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Diabetes mellitus, body size and bladder cancer risk in a prospective study of Swedish men

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ABSTRACT

Epidemiologic studies on diabetes and body size in relation to risk of bladder cancer have yielded inconsistent results. We examined prospectively the associations between a history of diabetes, height, weight, body mass index and waist circumference, and the incidence of bladder cancer in the Cohort of Swedish Men, a prospective study of 45,906 men aged 45–79 years at baseline. During follow-up from 1998 through December 2007, 414 incident cases of bladder cancer were ascertained. A history of diabetes was not associated with risk of bladder cancer (multivariate rate ratio = 1.16; 95% confidence interval = 0.81–1.64). Similarly, no associations were observed for height, weight, body mass index or waist circumference. These findings in men do not support a role for diabetes, height or excess body mass in the aetiology of bladder cancer.

1. Introduction

Bladder cancer is the 10th most common cancer worldwide, with the highest rates reported in southern and Western Europe and North America.[1] In Europe, bladder cancer is the 5th most commonly diagnosed malignancy and the 9th leading cause of cancer mortality.[2] The disease is more common in men than in women.[1] Established risk factors for bladder cancer include tobacco smoking, occupational exposure to aromatic amines and schistosomal infection.[3] However, differences in these factors cannot fully explain the variation in bladder cancer rates between countries or sex.

Ample evidence indicates that type 2 diabetes is a risk factor for several cancers,[4–7] but results for bladder cancer are inconsistent. Diabetes has been associated with an increased risk of bladder cancer in a few cohort studies,[8–10] but not in record linkage-based cohorts of diabetic patients,[11–17] and case-control studies[18–25] have yielded inconsistent results.

Obesity, especially abdominal obesity, increases the risk for type 2 diabetes[26] and has been associated with an elevated risk of cancer at many sites.[27] However, the majority of epidemiologic studies of weight or body mass index (BMI), as a measure of overall obesity, in relation to bladder cancer risk have been null.[8,28–42] Measures of abdominal obesity, such as waist circumference and waist-to-hip ratio, may be better measures of adiposity in terms of cancer risk, as is the case for cardiovascular disease.[43] Only one previous study has to our knowledge examined the relation between abdominal obesity and bladder cancer risk.[8]

The aim of this study was to investigate the associations of diabetes and anthropometric measures, including height, weight, BMI and waist circumference, with bladder cancer

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incidence amongst participants of the population-based Cohort of Swedish Men (COSM).

2. Materials and methods

2.1. Study population

The COSM is an ongoing population-based prospective cohort study designed primarily to investigate the relationship between nutrition, lifestyle factors and risk of chronic diseases. The COSM study was established in 1997–1998 when 48,850 men who were aged 45–79 years and who resided in the Västmanland and Örebro counties of central Sweden returned a mailed questionnaire that assessed information on diet, lifestyle factors, anthropometry and medical and smoking histories. The investigation was approved by the Regional Ethics Committee at the Karolinska Institutet in Stockholm, Sweden.

2.2. Assessment of exposures

At baseline, study participants completed a self-administered questionnaire that assessed information on demographic characteristics, cigarette smoking status and history, weight, height, waist circumference, physical activity, diet, alcohol intake and history of diabetes. BMI was estimated from self-reported weight and height (kg/height in m^2) and was used as a measure of overall obesity. We estimated pack-years (the equivalent of smoking 20 cigarettes per day for one year) from baseline smoking history by multiplying the number of packs of cigarettes smoked per day by the number of years of smoking.

2.3. Ascertainment of bladder cancer cases

Incident bladder cancer cases were identified by computerised record linkage of the study population (using the National Registration Number assigned to each Swedish resident) to the National Swedish Cancer Register and the Regional Cancer Register covering the study area. The completeness of cancer follow-up was estimated to be nearly 100%.[44] The end-point for the present analyses was incident bladder cancer coded according to the 2nd revision of the International Classification of Disease for Oncology (ICD-O-2, codes C67.0–C67.9). We excluded men who were diagnosed with *in situ* bladder cancer ($n = 16$). From information in the regional bladder cancer registry, we were able to determine tumor-node-metastasis (TNM) stage for 90.3% of the cases and grade for 89.6% of the cases. Cases with missing stage or grade were included in the analyses for total bladder cancer, but were excluded from the analyses for stage or grade. We categorised cases into two groups according to TNM stage: superficial bladder cancer ($n = 300$; stage Ta and T1) and invasive/advanced bladder cancer ($n = 78$; stage T2–T4). Invasive and advanced bladder tumours were combined because of the small number of men diagnosed with advanced disease ($n = 15$). We also categorised disease as lower grade ($n = 116$; grade I) or higher grade ($n = 255$; grades II and III). Information on dates of death for deceased participants was obtained from the Swedish Death Registry.

2.4. Statistical analysis

Person-time of follow-up for each participant was calculated from baseline until the date of bladder cancer diagnosis, the date of death or the end of follow-up (30th December, 2007), whichever came first. We excluded men with missing or erroneous National Registration Numbers ($n = 260$) and men with a previously diagnosed cancer at baseline ($n = 2684$). After these exclusions, 45,906 men remained and were included in the analysis of diabetes. For analyses using anthropometric measurements, we further excluded men with missing data on weight or height ($n = 2426$), leaving 43,480 men for analysis.

Cox proportional hazards regression [45] was used to estimate rate ratios (RRs) with 95% confidence intervals (CIs). Multivariate analyses were adjusted for education (primary school, high school or university) and cigarette smoking (never, past or current smoker; and pack-years of smoking history for past and current smokers, <20, 20–39 and ⩾40). Other variables evaluated for potential confounding were physical activity, aspirin use, and intakes of alcohol, red meat, fruits and vegetables. Adjustment for these variables did not change the results and were not included in the final models. Participants were categorised into quartiles of height, weight and waist circumference (using whole number cutpoints) based on the distribution of the entire study cohort, and into four groups of BMI that included widely used World Health Organisation definitions of overweight (25.0–29.9 kg/m^2) and obesity (⩾30.0 kg/m^2).[46] We tested the proportional hazard assumption using the likelihood ratio test and found no departure from the assumption.

To test for linear trends across categories of anthropometric variables, we used the median values for each category and treated those as a single continuous variable in the model. We used the likelihood ratio test to assess statistical interaction. Statistical analyses were performed using SAS software, release 9.1 (SAS Institute, Cary, NC). All statistical tests were two-sided, with P-value less than 0.05 considered to be statistically significant.

3. Results

Baseline characteristics of the study population according to history of diabetes and BMI are presented in Table 1. Compared to men without diabetes, those who reported diabetes at baseline were older and were less likely to have a post-secondary education and to be never smokers. Men with diabetes also had higher BMI than non-diabetics. Men with higher BMI were less likely to have a post-secondary education and to be never smokers and were more likely to have a history of diabetes than men with a low BMI. They also had higher waist circumference.

For the diabetes analysis, 45,906 men were followed for a total of 426,557 person-years (mean 9.3 years). During follow-up, 414 incident cases of bladder cancer were diagnosed in the cohort. A history of diabetes was not associated with risk of total bladder cancer after age adjustment or after multivariate adjustment (Table 2). However, diabetes was positively associated with risk of higher grade disease

Table 1 – Baseline characteristics[a] according to history of diabetes and body mass index

Characteristic	History of diabetes[b]		Body mass index (kg/m^2)			
	No	Yes	18.0–24.9	25.0–29.9	30.0–35.0	⩾35.0
Participants (*n*)	43,071	2835	19,143[c]	19,958	3772	607
Age, year	60.1	64.5	60.2	60.1	59.8	59.0
Post-secondary education, %	16.3	13.1	19.8	14.4	11.1	10.6
Body mass index, kg/m^2	25.7	27.4	23.0	27.0	31.7	37.6
Waist circumference, cm	96.0	100.2	90.0	99.0	109.5	119.9
History of diabetes, %	–	–	4.3	6.3	11.8	19.7
Never smokers, %	36.4	32.3	39.5	34.6	29.4	27.1
Past smokers, %	38.6	42.0	34.3	42.0	45.8	47.5
Current smokers, %	25.0	25.7	26.2	23.4	24.8	25.4
Pack-years of cigarettes[d]	20.2	23.1	19.8	20.4	22.4	24.7

a All values (except age) were standardised to the age distribution of the study population at baseline; values are means if not otherwise indicated.
b Tests for difference in characteristics between men with diabetes and men without diabetes were all statistically significant ($P < 0.05$), except for proportion of current smokers.
c Here were 127 men with BMI <18.0 kg/m^2 (median 17.4 kg/m^2).
d Amongst past and current smokers; pack-years = number of packs of cigarettes smoked per day multiplied by the number of years of smoking.

Table 2 – Rate ratios of bladder cancer according to history of diabetes in the Cohort of Swedish Men, 1997–2007

Bladder cancer	History of diabetes	
	No	Yes
Total		
Cases, *n*	380	34
Person-years	402,748	23,809
Age-adjusted RR (95% CI)	1.00 (reference)	1.18 (0.83–1.68)
Multivariate RR (95% CI)[a]	1.00 (reference)	1.16 (0.81–1.64)
Superficial		
Cases, *n*	272	28
Age-adjusted RR (95% CI)	1.00 (reference)	1.39 (0.94–2.05)
Multivariate RR (95% CI)[a]	1.00 (reference)	1.35 (0.91–2.00)
Invasive/advanced		
Cases, *n*	73	5
Age-adjusted RR (95% CI)	1.00 (reference)	0.82 (0.33–2.03)
Multivariate RR (95% CI)[a]	1.00 (reference)	0.81 (0.33–2.00)
Lower grade (grade I)		
Cases, *n*	110	6
Age-adjusted RR (95% CI)	1.00 (reference)	0.76 (0.33–1.73)
Multivariate RR (95% CI)[a]	1.00 (reference)	0.75 (0.33–1.71)
Higher grade (grades II and III)		
Cases, *n*	228	27
Age-adjusted RR (95% CI)	1.00 (reference)	1.52 (1.02–2.27)
Multivariate RR (95% CI)[a]	1.00 (reference)	1.48 (0.99–2.21)

a Adjusted for age, education, smoking status and pack-years of smoking.

(grades II and III) after adjustment for age (RR = 1.52; 95% CI = 1.02–2.27). The association between diabetes and higher grade disease was slightly attenuated and not statistically significant after multivariate adjustment (RR = 1.48; 95% CI = 0.99–2.21) and did not persist after excluding all cases diagnosed during the first 2 years of follow-up (RR = 1.30; 95% CI = 0.81–2.09). Diabetes was not significantly associated with either superficial or invasive/advanced bladder cancer (Table 2).

The cohort for analyses of anthropometric data comprised 43,480 men; 388 cases of bladder cancer were identified during 405,220 person-years of follow-up. We observed no association of height, weight, BMI or waist circumference with the risk of bladder cancer (Table 3). The associations did not differ by stage or grade of disease (data not shown). To prevent potential bias of altered body weight or composition that was due to undiagnosed disease, we performed analyses that removed all bladder cancer cases that were diagnosed within the first 2 years of follow-up. Results were similar to those based on all cases.

We assessed whether the associations between diabetes, height, weight, BMI and waist circumference, and risk of bladder cancer were modified by smoking status. We did not find any statistically significant interaction (all *P* for interaction >0.30).

4. Discussion

In this large prospective cohort of men, a history of diabetes, height, weight, BMI and waist circumference were not associated with the risk of bladder cancer overall. Diabetes was weakly positively associated with higher grade disease but the association did not remain after removing cases diagnosed within the first 2 years of follow-up. There was no evidence that the associations between diabetes, height, weight, BMI or waist circumference, and risk of bladder cancer were modified by smoking status.

Epidemiologic studies of diabetes and risk of bladder cancer have been inconsistent. Three cohort studies found that a history of diabetes was associated with a statistically significant 1.3-fold to 2.5-fold increased risk of bladder cancer;[8–10] none of those studies excluded cases diagnosed during the first years of follow-up. In cohorts of diabetic patients, no increased risk of bladder cancer has been observed amongst diabetic patients compared with the general population.[11–17]

Table 3 – Rate ratios of bladder cancer according to height, weight, body mass index and waist circumference in the Cohort of Swedish Men, 1997–2007

	Cases, *n*	Person-years	Age-adjusted RR	Multivariate RR[a]
Height, cm				
<173 (170)[b]	106	93,514	1.00 (reference)	1.00 (reference)
173–176 (175)	104	98,264	1.05 (0.80–1.37)	1.04 (0.79–1.36)
177–181 (179)	101	101,016	1.11 (0.84–1.45)	1.12 (0.85–1.48)
⩾182 (185)	77	112,426	0.84 (0.62–1.12)	0.83 (0.62–1.12)
P for trend			0.31	0.33
Weight, kg				
<73 (69)	108	102,498	1.00 (reference)	1.00 (reference)
73–80 (77)	120	110,578	1.14 (0.88–1.48)	1.17 (0.90–1.51)
80–87 (84)	72	90,412	0.89 (0.66–1.20)	0.90 (0.67–1.21)
⩾88 (94)	88	101,732	1.05 (0.79–1.40)	1.03 (0.77–1.37)
P for trend			0.92	0.78
Body mass index, kg/m^2				
18.0–24.9 (23.3)	176	177,924	1.00 (reference)	1.00 (reference)
25.0–29.9 (26.8)	177	187,037	0.98 (0.80–1.21)	0.98 (0.79–1.20)
30.0–34.9 (31.4)	31	34,835	0.98 (0.67–1.43)	0.92 (0.62–1.34)
⩾35.0 (36.9)	4	5424	0.88 (0.33–2.38)	0.79 (0.29–2.14)
P for trend			0.80	0.55
Waist circumference, cm				
<90 (85)	62[c]	78,063	1.00 (reference)	1.00 (reference)
90–94 (92)	83	78,167	1.24 (0.89–1.72)	1.22 (0.88–1.70)
95–101 (98)	102	98,743	1.15 (0.84–1.57)	1.12 (0.82–1.54)
⩾102 (107)	89	87,046	1.08 (0.78–1.50)	1.00 (0.72–1.39)
P for trend			0.89	0.71

a Adjusted for age, education, smoking status and pack-years of smoking.
b Median values in parentheses.
c The number of cases does not sum up to the total number of cases because of missing data on waist circumference.

Case-control studies relating diabetes to bladder cancer risk have yielded inconsistent results, with a statistically significant positive relationship found in some studies,[19,21,23,24] but not all.[20,22,25] A recent population-based study found that cancer patients with diabetes had a significant increase in overall mortality compared with cancer patients without diabetes.[47]

Our results for body size are consistent with findings from most previous cohort studies in which no significant association between weight or BMI and risk of bladder cancer have been observed.[8,32–35,41,42] However, in three obesity cohorts, persons hospitalised with a diagnosis of obesity had a statistically significant 13–20% increased risk of bladder cancer compared with other hospitalised patients[36] or the general population.[29,31] In a cohort study of men, weight during college was positively associated with the subsequent risk of bladder cancer.[28] In another cohort of United States men and women, a weak positive association between BMI and bladder cancer was observed only after excluding cases diagnosed within the first 4 years of follow-up (multivariate RR, 1.33; 95% CI 1.01–1.76 for BMI ⩾30.0 kg/m^2 versus 18.0–22.9 kg/m^2).[30] The four available case-control studies on BMI and bladder cancer risk have reported conflicting results. In a Canadian population-based case-control study,[37] men with a BMI of 30 kg/m^2 or greater had a significant 35% increased risk of bladder cancer compared with men with a BMI of less than 25 kg/m^2; no association was observed amongst women. In contrast, another case-control study amongst women found a non-significant inverse relation between BMI and bladder cancer risk (multivariate RR, 0.61; 95% CI 0.33–1.14 for BMI ⩾27.3 kg/m^2 versus <23.8 kg/m^2).[40] Two case-control studies showed no significant differences in BMI between cases and controls.[38,39]

Few studies have examined height and measures of abdominal obesity in relation to bladder cancer risk. A large cohort study of US men and women found a significant inverse association between height and bladder cancer risk in men (multivariate RR, 0.69; 95% CI, 0.50–0.95 for >6.00 ft versus ⩽5.60 ft), but no association in women.[30] Height was not associated with bladder cancer in a case-control study in Italy[48] and in a cohort study of cancer mortality.[49] The relationships of waist circumference and waist-to-hip ratio with bladder cancer risk have been examined previously in a cohort study of US women.[8] In that cohort, neither waist circumference nor waist-to-hip ratio was significantly associated with the risk of bladder cancer,[8] which is consistent with our results in men.

The strengths of our study include a population-based and prospective design and a large sample size. The prospective design precluded recall bias and the virtually complete follow-up of the study population through linkage to various population-based registers largely minimises the concern that our findings have been affected by differential loss to follow-up. Our study is limited by the reliance on self-reported information on diabetes and anthropometric measurements, and the lack of data on type of diabetes (type 1 or type 2).

Many persons with diabetes go undetected in the population and are therefore misclassified as non-diabetic.[50] This non-differential misclassification would attenuate a true relationship between diabetes and bladder cancer. Exposure information was obtained as baseline only, and changes in exposures during follow-up may also have attenuated any true association. We cannot rule out the possibility that measurement errors explain the lack of association with anthropometric measures in this study. However, high validity has been observed for self-reported weight ($r = 0.9$) and height ($r = 0.9$) compared with actual measurements amongst Swedish men.[51] Moreover, we have previously shown positive associations of BMI and waist circumference with risk of pancreatic and colorectal cancers,[52,53] suggesting that our assessments of BMI and waist are sufficiently accurate to detect true relationships. There is also the possibility that underlying disease may have affected current body mass and composition. However, analyses that excluded cases diagnosed within the first 2 years of follow-up did not change our results.

In summary, findings from this prospective cohort study suggest that diabetes and body size are not associated with the risk of developing bladder cancer.

Conflict of interest statement

None declared.

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