World Journal of Urology (2019) 37:2393–2400
https://doi.org/10.1007/s00345-019-02690-1

ORIGINAL ARTICLE

Association of body mass index with bladder cancer risk in men depends on abdominal obesity

Jin Bong Choi[1] · Jung Ho Kim[2] · Sung-Hoo Hong[3] · Kyung-Do Han[4] · U-Syn Ha[3,5]

Received: 22 November 2018 / Accepted: 18 February 2019 / Published online: 26 February 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

Purpose The previous epidemiological studies about the associations between obesity and bladder cancer risk have reported inconsistent results. Therefore, we analyzed whether the abdominal obesity effected on the risk of developing bladder cancer according to body mass index (BMI) using nationally representative data from the National Health Insurance System (NHIS).

Patients and methods Among people who underwent at least one health examination from 2009 to 2012 in Korea, 11,823,876 men without a previous diagnosis of bladder cancer were followed up until December 2015. Multiple Cox regression analysis was conducted to determine the hazard ratio (HR) and 95% confidence interval (CI) for the association between bladder cancer and BMI or waist circumference (WC).

Results Significant upward trends in the risk of bladder cancer were observed with increasing BMI or WC according to the multivariate-adjusted model. However, the association between BMI and bladder cancer is influenced by the presence of abdominal obesity. In the group with WC < 90 cm, there was no significant change in the HRs for bladder cancer development beyond the reference BMI. In contrast, the HRs for bladder cancer showed statistically significant increase as the BMI increased beyond the reference BMI in the group with WC ≥ 90 cm.

Conclusion This population-based study showed that increasing BMI and increasing WC were risk factors for developing bladder cancer in men, independent of confounding variables. However, there was a discrepancy in the trend of bladder cancer development according to BMI between the groups with abdominal obesity and without abdominal obesity.

Keywords Bladder cancer · Body mass index · Waist circumference

Introduction

Bladder cancer is the 11th most frequently diagnosed cancer worldwide [1]. In Korea, bladder cancer is the 8th most frequent cancer in males and the number of new cases continued to increase from 2235 cases in 2000 to 3949 cases in 2014 with a male-to-female ratio of approximately 4:1 [2]. Tobacco smoking, which is associated with 30% of cases in women and 50% of cases in men, is a major contributor to bladder cancer [3]. Other risk factors have been revealed including occupational exposure to carcinogens, genetic mutations, infections, hypertension and diabetes [4, 5].

In addition to these risk factors, obesity has been considered a risk factor for approximately 20% of all malignancies [6]. Associations have been reported for liver, kidney, colorectal, prostate, endometrial, and postmenopausal breast cancers [7, 8]. Associations between obesity and bladder cancer risk have also been reported in the past few decades. Most studies have used body mass index (BMI)

✉ U-Syn Ha
ushamd@catholic.ac.kr

1 Department of Urology, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

2 Department of Urology, Dongnam Institute of Radiological & Medical Sciences, Cancer Center, Busan, Republic of Korea

3 Department of Urology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

4 Department of Biostatistics, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

5 The Cancer Research Institute, The Catholic University of Korea, Seoul, Republic of Korea

to investigate the relationship between obesity and bladder cancer risk. However, these epidemiological studies have reported inconsistent results [8, 9].

We thought that these discrepancies might be due to the fact that BMI does not measure body fat directly. Although a large majority of individuals with high BMI have excess body fat, in some cases such as athletes, high BMI is due to muscle mass. Conversely, people with metabolically obese normal weight (MONW) and excess visceral fat might have a normal MI. In fact, waist circumference (WC) has been reported as a better measure of visceral and abdominal fat distribution than BMI in cardiovascular disease [10].

In our previous study using the National Health Insurance Service (NHIS) database, we already found that increasing age, BMI, smoking status, dyslipidemia, diabetes, and hypertension were risk factors [11]. Therefore, in this study, we examined the association between obesity and bladder cancer in men based on both BMI and WC using the NHIS database for the entire male population of Korea.

Patients and methods

Data source

We used the national health claims database from the NHIS of Korea [12]. The NHIS contains extensive health information for 97.1% of the Korean population. The remaining approximately 3% of the population is covered by the Medical Aid program due to low income. Information on the Medical Aid program has also been included in the NHIS database since 2006. Consequently, the NHIS database is thought to include data from the entire Korean population [13].

In the present study, the insurance claim code based on the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) was searched. Bladder cancer is coded C67. The Korean government has declared a plan to radically enhance the benefits coverage for four major conditions (cardiovascular diseases, cerebrovascular diseases, rare diseases, and cancers). Therefore, all cancer patients are considered to be enrolled in this database. The patient names and identification numbers were anonymized to protect individual privacy.

The Korean Health Examination database was used to obtain information about BMI, WC, and other confounding variables. A general health examination is not mandatory in Korea, but it is almost semi-mandatory for office employees, local household owners, and members of households. Patients were not covered by insurance if they did not get a health check-up. We used the linked NHIS database for the same patients to evaluate the development of bladder cancer.

Additionally, hypertension was defined as follows: a previous hypertension diagnosis (I10–13, I15) from the ICD-10-CM, blood pressure $\geq$ 140/90 mmHg, or a history of taking antihypertensive drugs. Diabetes was identified by the diagnostic codes E10–14, a fasting serum glucose level $\geq$ 126 mg/dl, or a self-reported medical history of diabetic drugs. Additionally, dyslipidemia was identified by the diagnostic code E78, a total cholesterol level $\geq$ 240 mg/dl, or self-reported use of lipid-lowering drugs. Alcohol consumption status was categorized into three groups: nondrinkers, mild-to-moderate drinkers who drank less than 30 g of alcohol a day, and heavy drinkers who drank more than 30 g of alcohol a day. Smoking status was also categorized as nonsmoker, current smoker, and ex-smoker. People were categorized as performing exercise regularly if they replied "Yes" to the question, "Did you exercise (running, aerobics, high-speed cycling, mountain hiking, etc.) for over 20 min until you were almost out of breath during the last week?"

WC was measured midway between the lower rib margin and the iliac crest in a standing position. The WC cutoff value for abdominal obesity was $\geq$ 90 cm for men [14]. We used the following BMI categories: underweight (under 18.5); normal weight (18.5–22.9); overweight (23–24.9); obese class 1 (25–29.9); and obese class 2 (over 30) from the Korean Society for the Study of Obesity [15].

Study population

Of the 45,850,458 people who underwent at least one health examination from 2009 to 2012, those aged < 20 years (n = 81,120) were excluded because bladder cancer is rare in this age group. Information regarding WC and BMI was reported in health examination databases. After excluding people with missing WC or BMI data from health examination databases (n = 628,528), duplicates (n = 21,787,540), people with bladder cancer diagnosed before January 2009 (n = 14,445), and women (n = 11,484,949), a total of 11,823,876 men without a previous diagnosis of bladder cancer were followed from the January 2009 to the December 2015. Events that did not occur during the follow-up time were censored, and Cox regression analysis was used for these censored data. The percentage of missing values was approximately 10% for the variables. Sensitivity analysis was used to handle these missing data. The study design and patient characteristics are shown in Fig. 1.

Statistical analysis

SAS version 9.4 (SAS Institute, Cary, NC, USA) was used. The data are presented as the mean ± standard deviation (SD) or proportion for continuous or categorical variables, respectively. Incidence rates are expressed as the number per 100,000 person-years. Multiple Cox regression analysis

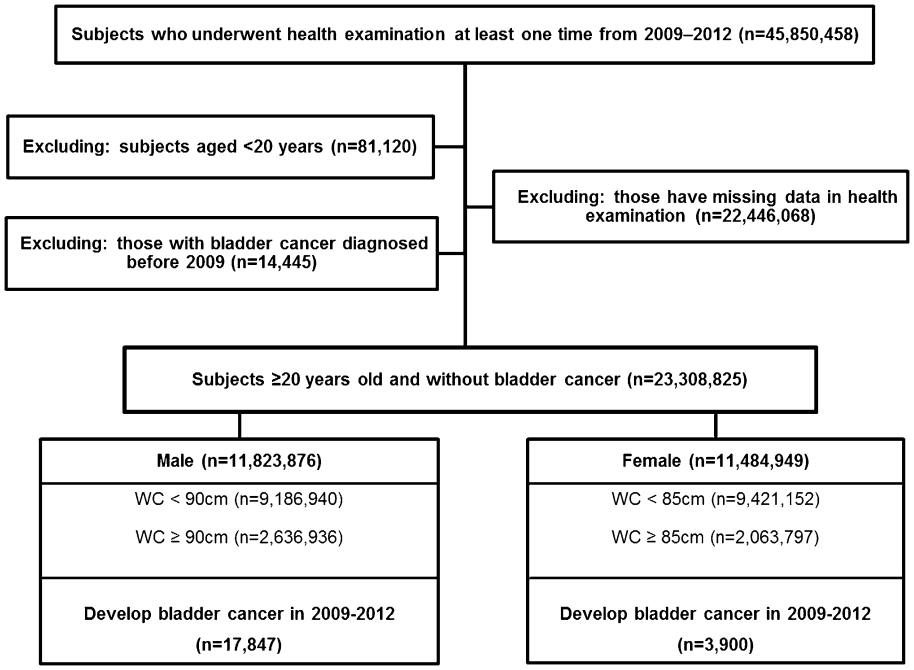

Fig. 1 Study design and disposition of subjects

was conducted to examine the hazard ratio (HR) and 95% confidence interval (CI) for the association between bladder cancer and obesity relative to the reference (patients with BMI 18.5–22.9 kg/m^2 or WC 85–90 cm). Calculations were made by adjusting for age in Model 1 and for age, diabetes, smoking status, exercise, and alcohol consumption in Model 2. The analyses of age- and multivariable-adjusted HRs for bladder cancer according to BMI stratified by abdominal obesity (WC < 90 cm and ≥ 90 cm) were also presented for each model. P values were used to assess linear trends in the HRs and interactions between BMI and WC. A value less than 0.05 was considered statistically significant.

Results

During 64,069,297.93 person-years of follow-up, 17,847 incident cases of bladder cancer developed between the beginning of 2009 and the end of 2015, and the incidence rate was 0.27 per 100,000 person-years.

General characteristics according to abdominal obesity

The general patient characteristics of the bladder cancer study cohort are summarized in Table 1. Among a total of 11,823,876 men, approximately 0.2% of the population categorized as WC ≥ 90 cm was diagnosed with bladder cancer, while approximately 0.14% of the population categorized as WC < 90 cm was diagnosed with bladder cancer. In the obese group, which was characterized by a BMI over 25, 23.2% were categorized as WC < 90 cm, while approximately 14% of the men categorized as WC ≥ 90 cm had a normal weight according to the BMI.

Risk of bladder cancer increases with increasing BMI or WC

Increasing BMI and increasing WC were risk factors for bladder cancer development in men. The HR for bladder cancer was lowest in people with a BMI < 18.5 and highest in those with 25.0 ≤ BMI < 30. A significant increasing trend in the risk of bladder cancer was observed with increasing BMI in the multivariate-adjusted model (*P* for trend < 0.001; Fig. 2). The HR for bladder cancer was lowest in people with a WC < 80 cm and highest in those with WC ≥ 100 cm in both models. A significant increasing trend in the risk of bladder cancer was observed with increasing WC in the multivariate-adjusted model (*P* for trend < 0.001; Fig. 3). Table 2 shows the incidence rate of bladder cancer per 100,000 person-years and the HRs for bladder cancer according to BMI or WC.

Impact of abdominal obesity on the association between BMI and bladder cancer development

There was a significant interaction between BMI and WC in the development of bladder cancer (*P* for interaction < 0.001; Table 3). Therefore, there was a discrepancy in the trend of bladder cancer development according to BMI between the groups with abdominal obesity and without abdominal obesity. In the group with WC < 90 cm,

Table 1 Clinical characteristics of population according to waist circumference in males

WC (cm)	WC < 90	WC ≥ 90	Total
No. in population	9,186,940	2,636,936	11,823,876
No. of diagnosed bladder cancer cases	12,456 (0.14)	5391 (0.2)	17,847 (0.15)
Age, years	45.7 ± 14.10	49.1 ± 13.70	46.45 ± 13.85
Age ≥ 65	1,034,297 (11.26)	399,236 (15.14)	1,433,533 (12.12)
BMI (kg/m^2)	23.19 ± 2.45	27.56 ± 2.60	24.16 ± 2.51
< 18.5	280,894 (3.06)	910 (0.03)	281,804 (2.38)
18.5–22.9	3,930,900 (42.79)	54,641 (2.07)	3,985,541 (33.71)
23.0–24.9	2,843,385 (30.95)	314,385 (11.92)	3,157,770 (26.71)
25.0–29.9	2,103,428 (22.9)	1,844,574 (69.95)	3,948,002 (33.39)
≥ 30	28,333 (0.31)	422,426 (16.02)	450,759 (3.81)
Smoking status			
Non	2,854,602 (31.07)	786,301 (29.82)	3,640,903 (30.79)
Former	2,170,963 (23.63)	749,583 (28.43)	2,920,546 (24.70)
Current	4,161,375 (45.3)	1,101,052 (41.75)	5,262,427 (44.51)
Alcohol consumption			
None	3,064,755 (33.36)	875,899 (33.22)	3,940,654 (33.33)
Mild to moderate	5,081,830 (55.32)	1,372,006 (52.03)	6,453,836 (54.58)
Heavy	1,040,355(11.32)	389,031(14.75)	1,429,386 (12.09)
Regularly exercise	5,142,550 (55.98)	1,448,889 (54.95)	6,591,439 (55.75)
Hypertension	2,146,147 (23.36)	1,166,636 (44.24)	3,312,783 (28.02)
Dyslipidemia	1,396,777 (15.2)	721,192 (27.35)	2,117,969 (17.91)
Diabetes	809,723 (8.81)	461,394 (17.5)	1,271,117 (10.75)

Data are presented as the mean ± SD, or % (SD)

WC waist circumference, *BMI* body mass index, *SD* standard deviation

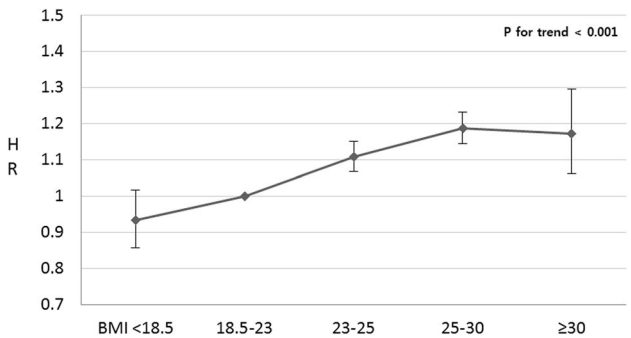

Fig. 2 Hazard ratio of bladder cancer according to body mass index in the multivariate-adjusted model (adjusted for age, diabetes, smoking status, exercise, and alcohol consumption). The error bars represent the upper and lower limits of the 95% confidence interval

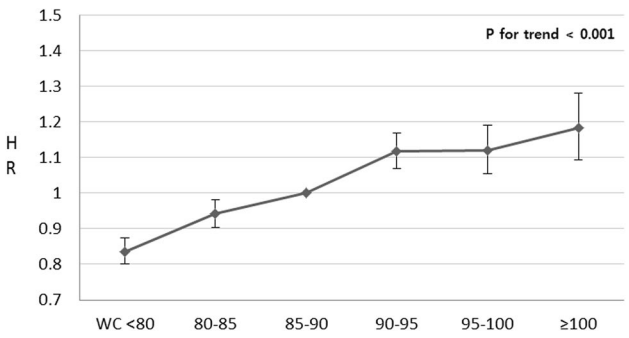

Fig. 3 Hazard ratio of bladder cancer according to waist circumference in the multivariate-adjusted model (adjusted for age, diabetes, smoking status, exercise, and alcohol consumption). The error bars represent the upper and lower limits of the 95% confidence interval

there was no significant change in the HRs for bladder cancer development beyond the reference BMI in the multivariable-adjusted models. The HRs (95% CI) were 1.05 (0.99, 1.10) in the obese group, which was characterized by a BMI over 25, and 0.96 (0.59, 1.54) in the class 2 obese group, which was characterized by a BMI over 30. However, in the group with WC ≥ 90 cm, the HRs for bladder cancer increased as the BMI increased beyond the reference BMI. The HRs (95% CI) were 1.19 (1.03, 1.39) in the overweight group, which was characterized by a BMI over 23, and 1.24 (1.07, 1.42) in the obese group, which was characterized by a BMI over 25. Figure 4 shows the HR for bladder cancer according to BMI when stratified by abdominal obesity in the multivariable-adjusted model.

Table 2 Age- and multivariate-adjusted HRs for bladder cancer according to BMI and WC in males

	Event	Person-years	Incidence*	HR (95% confidence interval)			
				Model 1†	*P* for trend	Model 2‡	*P* for trend
BMI (kg/m^2)							
< 18.5	575	1,464,863.71	0.39	0.96 (0.88, 1.05)	< 0.001	0.93 (0.86, 1.02)	< 0.001
18.5–22.9	6075	21,564,902.41	0.28	Ref.		Ref.	
23.0–24.9	4933	17,220,444.57	0.29	1.09 (1.05, 1.13)		1.11 (1.07, 1.15)	
25.0–29.9	5847	21,428,026.27	0.27	1.16 (1.12, 1.20)		1.19 (1.15, 1.23)	
≥ 30	417	2,391,060.97	0.17	1.15 (1.04, 1.27)		1.17 (1.06, 1.30)	
WC (cm)							
< 80	3833	18,658,970.36	0.21	0.85 (0.81, 0.88)	< 0.001	0.84 (0.80, 0.87)	< 0.001
80–85	4260	16,811,410.64	0.25	0.94 (0.91, 0.98)		0.94 (0.90, 0.98)	
85–90	4363	14,417,227.35	0.30	Ref.		Ref.	
90–95	3256	8,683,780.60	0.37	1.12 (1.07, 1.17)		1.12 (1.07, 1.17)	
95–100	1419	3,644,185.02	0.39	1.13 (1.06, 1.20)		1.12 (1.06, 1.20)	
≥ 100	716	1,853,723.95	0.39	1.20 (1.11, 1.30)		1.18 (1.09, 1.28)	

BMI body mass index, *WC* waist circumference, *HR* hazard ratio

*All rates are expressed as number per 100,000 person-years

†Adjusted for age

‡Adjusted for age, diabetes, smoking status, exercise, and alcohol consumption

Table 3 Age- and multivariable-adjusted HRs for bladder cancer according to BMI stratified by abdominal obesity in males

WC (cm)	BMI (kg/m^2)	Event	Person-years	Incidence*	HR (95% confidence interval)	
					Model 1†	Model 2‡
WC < 90	< 18.5	567	1,460,297.27	0.39	0.96 (0.88, 1.05)	0.93 (0.85, 1.01)
	18.5–22.9	5862	21,278,296.41	0.28	Ref.	Ref.
	23.0–24.9	3882	15,527,111.01	0.25	1.05 (1.01, 1.10)	1.08 (1.04, 1.13)
	25.0–29.9	2128	11,469,817.26	0.19	1.01 (0.96, 1.06)	1.05 (0.99, 1.11)
	≥ 30	17	152,086.41	0.11	0.92 (0.57, 1.49)	0.96 (0.59, 1.54)
WC ≥ 90	18.5–22.9	213	286,606.00	0.74	Ref.	Ref.
	23.0–24.9	1051	1,693,333.56	0.62	1.18 (1.02, 1.37)	1.19 (1.03, 1.39)
	25.0–29.9	3719	9,958,209.01	0.37	1.21 (1.05, 1.39)	1.24 (1.07, 1.42)
	≥ 30	400	2,238,974.56	0.18	1.20 (1.03, 1.30)	1.22 (1.05, 1.37)
§*P* for interaction					< 0.001	< 0.001

BMI body mass index, *WC* waist circumference, *HR* hazard ratio

*All rates are expressed as number per 100,000 person-years

†Adjusted for age

‡Adjusted for age, diabetes, smoking status, exercise, and alcohol consumption

§Interaction between BMI and WC

Discussion

The main findings of this population-based study are (1) men with a higher BMI are more likely to develop bladder cancer independent of confounding variables, (2) men with a larger WC are more likely to develop bladder cancer independent of confounding variables, and (3) there was a discrepancy in the trend of bladder cancer development according to BMI between the groups with abdominal obesity and without abdominal obesity.

Obesity is expected to increase and become the most important public health problem. In the United States, 40% of men and 30% of women are overweight, and 35% of men and 37% of women are obese according to the National Health and Nutrition Examination Survey [16]. In South Korea, although the prevalence of obesity has slightly

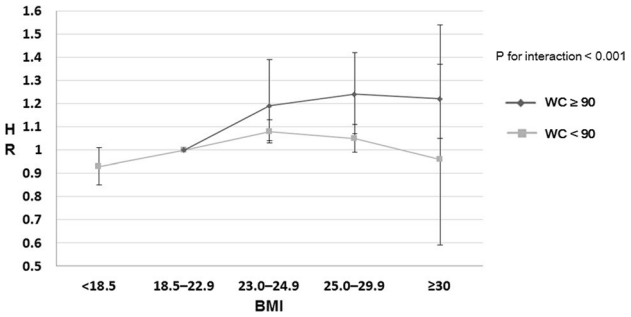

Fig. 4 Hazard ratio of bladder cancer stratified by body mass index according to abdominal obesity in the multivariate-adjusted model (adjusted for age, diabetes, smoking status, exercise, and alcohol consumption). The error bars represent the upper and lower limits of the 95% confidence interval. The subjects with BMI < 18.5 and WC ≥ 90 were excluded from the analysis because there were only 910 (0.03%)

decreased among women since 2001, obesity showed an upward trend among men from 1998 to 2009 [17]. In this regard, the evaluation about biological mechanisms linking obesity and carcinogenesis and the association of obesity with cancer development should be carried out in great account.

The biological mechanisms underlying the association between obesity and bladder cancer have not been clearly identified. However, this association might be partially explained by insulin resistance related to adipose tissue. Adiposity is positively correlated with insulin resistance, and this outcome is compensated for by the stimulation of pancreatic insulin secretion, which commonly results in hyperinsulinemia. Hyperinsulinemia decreases the hepatic secretion of IGF binding protein-1 and IGF binding protein-2, which increases circulating insulin-like growth factor-I (IGF-I) [18, 19]. IGF-I induces angiogenic and tumor-related lymphangiogenic effects. Several reports showed that IGF-I induces the synthesis of hypoxia inducible factor-1a, which induces neo-vascularization and metastases [20]. Furthermore, IGF-I prevents apoptosis and induces the spread of metastatic tumors [21]. Moreover, circulating IGF-I is higher in males than in females, which could partly explain the difference in the incidence of bladder cancer according to gender [22].

Especially, factors secreted by adipose tissue such as chemokine (C-X-C motif) ligand 1, plasminogen activator inhibitor 1, and interleukin-6 increase the migration of bladder tumor cells and increase risk of bladder cancer recurrence [23]. Maj et al. reported also that adipose-derived stem cells promoted bladder cancer cell growth and metastasis in vitro study [24].

BMI, a measure of weight that is adjusted for height, is a simple and noninvasive measurement. Therefore, BMI is the most commonly used measure for the evaluation of obesity. However, BMI is an imperfect tool as a measure of body composition, such as regional body fat distribution. BMI simply represents general obesity rather than central obesity or visceral obesity. BMI cannot separate those who are overweight due to excess fat mass from those who are overweight due to excess muscle mass or MONW people with excess visceral fat but with normal weight and BMI, as shown in our study. We found that 23% of those who were obese, as characterized by a BMI over 25, were categorized as WC < 90 cm, while approximately 14% of men categorized as WC ≥ 90 cm had normal weight according to BMI.

In recent decades, numerous epidemiological studies have reported associations between obesity and bladder cancer [25, 26]. However, these studies have reported variable conclusions because most studies used only BMI as the parameter to determine obesity. Although WC has been added to anthropometric measures, BMI and WC have been considered independently in assessing the risk of bladder cancer [27]. Furthermore, to the best of our knowledge, no study has examined the associations between BMI and bladder cancer after stratification by WC. Our results showed different associations between BMI and bladder cancer development according to the presence of abdominal obesity. In the group with WC < 90 cm, the HRs for bladder cancer increased as the BMI increased beyond the reference BMI; these results contrasted those observed in the group with WC ≥ 90 cm.

There were some limitations in this study. One limitation was that detailed biochemical information, such as cancer stage (nonmuscle invasive bladder cancer vs. muscle invasive bladder cancer), histologic grade, and molecular pathology, was not available for this cohort; thus, we could not adjust for these factors. In particular, there is mounting evidence that bladder cancer constitutes a group of molecularly heterogeneous diseases that undergo various clinical processes and exhibit various therapeutic responses [28, 29]. Nevertheless, the lifestyle variables such as smoking status, alcohol consumption status, and exercise status were adjusted relatively accurately. In fact, accurate analysis of smoking history was very important in this study because it is a major contributor to bladder cancer. Second, BMI and WC change over time, but our study used single measures of BMI and WC at baseline. Therefore, we do not know whether reducing fat mass will decrease the risk of bladder cancer development. Therefore, future studies should consider the effects of changes in anthropometric measures on bladder cancer risk.

Conclusions

This population-based study showed that increasing BMI and increasing WC were risk factors for developing bladder cancer in men, independent of confounding variables.

However, there was a discrepancy in the trend of bladder cancer development according to BMI between the groups with abdominal obesity and without abdominal obesity. Conclusively, this study showed that the association of BMI with risk of bladder cancer development in men depends on abdominal obesity.

Author contributions JBC and U-SH conceived and designed the experiments. Choi and Kim performed the experiments. JHK and S-HH were involved in samples recruitment. K-DH analyzed the data. JBC and U-SH wrote the first draft of the manuscript. All the authors reviewed and edited the manuscript and approved the final version of the manuscript.

Funding This research was supported by National Research Foundation of Korea (Grant number: NRF-2015R1C1A1A01051802).

Compliance with ethical standards

Conflict of interest The authors declare no competing financial interests.

Ethical approval This study was approved by the Institutional Review Board of the Catholic University of Korea (KC16RISI0944).

References

1. Chavan S, Bray F, Lortet-Tieulent J, Goodman M, Jemal A (2014) International variations in bladder cancer incidence and mortality. Eur Urol 66:59–73. https://doi.org/10.1016/j.eururo.2013.10.001
2. Jung KW, Won YJ, Oh CM, Kong HJ, Lee DH, Lee KH (2017) Cancer Statistics in Korea: Incidence, Mortality, Survival, and Prevalence in 2014. Cancer Res Treat. https://doi.org/10.4143/crt.2017.118
3. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC (2011) Association between smoking and risk of bladder cancer among men and women. JAMA 306:737–745. https://doi.org/10.1001/jama.2011.1142
4. Burger M, Catto JW, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, Kassouf W, Kiemeney LA, La Vecchia C, Shariat S, Lotan Y (2013) Epidemiology and risk factors of urothelial bladder cancer. Eur Urol 63:234–241. https://doi.org/10.1016/j.eururo.2012.07.033
5. Cantiello F, Cicione A, Salonia A, Autorino R, De Nunzio C, Briganti A, Gandaglia G, Dell'Oglio P, Capogrosso P, Damiano R (2015) Association between metabolic syndrome, obesity, diabetes mellitus and oncological outcomes of bladder cancer: a systematic review. Int J Urol 22:22–32. https://doi.org/10.1111/iju.12644
6. Wolin KY, Carson K, Colditz GA (2010) Obesity and cancer. Oncologist 15:556–565. https://doi.org/10.1634/theoncologist.2009-0285
7. Choi JB, Moon HW, Park YH, Bae WJ, Cho HJ, Hong SH, Lee JY, Kim SW, Han KD, Ha US (2016) The impact of diabetes on the risk of prostate cancer development according to body mass index: a 10-year nationwide cohort study. J Cancer 7:2061–2066. https://doi.org/10.7150/jca.16110
8. Qin Q, Xu X, Wang X, Zheng XY (2013) Obesity and risk of bladder cancer: a meta-analysis of cohort studies. Asian Pac J Cancer Prev 14:3117–3121
9. Sun JW, Zhao LG, Yang Y, Ma X, Wang YY, Xiang YB (2015) Obesity and risk of bladder cancer: a dose-response meta-analysis of 15 cohort studies. PLoS One 10:e0119313. https://doi.org/10.1371/journal.pone.0119313
10. Carlsson AC, Riserus U, Arnlov J, Borne Y, Leander K, Gigante B, Hellenius ML, Bottai M, de Faire U (2014) Prediction of cardiovascular disease by abdominal obesity measures is dependent on body weight and sex–results from two community based cohort studies. Nutr Metab Cardiovasc Dis 24:891–899. https://doi.org/10.1016/j.numecd.2014.02.001
11. Choi JB, Lee EJ, Han KD, Hong SH, Ha US (2018) Estimating the impact of body mass index on bladder cancer risk: stratification by smoking status. Sci Rep 8:947. https://doi.org/10.1038/s41598-018-19531-7
12. Song SO, Jung CH, Song YD, Park CY, Kwon HS, Cha BS, Park JY, Lee KU, Ko KS, Lee BW (2014) Background and data configuration process of a nationwide population-based study using the korean national health insurance system. Diabetes Metab J 38:395–403. https://doi.org/10.4093/dmj.2014.38.5.395
13. Lee SR, Choi EK, Han KD, Cha MJ, Oh S (2017) Trends in the incidence and prevalence of atrial fibrillation and estimated thromboembolic risk using the CHA2DS2-VASc score in the entire Korean population. Int J Cardiol. https://doi.org/10.1016/j.ijcard.2017.02.039
14. Yoon YS, Oh SW (2014) Optimal waist circumference cutoff values for the diagnosis of abdominal obesity in korean adults. Endocrinol Metab (Seoul) 29:418–426. https://doi.org/10.3803/EnM.2014.29.4.418
15. Korean Society for the Study of Obesity (2018) Clinical practice guidelines for overweight and obesity in Korea. Korean Society for the Study of Obesity, Seoul
16. Yang L, Colditz GA (2015) Prevalence of overweight and obesity in the United States, 2007–2012. JAMA Intern Med 175:1412–1413. https://doi.org/10.1001/jamainternmed.2015.2405
17. Kang HT, Shim JY, Lee HR, Park BJ, Linton JA, Lee YJ (2014) Trends in prevalence of overweight and obesity in Korean adults, 1998–2009: the Korean National Health and Nutrition Examination Survey. J Epidemiol 24:109–116
18. De Pergola G, Silvestris F (2013) Obesity as a major risk factor for cancer. J Obes 2013:291546. https://doi.org/10.1155/2013/291546
19. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M (2008) Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 371:569–578. https://doi.org/10.1016/s0140-6736(08)60269-x
20. Heron-Milhavet L, LeRoith D (2002) Insulin-like growth factor I induces MDM2-dependent degradation of p53 via the p38 MAPK pathway in response to DNA damage. J Biol Chem 277:15600–15606. https://doi.org/10.1074/jbc.M111142200
21. Canonici A, Steelant W, Rigot V, Khomitch-Baud A, Boutaghou-Cherid H, Bruyneel E, Van Roy F, Garrouste F, Pommier G, Andre F (2008) Insulin-like growth factor-I receptor, E-cadherin and alpha v integrin form a dynamic complex under the control of alpha-catenin. Int J Cancer 122:572–582. https://doi.org/10.1002/ijc.23164
22. Juul A, Bang P, Hertel NT, Main K, Dalgaard P, Jorgensen K, Muller J, Hall K, Skakkebaek NE (1994) Serum insulin-like growth factor-I in 1030 healthy children, adolescents, and adults: relation to age, sex, stage of puberty, testicular size, and body mass index. J Clin Endocrinol Metab 78:744–752. https://doi.org/10.1210/jcem.78.3.8126152
23. Hariharan N, Ashcraft KA, Svatek RS, Livi CB, Wilson D, Kaushik D, Leach RJ, Johnson-Pais TL (2018) Adipose tissue-secreted

factors alter bladder cancer cell migration. J Obes 2018:9247864. https://doi.org/10.1155/2018/9247864
24. Maj M, Kokocha A, Bajek A, Drewa T (2018) The interplay between adipose-derived stem cells and bladder cancer cells. Sci Rep 8:15118. https://doi.org/10.1038/s41598-018-33397-9
25. Haggstrom C, Stocks T, Rapp K, Bjorge T, Lindkvist B, Concin H, Engeland A, Manjer J, Ulmer H, Selmer R, Tretli S, Hallmans G, Jonsson H, Stattin P (2011) Metabolic syndrome and risk of bladder cancer: prospective cohort study in the metabolic syndrome and cancer project (Me-Can). Int J Cancer 128:1890–1898. https://doi.org/10.1002/ijc.25521
26. Koebnick C, Michaud D, Moore SC, Park Y, Hollenbeck A, Ballard-Barbash R, Schatzkin A, Leitzmann MF (2008) Body mass index, physical activity, and bladder cancer in a large prospective study. Cancer Epidemiol Biomarkers Prev 17:1214–1221. https://doi.org/10.1158/1055-9965.epi-08-0026
27. Roswall N, Freisling H, Bueno-de-Mesquita HB, Ros M, Christensen J, Overvad K, Boutron-Ruault MC, Severi G, Fagherazzi G, Chang-Claude J, Kaaks R, Steffen A, Boeing H, Arguelles M, Agudo A, Sanchez MJ, Chirlaque MD, Barricarte Gurrea A, Amiano P, Wareham N, Khaw KT, Bradbury KE, Trichopoulou A, Papatesta HM, Trichopoulos D, Palli D, Pala V, Tumino R, Sacerdote C, Mattiello A, Peeters PH, Ehrnstrom R, Brennan P, Ferrari P, Ljungberg B, Norat T, Gunter M, Riboli E, Weiderpass E, Halkjaer J (2014) Anthropometric measures and bladder cancer risk: a prospective study in the EPIC cohort. Int J Cancer 135:2918–2929. https://doi.org/10.1002/ijc.28936
28. Inamura K (2018) Bladder cancer: new insights into its molecular pathology. Cancers (Basel). https://doi.org/10.3390/cancers10040100
29. Robertson AG, Kim J, Al-Ahmadie H, Bellmunt J, Guo G, Cherniack AD, Hinoue T, Laird PW, Hoadley KA, Akbani R, Castro MAA, Gibb EA, Kanchi RS, Gordenin DA, Shukla SA, Sanchez-Vega F, Hansel DE, Czerniak BA, Reuter VE, Su X, de Sa Carvalho B, Chagas VS, Mungall KL, Sadeghi S, Pedamallu CS, Lu Y, Klimczak LJ, Zhang J, Choo C, Ojesina AI, Bullman S, Leraas KM, Lichtenberg TM, Wu CJ, Schultz N, Getz G, Meyerson M, Mills GB, McConkey DJ, Weinstein JN, Kwiatkowski DJ, Lerner SP (2018) Comprehensive molecular characterization of muscle-invasive bladder cancer. Cell 174:1033. https://doi.org/10.1016/j.cell.2018.07.036

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.