DOI: 10.4081/aiua.2023.11266

ORIGINAL PAPER

Anthropometric characteristics and relationship with non-muscle invasive bladder cancer in Greece: A case-control study

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Summary ***Background: Risk factors like smoking, radiation, chronic infections and exposure to occupational chemicals are strongly associated with occurrence of bladder cancer. Association between increased body weight and bladder cancer has been controversial. The aim of this case-control study is to evaluate association of anthropometric characteristics on bladder cancer incidence in Greek population.***
Methods: This case-control study was conducted at a tertiary hospital in Greece with cases being patients with bladder cancer diagnosed within the last 2 years and controls patients admitted to hospital for reason other than cancer and not related to common risk factors related to bladder cancer. Anthropometric characteristics like weight, height, body mass index, waist and hip circumference were measured. Analyses was done with R (Vienna, Austria).
Results: Comparison between groups showed that patients with bladder cancer had higher weight, BMI and waist circumference compared to controls. However, multivariate, binomial logistic regression showed that only age (OR 1.03, 95% CI: 1-1.05, p = 0.02), no use of smoke (OR 0.12, 95% CI: 0.07-0.23, p < 0.001) and occupation related to bladder cancer (OR 7.45, 95% CI: 2.53-27.93, p < 0.001) significantly predicted the incidence of bladder cancer.
Conclusions: Bladder cancer incidence is strongly linked with specific risk factors such as smoking, occupation with exposure to chemicals and smoke, increasing age, radiation and chronic infections. Several studies have shown a weak association between anthropometric characteristics and bladder cancer, although most studies in European populations did not confirm these findings. Similarly in our case-control study in a Greek population, we found potential relationship between increased weight/BMI and waist circumference with bladder cancer, but the association disappeared in multivariate analysis.

KEY WORDS: Bladder cancer; BMI; Anthropometric characteristics; Epidemiology; Weight; Height; Waist circumference; Hip circumference.

Submitted 19 February 2023; Accepted 6 March 2023

INTRODUCTION

Carcinoma of urinary bladder represents the tenth most common malignancy worldwide when both genders are considered, but the seventh for men and represents a major financial healthcare burden, with most recourses directed towards long-term follow-up and treatment of complications (1). Epidemiology differs among countries due to differences in lifestyle habits, environmental conditions, and diagnostic patterns (2), with reported incidence ratio in European countries ranging between 4.6 for women and 20 for men (1). One of the most identifiable causes of bladder cancer is use of tobacco, either directly or even through environmental exposure, due to contained polycyclic aromatic hydrocarbons and aromatic amines (3), with nearly one out of two cases being attributed to it (4). The relationship between tobacco use and disease incidence is considered dose-related and increases the risk by three-fivefold (5). Workers occupied in industry of painting/dye, metal, petroleum and ship construction are also at increased risk due to occupational exposure to aromatic amines/polycyclic hydrocarbons and chlorinated hydrocarbons, accounting for nearly 10% of diagnoses (2, 3, 6, 7). Studies have shown that miners, workers in leather and rubber industry, vehicle drivers, firefighters and hairdressers are more frequently diagnosed when working more than 10 years (8, 9). Quantity or arsenic and trihalomethanes in drinking water are potentially implicated according to some reports in bladder cancer pathogenesis as well (2, 7, 10). Exposure of pelvis to ionizing radiation and administration of pioglitazone or cyclophosphamide have also revealed a positive correlation with bladder cancer, while chronic mucosal lining irritation either from foreign bodies (long-term indwelling catheter) or infections (*Schistosoma haematobium*) are also considered risk factors (2, 7, 11).

Obesity is considered a pandemic with reported prevalence ranging between 30-60% across countries (12), while numerous studies have indicated increased *body mass index* (BMI) as an etiological factor for neoplastic disease (13). *Kanabrocki et al.* were the first who mentioned a positive correlation between bladder cancer and obesity back in 1965 (14), with subsequent cohort studies trying to quantify this risk showing conflicting results. Up to date the most comprehensive systematic review of literature including a total cohort of nearly 50 million participants and almost 90000 cases of bladder cancer

showed that increased risk existed in overweight men by 12% but not overweighted women, while both obese men and women shoed increased risk (14). Height did not seem to correlate with diagnosis, while data for waist circumference was limited and indicated an increased risk only in men by 18% (14). According to authors, subgroup analysis according to geographical region showed that for European populations all associations disappeared, while persisted for Asia, Australia, and America, raising the question whether Mediterranean diet which is commonly followed in several European countries accounted for these discrepancies (14).

The aim of this case-control study is to investigate the effect of increased BMI and anthropometric characteristics such as weight, height, waist, and hip circumference to bladder cancer diagnosis, in a sample of Greek patients.

Methods

Patients and controls

All participants in this case-control study were admitted in *Urology Department of Sismanoglio Hospital*, a tertiary hospital in Athens, Greece between 2018-2022. Cases were defined as patients older than 18 years old, men or women, diagnosed with transitional cell non-muscle invasive bladder cancer within the last two years from their entry in the study, who were admitted for management of their bladder cancer, or a complication related to it. Exclusion criteria were age < 18 y/o, denial to participate in the study, extreme weight gain or loss (> 15 kg) during the last 5 years, histological type other than pure urothelial carcinoma, stage ≥ T2, radiation treatment in the past, known history of long-term infection with *Schistosoma Haematobium* or history of other type of malignancy in the past. Controls were consecutive patients who were admitted at the *Urology Department* of the hospital between 2018-2022, did not have a history of bladder cancer or other neoplastic disease in the past and who were managed for a condition not related to smoking or other risk factors known to lead to bladder cancer (smoking, exposure to chemicals related to bladder cancer, radiation, chronic infections of the bladder). Such conditions were benign prostatic hyperplasia, urinary tract infections, hydrocele and varicocele. All patients, both cases and controls, were informed about the study and were included only when they provided a written informed consent regarding their participation. Study protocol was approved by the *Sismanoglio Hospital Institutional Review Board* and all principles of Helsinki Declaration regarding patients' rights were followed (15).

Data collection

After their admission all participants were interviewed regarding their baseline characteristics and disease specific history using a structured proforma. Age, presence of comorbidities (diabetes mellitus, ischemic heart disease, hypertension, chronic obstructive pulmonary disease), history of smoking, type of occupation and information regarding bladder cancer (TNM, previous treatment) were recorded. Smoking was stratified to the following categories: never used smoke, former smokers, current smoking < 20 cigarettes/day or current smoking ≥ 20 cigarettes/day. Occupation was categorized as non-related to bladder cancer or related to bladder cancer (working in industry where metal, paint/dye, tobacco, petroleum was manufactured or processed, hairdressers, firefighters, workers in ship construction).

Body weight and height were measured on the day of admission by hospital staff not aware of the presence or not of bladder cancer, while BMI was measured using the Quetelet's formula (weight divided by squared height - kg/m^2). Waist circumference was measured at the point lying in the middle of the distance between the lower rib and iliac crest, while hip circumference was measured above the buttocks. All measurements were performed with patients wearing only light clothes.

Sample size calculation

In order to calculate the sample size, we took into consideration the incidence of increased BMI in Greek population (30%) and we calculated the study sample size to 500 participants in total to test for a difference in BMI of 10% between cases and controls (the difference in risk according to literature) and achieve statistical power of 80%. The proportion of cases to controls was 1:1.

Statistical analysis

Continuous variables are described as mean ± standard deviation or median and range, according whether normal distribution was followed or not in each variable. Categorical outcomes are described with numbers and proportions. Two sample t-test or Wilcoxon rank sum test with continuity correction were used to compare groups regarding continuous outcomes, according to whether normal distribution was followed or not, respectively. Chi-square test or Fisher's test were used to compare groups regarding categorical outcomes. A univariate, binary, logistic regression analysis was performed to determine which independent variables show an important effect on incidence of bladder cancer, while multivariate, binary, logistic regression analysis was subsequently conducted to assess whether independent variables showing significant effect on univariate regression show effect also on multivariate analysis. *Odds ratios* (ORs) and the corresponding 95% *confidence intervals* (CI) were calculated by univariate and multivariate logistic regression analysis. Significance was set at $p < 0.05$. For all analyses, R statistical software (*Vienna, Austria*) was used.

Results

A total of 513 participants were included in this analysis, with 256 being cases and 257 controls. The majority of cases (85%) and controls (87%) were males, while comparison between groups revealed that presence of chronic obstructive pulmonary disease, ischemic heart disease, age, height, and hip circumference were not significantly difference between cases and controls. Controls reported more frequently zero use of smoke compared to cases (57% *versus* 14%, $p < 0.001$). Fewer cases reported residing in urban areas compared to controls (70% *versus* 85%, $p < 0.001$) and more cases answered being occupied to a field related to bladder cancer than controls

Table 1.
Baseline characteristics of patients and controls in overall sample population.

Variable	Values	Bladder cancer	Controls	p-value
Gender	Males Females	218 (85%) 38 (15%)	224 (87%) 33 (13%)	
Smoking	No Former < 20 cigarettes/day ≥ 20 cigarettes/day	36 (14%) 112 (44%) 49 (19%) 59 (23%)	146 (57%) 59 (23%) 28 (11%) 24 (9%)	< 0.001
Residence	Rural area Suburban area Urban area	20 (8%) 57 (22%) 179 (70%)	9 (4%) 28 (11%) 220 (85%)	< 0.001
Occupation	Not related to BCa Related to BCa	231 (90%) 25 (10%)	253 (98%) 4 (2%)	< 0.001
Diabetes mellitus	Yes No	107 (42%) 149 (58%)	62 (24%) 195 (76%)	< 0.001
Hypertension	Yes No	199 (78%) 57 (22%)	156 (60%) 101 (40%)	< 0.001
Chronic obstructive pulmonary disease	Yes No	24 (9%) 232 (91%)	28 (11%) 229 (89%)	0.672
Ischemic heart disease	Yes No	44 (17%) 212 (83%)	40 (16%) 217 (84%)	0.706
Age (years)		70.1 (10.1)	70 (9.8)	0.887
Weight (Kg)		87.8 (15.5)	83 (15)	< 0.001
Height (cm)		171.6 (7.5)	172.5 (8.4)	0.174
BMI (kg/m^2)		29.8 (5)	27.9 (4.7)	< 0.001
Waist circumference (cm)		105.6 (11.5)	103.6 (10.2)	0.046
Hip circumference (cm)		103.4 (5.4)	103 (4.5)	0.451
Waist-Hip ratio		1.02 (0.08)	1 (0.07)	0.024

BCa = bladder cancer; BMI = body mass index.
Categorical variables are presented as n (%) and continuous variables as and mean (± SD).

(10% *versus* 2%, p < 0.001). Both diabetes mellitus (42% *versus* 24%, p < 0.001) and hypertension (78% *versus* 60%, p < 0.001) were more frequent in cases than controls. Mean weight (87.8 *versus* 83, p < 0.001) and BMI (29.8 *versus* 27.9, p < 0.001) were higher in cases than controls, while the same applied for waist circumference although the statistical significance was marginal (105.6 *versus* 103.6, p = 0.046). Waist-Hip ratio was higher in cases than controls (1.02 *versus* 1, p = 0.024). All baseline characteristics both for groups and controls are shown in Table 1. Figures 1 and 2 are mosaic plots showing graphically the effect of smoking and type of occupation/residence on bladder cancer, respectively.

Figure 1.
Mosaic plot on effect of smoking on bladder cancer incidence.

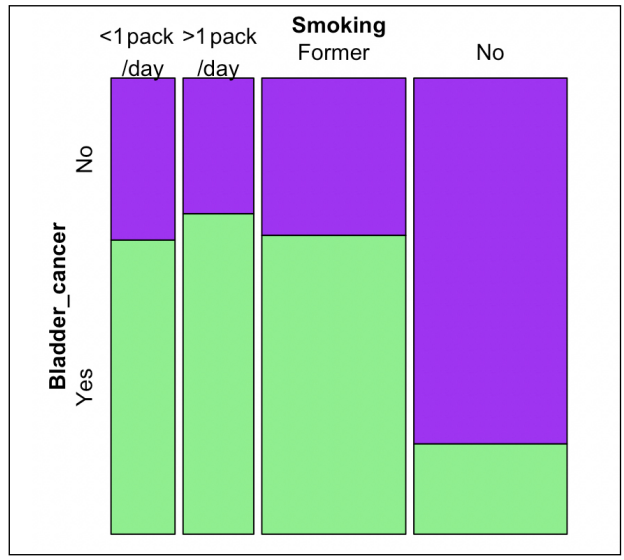

Figure 2.
Mosaic plot on effect of occupation/residence on bladder cancer incidence.

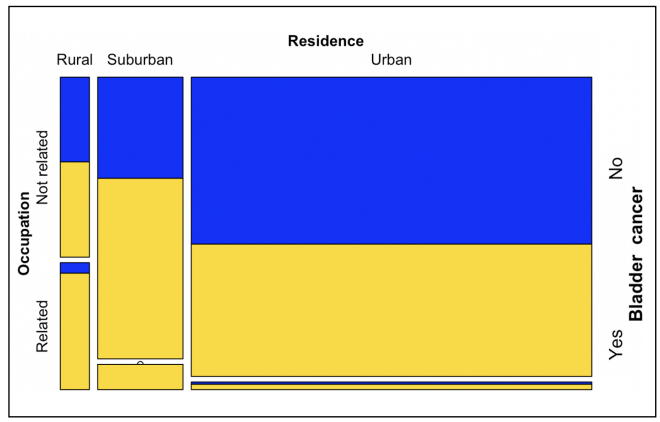

Table 2.
Anthropometric characteristics of patients and controls in females and males.

Variable	Bladder cancer	Females	p-value	Males	p-value
Weight (kg)	Yes No	74.5 (68-83) 67 (65-71)	< 0.001	89.4 (14.8) 85 (14.6)	< 0.001
Height (cm)	Yes No	160 (157-164) 160 (156-163)	0.922	173.4 (6.1) 174.2 (7.3)	0.194
BMI (kg/m^2)	Yes No	29.1 (26.3-33.5) 27 (24.7-27.9)	0.014	29.8 (4.9) 28 (4.8)	< 0.001
Waist circumference (cm)	Yes No	97 (88-113) 105 (88-108)	0.944	106.4 (10.7) 104.1 (9.7)	0.02
Hip circumference (cm)	Yes No	105 (97-111) 104 (103-106)	0.835	103.1 (4.8) 102.7 (4.1)	0.392
Waist-Hip ratio	Yes No	0.95 (0.85-1.02) 0.99 (0.85-1.05)	0.977	1.03 (0.07) 1.01 (0.07)	0.005

BMI = body mass index; SD = standard deviation.
Wilcoxon rank sum test with continuity correction was used for comparison of continuous data for females, while Welch two sample t-test for comparison of continuous date for males.
Continuous variables as median (25th-75th percentile) for females and mean (± SD) for males.

In a gender-specific analysis, in women height, waist circumference, hip circumference and waist-hip ratio were similar in controls and cases, while weight (74.5 versus 67, p < 0.001) and BMI (29.1 *versus* 27, p = 0.014) were higher in cases than controls. In men, height and hip circumference were similar. Weight (89.4 *versus* 85, p < 0.001), BMI (29.8 *versus* 28, p < 0.001), waist circumference (106.4 *versus* 104.1, p = 0.02) and waist circumference (1.03 *versus* 1.01, p = 0.005) were higher in cases compared to control. All anthropometric characteristics of cases and controls according to gender-specific analysis are shown in Table 2.

Table 3.
Results of binomial logistic regression for bladder cancer occurrence.

All variables				Significant predictors only			
Variable	**OR**	**95% CI**	**p-value**	**Variable**	**OR**	**95% CI**	**p-value**
Age	1.04	1.01-1.06	0.002	Age	1.03	1.00-1.05	0.02
BMI	1.14	0.07-1.88	0.6				
Weight	1.01	0.86-1.19	0.87				
Height	1.00	0.86-1.18	0.97				
Waist circumference	1.07	0.59-1.96	0.84				
Hip circumference	0.85	0.46-1.54	0.60				
Waist-Hip ratio	0.84	0.35-1.35	0.79				
Smoking ≥20 cigarettes/day	1.24	0.61-2.53	0.55				
Former smoker	0.9	0.49-1.65	0.74				
No smoking	0.13	0.07-0.24	< 0.001	No smoking	0.12	0.07-0.23	< 0.001
Suburban area	1.49	0.49-4.42	0.48				
Urban area	0.79	0.28-2.11	0.64				
Occupation related to BCa	8.05	2.49-33.45	0.001	Occupation related to BCa	7.45	2.53-27.93	< 0.001

BMI = body mass index; BCa = bladder cancer; OR = odds ratio; CI = confidence interval.

Univariate, binomial logistic regression evaluating all continuous (age, BMI, weight, height, waist circumference, hip circumference, waist-hip ratio) and categorical (smoking status, area of residence, occupation) independent variables revealed that significant effect on incidence of bladder cancer had age (OR 1.04, 95% CI: 1.01-1.06, p = 0.002), no use of smoke (OR 0.13, 95% CI: 0.07-0.24, p < 0.001) and occupation related to bladder cancer (OR 8.05, 95% CI: 2.49-33.45, p < 0.001). Similarly, multivariate, binomial logistic regression showed that age (OR 1.03, 95% CI: 1-1.05, p = 0.02), no use of smoke (OR 0.12, 95% CI: 0.07-0.23, p < 0.001) and occupation related to bladder cancer (OR 7.45, 95% CI: 2.53-27.93, p < 0.001) significantly predicted the incidence of bladder cancer. All results of binomial logistic regression are shown in Table 3.

Discussion

Increased body weight has been associated with several types of cancer. For bladder cancer conflicting data exist showing a potential relationship. In their meta-analysis, Qin et al pooled data from 11 cohort studies and showed an increased risk of bladder cancer incidence by 10% in obese people (16), while a more updated analysis showed that the association is stronger in men (12-14%) and in continents other than Europe (14). Increased height has also been implicated in carcinogenesis with the assumption that increased number of cells in taller people may be accompanied by increased chances for mutagenesis. However, several studies failed to detect such an association for bladder cancer (14). Waist circumference is considered an index of central obesity and is not well studies regarding its association with bladder cancer incidence (14). This case-control study is the first one performed in a Greek population regarding the effect of anthropometric characteristics on bladder cancer occurrence and showed a potential association between increased weight/BMI, increased waist circumference, use of smoke, occupation related to bladder cancer, hypertension, diabetes mellitus with bladder cancer, while multivariate regression analysis revealed that association exists between increasing age, use of smoke and occupation lying in agreement with existing literature.

Various pathophysiological mechanisms have been proposed to link obesity with increased risk for bladder cancer. One of the most established is the co-existence of obesity with insulin resistance which lead to overproduction of insulin; insulin induces mitosis and potentially carcinogenesis by increasing *insulin-like growth factor* (IGF-1), which initiates molecular pathways for cell proliferation and blocks programmed cell death (17). Link between diabetes mellitus and bladder cancer can be partially explained by this association as well. Another mechanism is the excess cholesterol in adipose tissue, with cholesterol serving as a prodrome molecule for testosterone production, which in turn stimulates proliferation of epithelial cells (18). Secretion of leptin by adipose tissue may also contribute to increased bladder risk, since leptin is a hormone leading to enhanced angiogenesis and subsequently can nourish tumor cells (19). Adipose tissue is considered to lead to impaired mitochondrial function and increased reactive oxygen species, due to reduced clearance, thus further increasing cellular oxidative stress and mutations (20).

Gender specific differences regarding the association of anthropometric characteristics with bladder cancer incidence are observed both in literature and in our study, since although increased BMI/weight was seen in both male and female cases compared to control, increased waist circumference was seen only in male cases. The potential protective role of estrogens can explain these differences (21). Embryological origin of bladder and prostate is the same from urogenital sinus and androgen-driven growth of bladder cancer cells can also be a potential mechanism in men (22). Continent-specific differences are best explained both by genetic differences on a population level, but also from dietary habits, which are known to play a major role in cancer pathophysiology. In Europe associations between increased BMI and bladder cancer were not significant in the updated meta-analysis of nearly 50 million participants (14). In the meta-analysis by *Xenou et al*, authors examined the association between fruit/vegetable consumption and bladder cancer (23). They found that citrus fruit consumption had a protective equipment, although not reaching statistical significance, while all analyses regarding consumption of leafy vegetables, dark green vegetables, berries, vegetable/fruit or overall vegetable and fruit consumption did not show a significant protective effect (23). In our study regarding a sample of Greek patients with bladder cancer, we detected a potential implication of weight/BMI and waist circumference in bladder cancer, but this was not confirmed in multivariate regression analysis where only well-established risk factors were significant. Height and hip circumference also were not significantly different between the groups.

This case-control study suffers from specific limitations

such as the relatively small sample size and lack of dietary habits assessment. However, it is the first one for studying association between a number of anthropometric characteristics with bladder cancer in the Greek population and may serve as a basis for future studies.

Conclusions

Bladder cancer incidence is strongly linked with specific risk factors such as smoking, occupation with exposure to chemicals and smoke, increasing age, radiation and chronic infections. Several studies have shown a weak association between anthropometric characteristics and bladder cancer, although most studies in European populations did not confirm these findings. Similarly in our case-control study in a Greek population, we found potential relationship between increased weight/BMI and waist circumference with bladder cancer, but the association disappeared in multivariate analysis.

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Conflict of interest: The authors declare no potential conflict of interest.