long-term survivors. Therefore, the purpose of this study was to assess the independent association between BMI and health-related quality of life (HRQoL) in Korean long-term cancer survivors.

Methods

Data sources and study population

Participants were enrolled from the fourth (2007–2009), fifth (2010–2012), sixth (2013–2015), and seventh (2016–2018) Korea National Health and Nutrition Examination Surveys (KNHANES), conducted by the Korea Centers for Disease Control and Prevention (KCDC). The survey was designed to obtain nationally representative information on the health and nutritional status of Koreans, and monitors trends in health risk factors and the prevalence of major chronic diseases. More detailed information on the survey design and protocol has been published elsewhere [26].

In total, 2779 (3.7%) of 75,968 adults aged ≥ 19 years in the fourth, fifth, sixth, and seventh KNHANES had a history of a cancer diagnosis; of these, 2605 who had never been diagnosed with a second primary cancer were included in this study. We included only long-term survivors (5 years post-diagnosis) of major cancers, excluding some specific cancer sites such as the brain, head and neck, central nervous system, and blood ($n = 1146$). The elapsed time of 5 years or more after initial treatment is considered "cured" from a medical point of view, and this criterion was based on the differences in follow-up care for patients and established knowledge regarding the long-term course of the disease [27]. Thyroid cancer, which has a better overall prognosis than other cancers, and lung cancer, for which only a small number of cases met the inclusion criteria, were not included in the study. Pregnant or breastfeeding women, and people who reported significant weight loss (≥ 6 kg) over the previous year, were also excluded from the analysis ($n = 42$). The final sample included 1104 individuals with no missing BMI or HRQoL data. The types of cancer were classified as follows: stomach and esophageal cancer, hepatobiliary (liver and gallbladder) and pancreatic cancer, colorectal cancer, breast cancer, gynecologic cancer (ovary, cervix uteri, and corpus uteri), and genitourinary cancer (prostate, kidney, and urinary organs). All participants provided written informed consent, and the institutional review board of the KCDC approved the study (2007-02CON-04-P; 2008-04EXP-01-C; 2009-01CON-03-2C; 2010-02CON-21-C; 2011-02CON-06-C; 2012-01EXP-01-2C; 2013-07CON-03-4C; 2013-12EXP-03-5C; and 2018–01-03-P-A).

Assessment of BMI

Anthropometric measurements of the participants were conducted by trained staff at a mobile examination center as part of their health examination. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2) and categorized into four groups according to the Asian-Pacific cutoff points [28]. Guidelines consider underweight to be a BMI < 18.5 kg/m^2, but we chose a higher cutoff point based on the literature [29–32] and initial analyses: underweight < 20 kg/m^2, healthy weight 20–22.9 kg/m^2, overweight 23–24.9 kg/m^2, and obese ≥ 25 kg/m^2. A BMI of 20 kg/m^2 has been accepted as the threshold for underweight in the elderly population [30].

Assessment of HRQoL

HRQoL was assessed using the three-level version of the European Quality of Life 5-Dimensions (EQ-5D)

questionnaire, a standardized instrument developed by the EuroQol Group for measuring health status that is widely used in population health surveys and clinical studies. Participants were asked to rate their own health status with respect to five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension had three severity levels (no, moderate, and severe problems). For each of the five dimensions, health problems were defined as either present (moderate or severe problems) or absent (no problems) in our analysis. A weighted EQ-5D index was calculated based on responses to questions on the five dimensions, with a score of 1 indicating optimal health or function status and lower scores indicating greater impairment of HRQoL. We defined the lowest quartile of the weighted EQ-5D index as "impaired HRQoL."

Other covariates

Survey year, age, sex, marital status, education level, and household income (quartiles) were included as sociodemographic characteristics, and smoking and drinking habits and physical activity were included as health behavior–related variables. For drinking habit, we categorized respondents into four groups according to their reported number of binge drinking episodes during the previous 12 months (abstainer, none, once or less once a month, and at least once a week to every day). Binge drinking was defined as consumption of ≥ 7 and ≥ 5 alcoholic drinks on a single occasion for men and women, respectively. Physical activity was divided into three categories according to the frequency of participation in moderate- or vigorous-intensity activities during the week (no physical activity, insufficiently active, and active). Participants reporting at least 150 min of moderate aerobic activity or 75 min of vigorous aerobic activity a week, or a combination of moderate and vigorous activity, were classified into the "active" group. When combining moderate- and vigorous-intensity activities, 1 min of vigorous-intensity activity was considered to correspond to 2 min of moderate-intensity activity.

In addition to cancer-related characteristics (cancer types and time since cancer diagnosis), the number of cardiometabolic risk factors (hypertension, diabetes mellitus, dyslipidemia), and lifetime history of other chronic diseases were included as clinical characteristics. Regarding cardiometabolic risk factors, hypertension was defined as systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 mmHg and/or current use of antihypertensive medication. Diabetes mellitus was defined as fasting glucose ≥ 126 mg/dL and/or current use of antidiabetic medication. Dyslipidemia was defined as the presence of at least one of the following conditions: hypercholesterolemia (total cholesterol ≥ 240 mg/dL), hypertriglyceridemia (triglycerides ≥ 200 mg/dL), low levels of high-density lipoprotein cholesterol (< 40 mg/dL), and taking any medication for dyslipidemia. The number of cardiometabolic risk factors, including hypertension, diabetes mellitus, and dyslipidemia, was calculated for each individual (0, 1, 2, or 3 diseases). A lifetime history of a chronic disease other than cancer was defined as having a medical history of physician-diagnosed stroke, myocardial infarction, angina pectoris, renal failure, liver cirrhosis, asthma, chronic obstructive pulmonary disease, arthritis, or thyroid disease.

Statistical analyses

The general characteristics of the cancer survivors according to BMI were compared using one-way analysis of variance for continuous variables and the chi-square test for categorical variables. The proportions of cancer survivors with moderate or severe problems in each EQ-5D dimension, or impaired HRQoL (lowest quartile of EQ-5D scores), were compared among the four BMI groups using the chi-square test. The distributions of overall HRQoL scores (EQ-5D index) according to BMI were analyzed and compared using a general linear model, after adjusting for survey year, age, sex, cancer type, and time since cancer diagnosis. We used multivariate logistic regression to assess the associations between BMI categories and impaired HRQoL in cancer survivors, and calculated odds ratios (ORs) and 95% confidence intervals (CIs) for impaired HRQoL. We also investigated whether the association between BMI and impaired HRQoL varied by cancer group and sex. Stratified analyses were conducted by cancer group (GI, breast, gynecologic and genitourinary cancer) and sex. We also analyzed interaction effects in the adjusted multivariate model, and conducted a likelihood-ratio test to compare models with and without interaction terms. All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA).

Results

Characteristics of the study population

Of the 1104 cancer survivors who were alive at least 5 years after being diagnosed with cancer, about 51.7% were overweight or obese while 14.2% were classified as underweight (Table 1). The mean age of the cancer survivors was 64.7 ± 11.0 years, and the mean time since cancer diagnosis was 12.6 ± 7.8 years. The most common types of cancer were stomach and esophageal cancer (26.8%), gynecologic cancer (26.4%), and breast cancer (18.9%). Underweight cancer survivors with a BMI < 20 kg/m^2 were more likely to be diagnosed with stomach or esophageal cancer than were cancer survivors in other BMI groups; obese cancer survivors with a BMI ≥ 25 kg/m^2 were more

Table 1 General characteristics of cancer survivors according to body mass index

	Total population	BMI categories				*P* value
		Underweight <20 kg/m^2	Healthy weight 20–22.9 kg/m^2	Overweight 23–24.9 kg/m^2	Obese ≥ 25 kg/m^2	
All participants	1,104 (100.0)	157 (14.2)	376 (34.1)	251 (22.7)	320 (29.0)	
BMI, kg/m^2	23.4 ± 3.2	18.6 ± 1.1	21.7 ± 0.8	24.0 ± 0.6	27.2 ± 2.1	< 0.001
Waist circumference, cm	81.4 ± 9.4	69.1 ± 5.5	77.5 ± 5.6	82.9 ± 6.0	90.8 ± 6.7	< 0.001
Survey phase						0.831
Fourth (2007–2009)	181 (16.4)	28 (17.8)	64 (17.0)	42 (16.7)	47 (14.7)	
Fifth (2010–2012)	266 (24.1)	42 (26.8)	87 (23.1)	58 (23.1)	79 (24.7)	
Sixth (2013–2015)	300 (27.2)	35 (22.3)	105 (27.9)	64 (25.5)	96 (30.0)	
Seventh (2016–2018)	357 (32.3)	52 (33.1)	120 (31.9)	87 (34.7)	98 (30.6)	
Cancer types						< 0.001
Stomach and esophageal cancer	296 (26.8)	89 (56.7)	115 (30.6)	47 (18.7)	45 (14.1)	
Hepatobiliary and pancreatic cancer	41 (3.7)	6 (3.8)	15 (4.0)	9 (3.6)	11 (3.4)	
Colorectal cancer	173 (15.7)	13 (8.3)	51 (13.6)	54 (21.5)	55 (17.2)	
Breast cancer	209 (18.9)	18 (11.5)	71 (18.9)	44 (17.5)	76 (23.8)	
Gynecologic cancer	291 (26.4)	22 (14.0)	92 (24.5)	73 (29.1)	104 (32.5)	
Genitourinary cancer	94 (8.5)	9 (5.7)	32 (8.5)	24 (9.6)	29 (9.1)	
Time since cancer diagnosis, years						
Mean ± SD	12.6 ± 7.8	12.1 ± 7.1	12.3 ± 7.8	11.5 ± 6.4	12.1 ± 7.9	0.204
5–6	259 (23.5)	30 (19.1)	95 (25.3)	66 (26.3)	68 (21.3)	0.352
7–9	224 (20.3)	41 (26.1)	80 (21.3)	41 (16.3)	62 (19.4)	
10–14	285 (25.8)	38 (24.2)	91 (24.2)	70 (27.9)	86 (26.9)	
≥ 15	336 (30.4)	48 (30.6)	110 (29.3)	74 (29.5)	104 (32.5)	
Age, years						
Mean ± SD	64.7 ± 11.0	65.6 ± 12.0	63.5 ± 11.1	63.4 ± 11.0	63.8 ± 11.1	0.236
19–49	119 (10.8)	18 (11.5)	41 (10.9)	27 (10.8)	33 (10.3)	0.052
50–59	226 (20.5)	32 (20.4)	80 (21.3)	53 (21.1)	61 (19.1)	
60–69	318 (28.8)	28 (17.8)	109 (29.0)	78 (31.1)	103 (32.2)	
70–79	356 (32.3)	58 (36.9)	124 (33.0)	79 (31.5)	95 (29.7)	
≥ 80	85 (7.7)	21 (13.4)	22 (5.9)	14 (5.6)	28 (8.8)	
Sex						< 0.001
Male	381 (34.5)	72 (45.9)	143 (38.0)	89 (35.5)	77 (24.1)	
Female	723 (65.5)	85 (54.1)	233 (62.0)	162 (64.5)	243 (75.9)	
Marital status						0.163
Living with a spouse	813 (73.6)	121 (77.1)	283 (75.3)	188 (74.9)	221 (69.1)	
Not living with a spouse	291 (26.4)	36 (22.9)	93 (24.7)	63 (25.1)	99 (30.9)	
Education level						0.165
Elementary school graduate or less	516 (47.0)	80 (51.6)	162 (43.2)	108 (43.0)	166 (52.4)	
Middle school graduate	143 (13.0)	17 (11.0)	47 (12.5)	36 (14.3)	43 (13.6)	
High school graduate	267 (24.3)	34 (21.9)	100 (26.7)	61 (24.3)	72 (22.7)	
College graduate or more	172 (15.7)	24 (15.5)	66 (17.6)	46 (18.3)	36 (11.4)	
Household income						0.496
First quartile (lowest)	394 (36.0)	56 (36.1)	120 (32.2)	90 (36.3)	128 (40.1)	
Second quartile	276 (25.2)	44 (28.4)	102 (27.4)	54 (21.8)	76 (23.8)	
Third quartile	219 (20.0)	28 (18.1)	75 (20.1)	53 (21.4)	63 (19.8)	
Fourth quartile (highest)	206 (18.8)	27 (17.4)	76 (20.4)	51 (20.6)	52 (16.3)	
Smoking status						0.002
Non-smoker	723 (65.9)	88 (56.4)	231 (61.8)	167 (66.8)	237 (74.8)	
Former smoker	236 (21.5)	41 (26.3)	88 (23.5)	52 (20.8)	55 (17.4)	

Table 1 (continued)

	Total population	BMI categories				*P* value
		Underweight <20 kg/m^2	Healthy weight 20–22.9 kg/m^2	Overweight 23–24.9 kg/m^2	Obese ≥ 25 kg/m^2	
Current smoker	138 (12.6)	27 (17.3)	55 (14.7)	31 (12.4)	25 (7.9)	
Frequency of binge drinking						0.266
Abstainer	519 (47.3)	82 (52.6)	169 (45.1)	112 (44.8)	156 (49.2)	
None	329 (30.0)	45 (28.9)	126 (33.6)	73 (29.2)	85 (26.8)	
Once or less once a month	165 (15.0)	15 (9.6)	57 (15.2)	41 (16.4)	52 (16.4)	
At least once a week to every day	85 (7.7)	14 (9.0)	23 (6.1)	24 (9.6)	24 (7.6)	
Physical activity						0.840
No physical activity	739 (67.2)	108 (69.2)	246 (65.6)	170 (68.0)	215 (67.4)	
Insufficiently active	102 (9.3)	10 (6.4)	36 (9.6)	26 (10.4)	30 (9.4)	
Active	259 (23.6)	38 (24.4)	93 (24.8)	54 (21.6)	74 (23.2)	
Number of cardiometabolic risk factors						<0.001
0 condition	392 (35.5)	88 (56.1)	168 (44.7)	69 (27.5)	67 (20.9)	
1 condition	397 (36.0)	52 (33.1)	135 (35.9)	106 (42.2)	104 (32.5)	
2 conditions	234 (21.2)	14 (8.9)	57 (15.2)	59 (23.5)	104 (32.5)	
3 conditions	81 (7.3)	3 (1.9)	16 (4.3)	17 (6.8)	45 (14.1)	
Lifetime history of other chronic diseases						<0.001
Absence	672 (60.9)	113 (72.0)	238 (63.3)	162 (64.5)	159 (49.7)	
Presence	432 (39.1)	44 (28.0)	138 (36.7)	89 (35.5)	161 (50.3)	

BMI, body mass index; *SD*, standard deviation

Data were expressed as frequency (percentage) or mean ± SD

likely to be diagnosed with breast or gynecologic cancer ($P<0.001$). In addition, obese cancer survivors were more likely to be female ($P<0.001$) and non-smokers ($P=0.002$), and to have cardiometabolic risk factors such as hypertension, diabetes mellitus, or dyslipidemia ($P<0.001$), and a lifetime history of other chronic diseases ($P<0.001$).

Distribution of EQ-5D index scores according to BMI and cancer type

Table 2 shows the distributions of EQ-5D index scores by cancer type. In the analysis of all cancer survivors, mean EQ-5D index scores differed significantly among the BMI groups ($P<0.001$). In particular, obese and underweight

Table 2 Distribution of EQ-5D index scores according to body mass index and cancer type

	BMI categories				*P* value
	Underweight <20 kg/m^2	Healthy weight 20–22.9 kg/m^2	Overweight 23–24.9 kg/m^2	Obese ≥ 25 kg/m^2	
All subjects	0.875 ± 0.201*	0.921 ± 0.130	0.905 ± 0.135	0.862 ± 0.170*	<0.001
Cancer types					
Stomach and esophageal cancer	0.863 ± 0.204*	0.917 ± 0.123	0.921 ± 0.096	0.852 ± 0.184	0.016
Hepatobiliary and pancreatic cancer	0.846 ± 0.153*	0.958 ± 0.070	0.978 ± 0.066	0.926 ± 0.098	0.052
Colorectal cancer	0.729 ± 0.357*	0.902 ± 0.131	0.851 ± 0.188	0.876 ± 0.159	0.022
Breast cancer	0.928 ± 0.112	0.955 ± 0.078	0.912 ± 0.106	0.859 ± 0.181*	<0.001
Gynecologic cancer	0.964 ± 0.077	0.897 ± 0.173	0.912 ± 0.132	0.850 ± 0.164	0.004
Genitourinary cancer	0.911 ± 0.135	0.938 ± 0.112	0.931 ± 0.110	0.875 ± 0.184	0.323

EQ-5D, European Quality of Life 5-Ddimensions questionnaire; *BMI*, body mass index; *SD*, standard deviation

Data were expressed as mean ± SD, and *P* values were generated by one-way analysis of variance

A single asterisk (*) represents value significantly different ($P<0.05$) from control group (BMI of 20–22.9 kg/m^2) by the one-way analysis of variance followed by the Dunnett's post hoc analysis

cancer survivors had significantly lower EQ-5D index scores than those in the healthy weight (BMI 20–22.9 kg/m^2) category ($P < 0.05$). The EQ-5D index scores of survivors who had been diagnosed with stomach or esophageal cancer ($P = 0.016$), hepatobiliary or pancreatic cancer ($P = 0.052$), colorectal cancer ($P = 0.022$), breast cancer ($P < 0.001$), or gynecologic cancer ($P = 0.004$) also differed significantly by BMI category. Underweight GI cancer survivors and obese breast cancer survivors had lower EQ-5D index scores compared to healthy weight cancer survivors ($P < 0.05$).

Comparison of HRQoL according to BMI category in all cancer survivors

Underweight and obese cancer survivors were more likely to report moderate or severe problems in a single domain of the EQ-5D, such as mobility ($P < 0.001$), usual activities ($P < 0.001$), pain/discomfort ($P < 0.05$), and anxiety/depression ($P < 0.05$) compared to the other BMI groups (Fig. 1a). Moreover, an inverse *U*-shaped association between BMI and overall HRQoL score was observed, and the highest EQ-5D index scores were seen in the BMI 20–22.9 kg/m^2 group (Fig. 1b; P trend = 0.013). In particular, based on a Dunnett's multiple comparison test, cancer survivors with a BMI < 20 or ≥ 25 kg/m^2 had significantly lower EQ-5D index scores than those in the healthy weight (BMI 20–22.9 kg/m^2) category ($P < 0.05$). Impaired HRQoL (lowest quartile of EQ-5D index scores) was more prevalent at the two extremes of the BMI distribution (Fig. 1c; 29.3% in cancer survivors with a BMI < 20 kg/m^2 and 35.6% in cancer survivors with a BMI ≥ 25 kg/m^2; P trend = 0.002).

Association between BMI and impaired HRQoL

Multivariate logistic regression analyses showed that low (< 20 kg/m^2) and high (≥ 25 kg/m^2) BMI were both significantly associated with greater odds of impaired HRQoL in cancer survivors (Table 3). Although statistical significance was reduced after adjusting for sociodemographic, cancer-related and clinical characteristics and other covariates, cancer survivors with a BMI of < 20 or ≥ 25 kg/m^2 had 1.73-fold (95% CI = 1.05–2.86) and 2.14-fold (95% CI = 1.41–3.25) higher odds of having impaired HRQoL than those with a BMI of 20–22.9 kg/m^2, respectively (model 3; P trend = 0.049).

We also examined whether the association between BMI and impaired HRQoL differed according to cancer group and sex. A significant association between a BMI of < 20 or ≥ 25 kg/m^2 and impaired HRQoL was observed in GI cancer survivors, including stomach and esophageal, hepatobiliary and pancreatic, and colorectal cancers; however, among the survivors of other cancers, increased odds of impaired HRQoL were observed only when BMI was ≥ 25 kg/m^2 (P heterogeneity = 0.007). The association between underweight and impaired HRQoL was found only in men, and the association between obesity and impaired HRQoL was found only in women (P heterogeneity = 0.019).

Discussion

As survival times after a cancer diagnosis continue to increase, more attention is being paid to the management of long-term health issues [20]. In recent years, research has started to focus on QoL and the importance of a healthy lifestyle after cancer treatment. In particular, there is increasing evidence that being under- or overweight can adversely affect the health of cancer survivors. Our findings show a significant association between deviation from a normal BMI and a worse HRQoL in long-term survivors of a variety of major cancers. The study included adult cancer survivors of all ages and was not restricted to a specific type of cancer or treatment. To the best of our knowledge, this is the first study of its kind to be conducted in Asia, and to include a nationally representative sample of Koreans. Even after adjusting for cancer-specific variables and conventional risk factors for poor HRQoL, including sociodemographic and lifestyle factors and chronic diseases, the positive associations of extreme BMI categories (< 20 or ≥ 25 kg/m^2) with impaired HRQoL remained strong and differed according to cancer type and sex.

In Western countries, the relationship between BMI and HRQoL has been investigated in a variety of settings, in both cancer survivors and patients with chronic disease [33–36]. In a large sample of adults drawn from the general population of the USA, low (< 18.5 kg/m^2) and high BMI (≥ 30 kg/m^2) values were associated with impaired HRQoL, particularly in terms of physical (rather than mental) functioning [37]. Systematic reviews of observational studies in a general population showed that mortality increased with extreme BMI values [32]. Similar results were obtained in studies of cancer survivors. Evidence from seven randomized clinical trials (RCTs) revealed reduced overall survival in both underweight and obese colon cancer survivors [38]. In long-term (≥ 5 years post-diagnosis) survivors of breast, prostate, and colorectal cancers, a higher BMI was associated with a worse physical QoL, including more severe pain and role limitations due to physical problems, and poorer perceived health, physical functioning, and vitality [19]. Moreover, a comprehensive review of observational studies and RCTs that considered the role of lifestyle in the prognoses of breast, colorectal, and prostate cancer survivors suggested that excess weight is an important risk factor for cancer prognosis, and that it can be modified through diet and physical activity interventions [10].

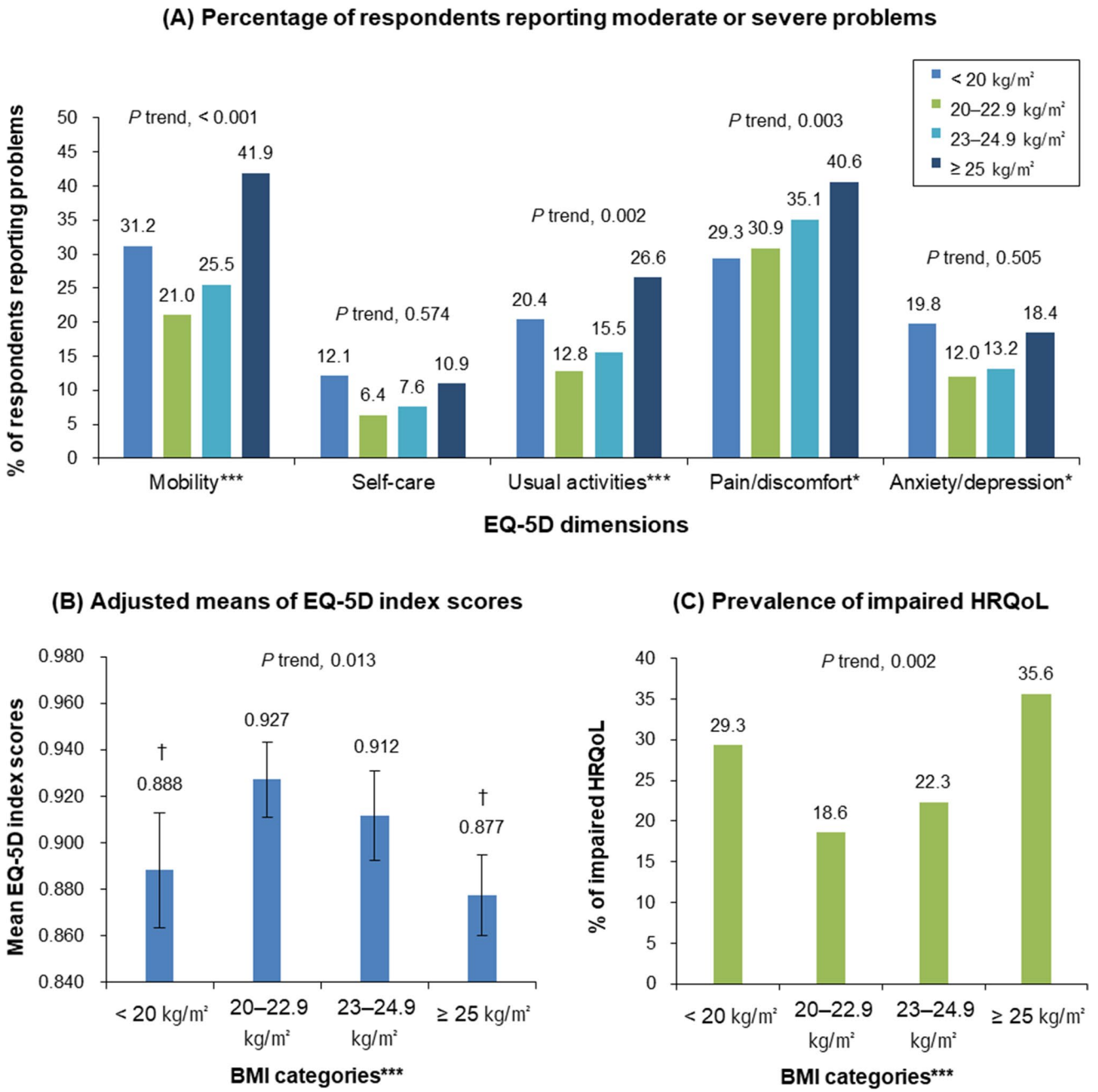

Fig. 1 Comparison of HRQoL among BMI categories in all cancer survivors. **a** Percentage of participants reporting moderate or severe problems for each dimension of the EQ-5D. **b** Mean and 95% confidence limits of the EQ-5D index scores, adjusted for survey year, age, sex, cancer type, and time since cancer diagnosis. **c** Prevalence of impaired HRQoL (lowest quartile of EQ-5D index scores). Asterisks (*) indicate statistically significant differences among BMI categories (*$P<0.05$; **$P<0.01$; ***$P<0.001$). A dagger (†) indicates a significant difference ($P<0.05$) from the control group (BMI of 20–22.9 kg/m^2) by Dunnett's post hoc analysis

We also assessed whether the association of BMI with HRQoL differ by cancer type and sex; the results were inconsistent. GI cancers, including stomach, colorectal, and liver cancers, are the most commonly diagnosed cancers in Korean men [4]. In our study, the percentage of men in the GI cancer group was 60.4% (stomach and esophageal cancer, 60.1%; hepatobiliary and pancreatic cancer, 68.3%; colorectal cancer, 60.0%). Most GI cancer survivors experience a deterioration in QoL due to a variety of functional and nutritional problems including poor social functioning, nausea/vomiting, dysphagia, and dietary restrictions [39, 40]. Various nutritional and functional factors after cancer treatment can lead to weight loss and poor HRQoL. In a Korean study that investigated the association between BMI

Table 3 Association between body mass index and impaired health-related quality of life

	BMI categories				*P* for trend	*P* heterogeneity
	Underweight <20 kg/m^2	Healthy weight 20–22.9 kg/m^2	Overweight 23–24.9 kg/m^2	Obese ≥ 25 kg/m^2		
All subjects						
No. of cases of impaired HRQoL	46/157	70/376	56/251	114/320		
Model 1: crude OR (95% CI)	1.81 (1.18–2.79)	1.00 (ref.)	1.26 (0.85–1.86)	2.42 (1.71–3.42)	0.002	
Model 2: age- and sex-adjusted OR (95% CI)[a]	1.76 (1.10–2.81)	1.00 (ref.)	1.31 (0.86–2.00)	2.35 (1.61–3.42)	0.006	
Model 3: Mmultivariate-adjusted OR (95% CI)[b]	1.73 (1.05–2.86)	1.00 (ref.)	1.25 (0.79–1.97)	2.14 (1.41–3.25)	0.049	
By cancer group						0.007
Gastrointestinal cancer[c]						
No. of cases of impaired HRQoL	39/108	36/181	30/110	36/111		
Model 3: multivariate-adjusted OR (95% CI)[b]	2.86 (1.43–5.71)	1.00 (ref.)	1.71 (0.87–3.37)	2.12 (1.03–4.37)	0.794	
Breast cancer						
No. of cases of impaired HRQoL	2/18	6/71	7/44	27/76		
Model 3: multivariate-adjusted OR (95% CI)[b]	1.04 (0.15–7.09)	1.00 (ref.)	1.48 (0.38–5.67)	3.38 (1.05–10.85)	0.030	
Genitourinary and gynecologic cancer						
No. of cases of impaired HRQoL	5/31	28/124	19/97	51/133		
Model 3: multivariate-adjusted OR (95% CI)[b]	0.73 (0.22–2.45)	1.00 (ref.)	0.93 (0.43–2.03)	2.10 (1.08–4.09)	0.012	
By sex						0.019
Male						
No. of cases of impaired HRQoL	26/72	19/143	16/89	17/77		
Model 3: multivariate-adjusted OR (95% CI)[b]	4.17 (1.79–9.70)	1.00 (ref.)	1.31 (0.56–3.09)	1.74 (0.69–4.35)	0.121	
Female						
No. of cases of impaired HRQoL	20/85	51/233	40/162	97/243		
Model 3: multivariate-adjusted OR (95% CI)[b]	0.98 (0.48–1.99)	1.00 (ref.)	1.28 (0.73–2.26)	2.30 (1.39–3.80)	<0.001	

BMI, body mass index; *HRQoL*, health-related quality of life; *OR*, odds ratio; *CI*, confidence interval

[a]Adjusted for survey year, age, and sex

[b]Adjusted for model 2 + marital status, education level, household income, smoking status, frequency of binge drinking, physical activity, cancer type, time since cancer diagnosis, number of cardiometabolic risk factors, and lifetime history of other chronic diseases

[c]Includes cancer of the gastrointestinal tract and accessory organs of digestion, including the esophagus, stomach, liver, biliary system, pancreas, colon, and rectum

and QoL in gastric cancer survivors who underwent gastrectomy, significantly greater decreases in QoL were seen in patients whose BMI dropped postoperatively [40, 41].

Conflicting findings have been reported regarding the associations of obesity status and sex with prognosis in cancer survivors. A long-term follow-up study examining the association between BMI and the prognosis of colon cancer survivors found that obesity was associated with a significant increase in overall mortality in women but not in men [42]. In the general population of Canada, the association between body weight and the trajectory of HRQoL was highly sex-specific. Among men, there was a substantial HRQoL burden associated with being underweight, whereas no decrease in HRQoL was demonstrated in obese males [43]. A nationally representative French cross-sectional study revealed that the association between BMI and HRQoL generally exhibited an inverted *J*-shaped curve, with a steeper decrease seen in men with a BMI <20 kg/m^2; this was particularly apparent for physical functioning and general health [33].

The negative effects of obesity on HRQoL may be partly explained by the presence of comorbidities [9, 42]. For example, health problems caused by obesity, such as type 2 diabetes and cardiovascular and musculoskeletal diseases, can lead to poor HRQoL and functional impairment [37, 44, 45]. Moreover, the rates of psychological comorbidities,

including depression, are high in obese people; such comorbidities are also associated with a variety of medical and dietary problems [46]. Obesity may also increase the risk of lymphedema, fatigue, and other side effects of cancer and its treatment [47].

Weight management is a very important health issue for many cancer survivors [6, 18, 48]. Some patients begin the treatment process with overweight or obese status, while others gain weight during treatment; still others may become underweight due to treatment-related side effects such as nausea, vomiting, and difficulty in swallowing [6]. Therefore, oncology healthcare professionals should encourage maintenance of a healthy weight and lifestyle in all stages of cancer care, both to avoid adverse sequelae and to improve overall health and survival [17, 18, 48].

This study had several strengths. Firstly, we used data from a nationally representative survey of the Korean population. The KNHANES includes non-institutionalized Korean citizens enrolled via a multi-stage cluster probability sampling method, ensuring a homogeneous and representative sample [26]. Secondly, the analysis of various types of cancer made it possible to identify specific cancers that require more attention to weight conditions such as being underweight or obese after treatment. Thirdly, we tried to adjust for all factors that could confound the results. A wide range of health factors and behaviors, and cancer-specific variables, which may affect HRQoL, were controlled for in the final multivariate logistic regression model. Finally, BMI values were calculated based on height and weight measurements obtained by trained professionals, rather than self-reported information. Many previous studies used self-reported BMI, which can lead to underreporting bias.

This study also had several limitations. Firstly, we could not establish a causal relationship between BMI and HRQoL based on the results of our study. In other words, due to the cross-sectional design of the study, the effect of BMI on QoL cannot be directly determined. In addition, although we tried to include only patients who do not suffer from problems directly associated with cancer and its treatment, this study cannot definitively claim that a decrease in QoL was not a result of cancer or its treatment. Secondly, HRQoL was measured using generic rather than cancer survivor–specific instruments, such as the European Organization for Research and Treatment of Cancer-Quality of Life Core 30 or the Functional Assessment of Cancer Therapy-General, which are the most widely used instruments to assess QoL in oncology research. The EQ-5D is a generic instrument designed for rapid assessments; disease-specific instruments can better detect subtle changes in health conditions [49]. Thirdly, although BMI was used to define obesity and underweight in our current data, it may be an imprecise measure of body composition, e.g., the amount and distribution of muscle and specific adipose tissue compartments. That is, BMI does not measure muscle and adipose tissue nor distribution, an important predictor of cancer mortality [16]. Studies show that low muscle mass is associated with outcomes such as higher surgical complications, treatment-related toxicities, lower physical function, poorer QoL, and shorter survival, and that patients with higher BMIs do not necessarily have worse cancer outcomes due to excess adipose tissue [16, 50]. Future studies should consider body composition to clearly understand the relationship between obesity status and QoL in cancer survivors. Finally, although we adjusted the analyses for major confounders, the relationship between BMI and HRQoL may have been affected by some unmeasured variables.

Observational follow-up studies and RCTs are needed to investigate the direct and long-term effects of changes in body composition and BMI on HRQoL in cancer survivors. Programs for cancer survivors who have recently completed treatment, and those living with cancer as a chronic condition, should emphasize the importance of reaching or maintaining a healthy body weight to improve physical, emotional, and functional outcomes.

Conclusion

In 15, deviations from a normal BMI value were associated with reduced HRQoL in cancer survivors who survived at least 5 years after diagnosis, even after controlling for important sociodemographic characteristics, health risk behaviors, prior history of disease, and multimorbidity. Therefore, weight management should be emphasized to cancer survivors even after treatment as a long-term goal. More research is warranted to elucidate the mechanisms underlying the bidirectional relationship between BMI and HRQoL.

Author contribution JEP, KEY, SYK, CWK, and JHP contributed to the study concept and design. JEP and SYK analyzed and interpreted the data. JEP and KEY drafted the initial manuscript. SYK, CWK, HSH, and JHP made critical revisions to the manuscript and approved the final draft. JHP acted as the study supervision. All authors read and approved the final manuscript.

Funding The design of this study was developed from an abstract presented at the 25th European Congress on Obesity (ECO 2018). The research was financially supported by the Chungbuk National University Korea National University Development Project (2020).

Data availability The data of the current study are available from the Korea Disease Control and Prevention Agency (https://knhanes.kdca.go.kr/knhanes/main.do) on reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

Ethics approval. This study was approved by the institutional review board of the Korea Disease Control and Prevention Agency (2007-02CON-04-P; 2008-04EXP-01-C; 2009-01CON-03-2C; 2010-02CON-21-C; 2011-02CON-06-C; 2012-01EXP-01-2C; 2013-07CON-03-4C; 2013-12EXP-03-5C; and 2018–01-03-P-A). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent to participate. All study participants provided written informed consent.

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