Body Mass Index, Physical Activity, and Bladder Cancer in a Large Prospective Study

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Abstract

Increased body size and lack of physical activity are associated with increased risk of several cancers, but the relations of body mass index (BMI) and physical activity to bladder cancer are poorly understood. We investigated the associations between BMI, physical activity, and bladder cancer in the NIH-AARP Diet and Health Study, a prospective cohort of 471,760 U.S. men and women, followed from 1995 to 2003. During 3,404,642 person-years of follow-up, we documented 1,719 incident cases of bladder cancer. Compared with normal weight, obesity was associated with an up to 28% increased risk for bladder cancer. The multivariate relative risks of bladder cancer for BMI values of 18.5 to 24.9 (reference), 25.0 to 29.9, 30.0 to 34.9, and ≥35 kg/m^2 were 1.0, 1.15, 1.22, and 1.28 (95% confidence interval, 1.02-1.61; P_{trend} = 0.028). The association between BMI and bladder cancer was consistent among subgroups defined by gender, education, smoking status, and other potential effect modifiers. In contrast, physical activity showed no statistically significant relation with bladder cancer. After multivariate adjustment, including BMI, the relative risks of bladder cancer for increasing frequency of physical activity [0 (reference), <1, 1-2, 3-4, and ≥5 times a week] were 1.0, 0.85, 0.89, 0.91, and 0.87 (95% confidence interval, 0.74-1.02; P_{trend} = 0.358), respectively. In conclusion, these findings provide support for a modest adverse effect of adiposity on risk for bladder cancer. In contrast, our results do not suggest a relation between physical activity and bladder cancer. (Cancer Epidemiol Biomarkers Prev 2008;17(5):1214–21)

Introduction

Bladder cancer is the fourth most common malignancy in men and the ninth most common in women in the United States (1). In the United States in 2007, an estimated 67,000 new bladder cancer cases will occur and 13,750 people will die from this disease (1). Established risk factors for bladder cancer include tobacco use, occupational exposure to specific carcinogens such as aromatic amines, schistosomiasis, drinking tap water with arsenic, certain drugs such as phenacetin-containing analgesics, and familial history of bladder cancer (2).

Nearly two thirds of U.S. adults are currently overweight [body mass index (BMI) between 25.0 and 29.9 kg/m^2] or obese (BMI ≥ 30.0 kg/m^2; ref. 3) and more than half are insufficiently physically active (4). Substantial epidemiologic evidence suggests that adiposity is related to increased risk and physical activity to decreased risk of cancer (5), but bladder cancer has not been consistently linked to either body size or physical activity. In epidemiologic studies examining adiposity and bladder cancer (6-20), no statistically significant association has been seen in most (7-9, 11, 13-16, 18-20), but the majority of those studies has been limited by small numbers of cases, especially cases with a BMI ≥ 30.0 kg/m^2. Although three prospective studies (6, 10, 12) and one large case-control study (17) found a positive relation of adiposity to risk of bladder cancer, only one (12) of those studies explored this association in detail. Likewise, few studies have investigated physical activity in relation to bladder cancer (12, 15, 21-28). An apparent protective effect of physical activity on risk for bladder cancer is limited to results from one study (27).

Given the high prevalence of adiposity and physical inactivity in the United States (3, 4), we conducted a detailed, prospective investigation in the NIH-AARP Diet and Health Study. With over 1,700 bladder cancer cases, this is the largest study to date to examine BMI and physical activity in relation to this important malignancy.

Materials and Methods

Study Population. In 1995 to 1996, 566,402 members of AARP ages 50 to 71 years and residing in one of six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) or two metropolitan areas (Atlanta, GA, and Detroit, MI) satisfactorily completed and returned a mailed questionnaire on medical history, diet, and physical activity to initiate the NIH-AARP Diet and Health Study (29). The study was approved by the

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Table 1. Baseline characteristics according to BMI and physical activity

Characteristics	BMI (kg/m^2)				Physical activity (times a week)*				
	18.5-24.9	25.0-29.9	30.0-34.9	≥35.0	0	<1	1-2	3-4	≥5
Participants (*n*)	162,353	204,189	75,350	29,886	83,558	64,730	102,945	128,003	92,524
Age (y)	62.1	62.1	61.6	60.8	62.0	61.1	61.5	62.2	62.4
Gender (%)									
Men	51.9	71.2	64.6	46.0	52.2	58.9	61.9	63.4	67.2
Women	49.1	29.8	36.4	54.0	48.8	41.1	38.1	36.6	32.8
Race									
White	92.4	91.9	90.9	88.7	89.5	91.8	92.5	91.8	92.6
Non-White	7.6	8.1	9.1	11.3	10.5	8.2	7.5	8.2	7.4
Smoking status (%)									
Current smoker	17.0	12.5	10.8	9.2	20.4	16.9	14.1	10.0	9.3
Former smoker	43.8	53.3	54.9	52.9	45.3	48.3	49.2	52.8	53.9
Never smoker	39.2	34.2	34.3	37.9	34.4	34.8	36.7	37.2	36.8
BMI (kg/m^2)	22.8	27.2	31.9	39.5	28.7	27.9	27.3	26.6	26.1
Physical activity (times a week)	2.7	2.5	2.0	1.5	0	0.5	1.5	3.5	5.5
College education (%)	44.3	40.4	34.4	29.3	28.3	37.6	41.2	44.8	44.6
Married or living as married (%)	66.1	75.2	70.6	58.5	62.4	68.6	71.1	72.8	74.1
Red meat intake (servings/1,000 kcal/d)	29.6	35.8	39.4	41.0	37.9	37.3	36.2	32.5	30.8
Fruit and vegetable intakes (servings/1,000 kcal/d)	3.7	3.4	3.4	3.4	3.1	3.2	3.4	3.7	3.9
Nonalcoholic beverage intake (mL/d)	1,865	2,020	2,068	2,023	2,004	1,969	1,972	1,937	2,012
Alcohol intake (servings/wk)	6.7	7.5	6.6	4.5	6.8	6.9	6.8	6.6	7.4
Menopausal hormone therapy (%) †									
Current users	50.9	54.2	37.1	29.3	38.1	43.8	45.4	48.9	47.2
Former users	8.5	9.4	9.8	8.9	8.7	9.5	9.0	9.3	8.6
Never users	40.5	46.4	53.1	61.7	53.2	46.6	45.6	41.8	44.2
Ever used oral contraceptive use (%) †	42.2	39.5	36.8	34.3	37.1	39.9	40.4	41.5	39.7
Parity (no. live-born children) †	2.1	2.2	2.3	2.3	2.2	2.2	2.2	2.2	2.2
NSAID use (%)	49.1	51.3	54.4	57.2	49.6	52.5	52.1	52.4	49.6

NOTE: All values (except age) were directly standardized to the age distribution of the cohort.
*Physical activity was defined as activity that lasted ≥20 min and caused either increases in breathing or heart rate or working up a sweat.
† Among women only.

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At baseline, we excluded individuals with diagnosed cancer other than nonmelanoma skin cancer (n = 52,561), participants with emphysema (n = 13,764), those with missing data on body weight or height (n = 12,118), those who were underweight (defined as BMI < 18.5 kg/m^2; n = 4,825), and subjects with missing information on physical activity (n = 5,106) or smoking (n = 6,268). The remaining analytical cohort comprised 287,941 men and 183,819 women.

Identification of Incident Bladder Cancer Cases. We identified incident cases of bladder cancer by probabilistic linkage to the state cancer registries serving our cohort. Beyond the eight original states of our cohort, our cancer registry ascertainment area was recently expanded by three additional states (Texas, Arizona, and Nevada) to capture cancer cases occurring among participants who moved to those states during follow-up. The North American Association of Central Cancer Registries certifies all 11 cancer registries (30). We conducted a validation study comparing registry findings with self-reports and medical records and found that ~90% of all cancer cases in our cohort were validly identified using linkage to cancer registries (31). Vital status was ascertained by linkage of the cohort to the Social Security Administration Death Master file. Additional cases of fatal bladder cancer were identified through linkage to the National Death Index Plus, which provided verification of death and information on cause of death. For matching purposes, we have virtually complete data on first and last name, address history, gender, and date of birth. Social Security number is available for 85% of the NIH-AARP cohort.

Cancer sites were identified by anatomic site and histologic code of the *International Classification of Disease for Oncology, Second and Third Editions* (32). The primary endpoint for the present analysis was total bladder cancer (*International Classification of Disease for Oncology, Third Edition* code C67.0-C67.9), which included cancers with the following morphology: transitional cell carcinoma (8050, 8120-8122, 8130), squamous cell carcinoma (8051-8076), adenocarcinoma (8140-8145, 8190-8231, 8260-8263, 8310, 8480-8490, 8560, 8570), and not otherwise specified carcinomas (8010-8034). A total of 87.4% were transitional cell, 1.3% were squamous cell, 1.4% were adenocarcinoma, and 9.9% were other or not specified bladder cancers.

Assessment of BMI and Physical Activity. Information on weight and height was collected using the baseline questionnaire and was used to calculate BMI and to divide participants into four BMI categories (18.5-24.9, 25.0-29.9, 30.0-34.9, and ≥35.0 kg/m^2) hat incorporated the definitions of normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obesity (≥30.0 kg/m^2), respectively, proposed by the WHO (33).

In correspondence with the American College of Sports Medicine physical activity guidelines that recommend at least 20 min of continuous vigorous exercise three times a week for improving cardiorespiratory fitness (34), we asked participants to report the average

frequency (never, rarely, 1-3 times a month, 1-2 times a week, 3-4 times a week, and ≥5 times a week) during the past year that they engaged in activities of any type that lasted ≥20 min and caused either increases in breathing or heart rate or working up a sweat. We collapsed the bottom two categories to ensure sufficient numbers of cases in the reference category. A questionnaire similar to the one used in this cohort showed good interrater reliability (percentage agreement = 0.76; κ = 0.53) and reasonable validity (percentage agreement = 0.71; κ = 0.40) as assessed by a computer science and applications activity monitor (35). Additional evidence of the validity of our physical activity instrument is shown by the capability of our assessment of physical activity to predict lower risk of mortality from coronary heart disease (36).

In a supplementary questionnaire mailed in 1996 to 1997, we requested information on sedentary behavior by asking about the average number of hours a day currently spent watching television or videos (0, <1, 1-2, 3-4, 5-6, 7-8, and ≥9 h). We collapsed the bottom three categories to provide adequate statistical power. We also requested information on weight and height at age 18 and physical activity at age 15 to 18 years. The supplementary questionnaire was mailed 6 months after baseline and was returned by 60% of the baseline questionnaire respondents. Thus, in analyses involving sedentary behavior, we began follow-up in 1996 and excluded participants who had a cancer diagnosis before return of the supplementary questionnaire.

Statistical Analysis. Each participant accrued follow-up time beginning at the scan date of the baseline questionnaire and ending at the date of diagnosis of bladder cancer, move out of the registry ascertainment area, death, or the end of follow-up in December 31, 2003, whichever came first. Cox proportional hazards regression (37) with age as the underlying time metric was used to estimate the relations of BMI and physical activity to bladder cancer. We examined potential violation of the proportional hazards assumption and found no discrepancies from the assumption of proportional hazards.

The relation of BMI to bladder cancer was estimated in three models. One model was adjusted for age and gender. A second model was additionally adjusted for race/ethnicity; education; a combination of smoking status, time since quitting for former smokers, and smoking intensity for former and current smokers; family history of any cancer, marital status; intakes of red meat; the combination of fruit and vegetables; total beverages, except alcohol; alcohol; menopausal hormone therapy; use of oral contraceptives; and parity (the latter three variables for women only). A third model was additionally adjusted for physical activity. The association between physical activity and bladder cancer was estimated in three similar models, with the exception that physical activity was replaced by BMI in the third model.

In a subset of study participants, we collected information on use of nonsteroidal anti-inflammatory drugs (NSAID). We used those data to assess whether the relations of BMI or physical activity to bladder cancer were confounded by NSAID use. Tests of linear trend across categories were conducted by modeling the mean values of exposures as a single continuous variable in the multivariate model, the coefficient for which was evaluated using a Wald test.

To examine whether the associations of BMI or physical activity to bladder cancer risk were modified by other potential risk factors for bladder cancer, such as gender, age at baseline, race/ethnicity, education, smoking status, intakes of fruits and vegetables, red meat, beverages, and alcohol, and NSAID use, we conducted tests for multiplicative interaction using likelihood ratio tests. We also evaluated the relations of BMI and physical activity to bladder cancer within strata of potential effect modifying variables. All relative risks (RR) are presented with 95% confidence intervals (95% CI), and reported P values are based on two-sided tests. All analyses were conducted using SAS release 9.1 (SAS Institute).

Results

During 3,404,642 person-years of follow-up, we documented 1,719 newly incident cases of bladder cancer, of which 1,470 were diagnosed in men and 249 in women. Participants with high BMI were less physically active, were more likely to be NSAID users, had a lower education level, and consumed less fruit and vegetables than those with normal BMI. In contrast, subjects with high physical activity were leaner, were more educated, and consumed more fruit and vegetables than less active subjects. At baseline, participants with high BMI or those

Table 2. RR of bladder cancer according to BMI

Variable	BMI (kg/m^2)				P_{trend}
	18.5-24.9	25.0-29.9	30.0-34.9	≥35.0	
Person-years	1,174,879	1,474,882	541,963	212,917	
No. cases	479	845	301	94	
Age- and sex-adjusted RR (95% CI)	1.0	1.18 (1.05-1.32)	1.29 (1.11-1.49)	1.34 (1.08-1.68)	0.002
Multivariate RR without physical activity (95% CI)*	1.0	1.16 (1.03-1.29)	1.23 (1.06-1.43)	1.30 (1.04-1.63)	0.016
Multivariate RR with physical activity (95% CI)†	1.0	1.15 (1.03-1.29)	1.22 (1.05-1.42)	1.28 (1.02-1.61)	0.028

*The multivariate model used age as the underlying time metric and included the following covariates: gender (women, men), a combination of smoking status (never, former, current), time since quitting for former smokers (≥10, 5-9, 1-4, <1 y) and smoking intensity for former and current smokers (1-10, 11-20, 21-30, 31-40, 41-60, ≥61 cigarettes per day), race/ethnicity (White, Black, Hispanic, other race/ethnicity), education (less than high school, high school, vocational school or some college, college graduate, postgraduate), marital status (married or living as married, other), family history of cancer (yes, no), intakes of red meat (quintiles), fruit and vegetables combined (quintiles), nonalcoholic beverages (quintiles), and alcohol (0, <1, 1-3, >3 servings/d), menopausal hormone therapy (current, past, never), oral contraceptive use (ever, never), and parity (0, 1-2, ≥3).
† Adjustment for physical activity included the following categories: 0, <1, 1-2, 3-4, ≥5 times a week.

Table 3. Multivariate relative risk of bladder cancer to according BMI in participants defined by selected variables

Variable	No. cases	BMI (kg/m^2)				P_{trend}	$P_{interaction}$
		18.5-24.9	25.0-29.9	30.0-34.9	≥35.0		
Gender							
Men	1,470	1.0	1.21 (1.07-1.37)	1.21 (1.03-1.43)	1.25 (0.96-1.63)	0.079	0.061
Women	249	1.0	0.84 (0.62-1.15)	1.38 (0.96-1.96)	1.37 (0.87-2.18)	0.146	
Age at baseline (y)							
<65	798	1.0	1.14 (0.96-1.36)	1.27 (1.02-1.57)	1.26 (0.92-1.72)	0.026	0.919
≥65	921	1.0	1.16 (0.99-1.35)	1.17 (0.95-1.45)	1.32 (0.94-1.84)	0.376	
Race/ethnicity							
White	1,629	1.0	1.16 (1.03-1.31)	1.22 (1.05-1.43)	1.29 (1.02-1.64)	0.024	0.849
Non-White	90	1.0	0.99 (0.61-1.64)	1.19 (0.63-2.24)	0.93 (0.24-2.50)	0.942	
Education							
Some college or less	1,097	1.0	1.13 (0.98-1.31)	1.25 (1.04-1.49)	1.19 (0.89-1.57)	0.137	0.662
College graduate or postgraduate	622	1.0	1.19 (0.99-1.43)	1.15 (0.89-1.49)	1.47 (0.99-1.19)	0.104	
Smoking status							
Current smoker	389	1.0	1.13 (0.89-1.41)	1.17 (0.88-1.61)	1.07 (0.62-1.87)	0.502	0.862
Former smoker	1,047	1.0	1.20 (1.03-1.40)	1.24 (1.02-1.51)	1.32 (0.99-1.76)	0.179	
Never smoker	283	1.0	1.05 (0.79-1.38)	1.29 (0.89-1.86)	1.42 (0.82-2.46)	0.028	
Physical activity*							
Inactive	914	1.0	1.09 (0.92-1.28)	1.06 (0.86-1.29)	1.33 (1.01-1.74)	0.352	0.087
Active	805	1.0	1.22 (1.03-1.43)	1.44 (1.16-1.79)	0.98 (0.61-1.57)	0.020	
Fruit and vegetable intakes †							
Low	998	1.0	1.07 (0.92-1.25)	1.17 (0.96-1.42)	1.41 (1.07-1.87)	0.102	0.107
High	721	1.0	1.26 (1.06-1.50)	1.29 (1.02-1.64)	1.05 (0.70-1.55)	0.171	
Red meat intake ‡							
Low	750	1.0	1.21 (1.02-1.43)	1.34 (1.06-1.69)	1.19 (0.79-1.79)	0.023	0.606
High	969	1.0	1.11 (0.95-1.30)	1.15 (0.94-1.39)	1.30 (0.98-1.72)	0.289	
Nonalcoholic beverage intake§							
Low	751	1.0	1.11 (0.93-1.31)	1.08 (0.85-1.36)	0.95 (0.65-1.39)	0.474	0.179
High	968	1.0	1.21 (1.03-1.41)	1.36 (1.12-1.66)	1.56 (1.17-2.07)	0.017	
Alcohol use							
No	360	1.0	1.15 (0.89-1.49)	1.21 (0.88-1.66)	1.32 (0.85-2.40)	0.175	0.989
Yes	1,359	1.0	1.16 (1.02-1.32)	1.23 (1.04-1.46)	1.27 (0.97-1.66)	0.071	
NSAID use‖							
No	480	1.0	1.23 (0.99-1.52)	1.22 (0.91-1.64)	1.20 (0.74-1.96)	0.183	0.458
Yes	406	1.0	1.02 (0.80-1.29)	1.24 (0.92-1.66)	0.80 (0.47-1.37)	0.989	

NOTE: The multivariate models were adjusted for covariates listed in Table 2 footnote. In each case, the stratification variable was excluded from the model. Within each stratum, the category of subjects with a BMI of 18.5 to 24.9 served as the reference group.

* Inactive was defined as engaging in <20 min of continuous vigorous exercise three times a week. Active was defined as engaging in at least 20 min of continuous vigorous exercise three times a week.

† The strata of low and high fruit and vegetable intakes were defined based on the cut point representing the median value of 3.2 servings/1,000 kcal/d.

‡ The strata of low and high red meat intakes were defined based on the cut point representing the median value of 31.4 g/1,000 kcal/d.

§ The strata of low and high nonalcoholic beverage intakes were defined based on the cut point representing the median value of 1,782 mL/d.

‖ The analysis that was stratified by NSAID use was conducted using data from a subcohort of study participants for whom we had collected information regarding NSAID use.

with high physical activity levels were less likely to currently smoke but were more likely to have formerly smoked than their lean or less active counterparts (Table 1).

Participants who were overweight or obese had a greater risk of bladder cancer than normal weight subjects. After adjustment for age and gender, individuals with BMI levels of 18.5 to 24.9 (reference), 25.0 to 29.9, 30.0 to 34.9, and ≥ 35 kg/m^2 had RRs of 1.0, 1.18, 1.29, and 1.34 (95% CI, 1.08-1.68; P_{trend} = 0.002; Table 2). After additional adjustment for multiple variables, the inverse association was slightly attenuated (RR comparing extreme BMI categories, 1.30; 95% CI, 1.04-1.63; P_{trend} = 0.016). Further adjustment for physical activity had only minor effect (RR comparing extreme BMI categories, 1.28; 95% CI, 1.02-1.61; P_{trend} = 0.028). When we limited the analyses to transitional cell carcinomas (n = 1,503), statistical power was slightly reduced, but results were essentially unaltered (multivariate RR comparing extreme BMI categories, 1.23; 95% CI, 0.96-1.58; P_{trend} = 0.044).

In a secondary analysis, we repeated our main analysis after excluding all cases of bladder cancer that occurred during the first 2 years of follow-up (n = 423 cases excluded). Results were somewhat attenuated, showing a multivariate RR for the highest versus lowest category of BMI of 1.19 (95% CI, 0.91-1.56; P_{trend} = 0.165).

We examined BMI at age 18 and physical activity at age 15 to 18 in relation to bladder cancer risk. The multivariate RRs for the highest versus lowest categories of BMI at age 18 and physical activity at age 15 to 18 years were 1.76 (95% CI, 1.13-2.76) and 0.92 (95% CI, 0.77-1.09), respectively.

To investigate whether the association between BMI and bladder cancer varied across strata defined by gender, age, race/ethnicity, education, smoking, physical activity, intakes of fruit and vegetables, beverages, and alcohol, and NSAID use, stratified models were fit according to levels of those variables (Table 3). A positive association between BMI and bladder cancer was observed in virtually all subgroups. The relation of BMI to bladder cancer appeared to be strong among never

smokers, modest among former smokers, and weak among current smokers, but tests of interaction indicated no differences across strata.

In age- and gender-adjusted analyses, participants who reported engaging in increasing levels of physical activity [0 (reference), <1, 1-2, 3-4, and ≥5 more times a week] had RRs of 1.0, 0.80, 0.79, 0.75, and 0.71 (95% CI, 0.61-0.82; $P_{trend} < 0.001$; Table 4). After adjustment for multiple potential confounders, except BMI, the inverse association was substantially attenuated, but the point estimate for the highest physical activity level remained statistically significant, with a RR comparing the highest with the lowest level of physical activity of 0.85 (95% CI, 0.73-0.99; $P_{trend} = 0.188$). After further adjustment for BMI, the relation between physical activity and bladder cancer was no longer statistically significant (RR, 0.87; 95% CI, 0.74-1.02; $P_{trend} = 0.358$). When we limited the analyses to transitional cell cancers ($n = 1{,}503$), results were essentially unchanged (multivariate RR comparing extreme physical activity categories, 0.85; 95% CI, 0.72-1.01; $P_{trend} = 0.131$).

Statistically nonsignificant inverse associations between physical activity and bladder cancer were noted for virtually all subgroup analyses defined by gender, age, race/ethnicity, education, smoking, BMI, intakes of fruit and vegetables, beverages, and alcohol, and NSAID use. Formal tests of interaction were not statistically significant (Table 5). The relations of BMI or physical activity with bladder cancer risk were not confounded by NSAID use (data not shown).

We investigated the association between sedentary behavior and bladder cancer. In an analysis that was adjusted for multiple variables, including physical activity, the RRs of bladder cancer for watching television or videos for <3 (reference), 3 to 4, 5 to 6, 7 to 8, and ≥9 h/d were 1.0, 1.01, 0.94, 1.05, and 0.99 (95% CI, 0.66-1.51). Additional control for BMI yielded risk estimates of 1.0, 1.00, 0.93, 1.03, and 0.98 (95% CI, 0.65-1.49).

Discussion

In this prospective study of nearly 500,000 men and women followed for up to 8 years, we found a modest but graded positive association between BMI and risk of bladder cancer. Compared with normal weight, overweight was associated with 15% increase in risk, and obesity was related to an up to 28% increased risk. The positive association between BMI and bladder cancer was independent of other known risk factors for bladder cancer, including age, race, and smoking, suggesting that avoidance of adiposity may play an important role in the prevention of bladder cancer.

In addition, initial analyses suggested that physical activity was associated with reduced risk of bladder cancer. However, part of the effect of physical activity may be related to its influence on weight control because the inverse association between physical activity and bladder cancer did not persist after adjustment for BMI. This suggests that the apparent protective influence of physical activity on bladder cancer operates through a mechanism involving reduced body mass. Findings for BMI and physical activity from earlier in life were consistent with those based on current BMI and physical activity.

Our finding of a modest positive relation between BMI and bladder cancer is consistent with results from 8 (6-12, 16) of a total of 11 (6-16) prospective studies on this topic. Three record linkage–based cohort studies (6-8) compared high with low BMI levels and reported RRs of bladder cancer of 1.13 (95% CI, 1.06-1.20), 1.2 (95% CI, 1.0-1.5), and 1.2 (95% CI, 1.0-1.6), respectively. Those studies (6-8) did not control for smoking; failure to adjust for smoking may have resulted in an overestimation of the positive association between BMI and bladder cancer in those studies because most adult ever smokers are former smokers and BMI is positively related both to former smoking and to bladder cancer risk. In contrast, failure to adjust for current smoking may have resulted in an underestimation of the relation. One cohort study (16) noted a bladder cancer risk of 1.28 (95% CI, 0.73-2.25) for obese versus normal weight women, whereas a cohort study of men (9) found a RR of 2.3 (95% CI, 0.9-5.7) for high versus low body weight. A cohort study (11) that used mortality from bladder cancer as an endpoint compared obese with normal weight subjects and published RRs of 1.14 (95% CI, 0.88-1.46) for men and 1.34 (95% CI, 0.91-1.95) for women. In another cohort study of bladder cancer mortality (10), a statistically significant positive association with adiposity emerged only after excluding the first 20 years of follow-up (RR comparing overweight with normal weight men,

Table 4. RR of bladder cancer according to physical activity

Variable	Physical activity (times a week)*					P_{trend}
	0	<1	1-2	3-4	≥5	
Person-years	591,296	467,197	745,4094	929,663	671,077	
No. cases	334	217	363	469	336	
Age- and sex-adjusted RR (95% CI)	1.0	0.80 (0.68-0.95)	0.79 (0.68-0.91)	0.75 (0.65-0.86)	0.71 (0.61-0.82)	<0.001
Multivariate RR without BMI (95% CI) †	1.0	0.85 (0.72-1.01)	0.88 (0.75-1.02)	0.89 (0.77-1.03)	0.85 (0.73-0.99)	0.188
Multivariate RR with BMI (95% CI) ‡	1.0	0.85 (0.72-1.02)	0.89 (0.76-1.03)	0.91 (0.78-1.05)	0.87 (0.74-1.02)	0.358

* Physical activity was defined as activities that lasted ≥20 min and caused either increases in breathing or heart rate or working up a sweat.

† The multivariate model used age as the underlying time metric and included the following covariates: gender (women, men), a combination of smoking status (never, former, current), time since quitting for former smokers (≥10, 5-9, 1-4, <1 y) and smoking intensity for former and current smokers (1-10, 11-20, 21-30, 31-40, 41-60, ≥61 cigarettes per day), race/ethnicity (White, Black, Hispanic, other race/ethnicity), education (less than high school, high school, vocational school or some college, college graduate, postgraduate), marital status (married or living as married, other), family history of cancer (yes, no), intakes of red meat (quintiles), fruit and vegetables combined (quintiles), nonalcoholic beverages (quintiles) and alcohol (0, <1, 1-3, >3 servings/d), menopausal hormone therapy (current, past, never), oral contraceptive use (ever, never), and parity (0, 1-2, ≥3).

‡ Adjustment for BMI included the following categories: 18.5-24.9, 25.0-29.9, 30.0-34.9, ≥35.0 kg/m^2.

Table 5. Multivariate RR of bladder cancer according to physical activity in participants defined by selected variables

Variable	No. cases	Physical activity (times a week)					P_{trend}	$P_{interaction}$
		0	<1	1-2	3-4	≥5		
Gender								
Men	1,470	1.0	0.84 (0.69-1.02)	0.86 (0.73-1.02)	0.86 (0.73-1.01)	0.87 (0.73-1.03)	0.345	0.317
Women	249	1.0	0.88 (0.58-1.34)	0.98 (0.68-1.42)	1.19 (0.84-1.69)	0.78 (0.49-1.23)	0.879	
Age at baseline (y)								
<65	798	1.0	0.78 (0.62-0.99)	0.83 (0.67-1.03)	0.81 (0.66-1.01)	0.89 (0.71-1.12)	0.685	0.652
≥65	921	1.0	0.93 (0.73-1.28)	0.94 (0.67-1.16)	0.98 (0.81-1.19)	0.86 (0.69-1.07)	0.343	
Race/ethnicity								
White	1,629	1.0	0.86 (0.72-1.02)	0.88 (0.76-1.03)	0.89 (0.77-1.04)	0.87 (0.74-1.03)	0.336	0.892
Non-White	90	1.0	0.75 (0.35-1.60)	0.89 (0.47-1.72)	1.12 (0.62-2.01)	0.82 (0.41-1.66)	0.952	
Education								
Some college or less	1,097	1.0	0.80 (0.65-0.99)	0.92 (0.76-1.10)	0.98 (0.83-1.17)	0.93 (0.76-1.12)	0.796	0.131
College graduate or postgraduate	622	1.0	0.93 (0.69-1.24)	0.81 (0.62-1.06)	0.77 (0.59-0.99)	0.78 (0.59-1.02)	0.064	
Smoking status								
Current smoker	389	1.0	0.93 (0.68-1.27)	0.93 (0.69-1.24)	0.91 (0.67-1.23)	1.14 (0.83-1.58)	0.509	0.489
Former smoker	1,047	1.0	0.83 (0.66-1.04)	0.87 (0.72-1.06)	0.86 (0.72-1.04)	0.78 (0.64-0.96)	0.064	
Never smoker	283	1.0	0.80 (0.50-1.29)	0.84 (0.56-1.27)	1.01 (0.69-1.48)	0.97 (0.65-1.45)	0.509	
BMI (kg/m^2)								
<25.0	479	1.0	0.80(0.57-1.03)	0. 83 (0.62-1.11)	0.79 (0.60-1.06)	0.79 (0.59-1.06)	0.224	0.928
25.0-29.9	845	1.0	0.85 (0.66-1.09)	0.83 (0.66-1.03)	0.87 (0.70-1.07)	0.85 (0.68-1.07)	0.429	
≥30.0	395	1.0	0.89 (0.65-1.25)	1.04 (0.78-1.39)	1.11 (0.83-1.48)	1.02 (0.73-1.44)	0.498	
Fruit and vegetable intakes*								
Low	998	1.0	0.88 (0.72-1.09)	0.93 (0.77-1.12)	0.95 (0.79-1.14)	0.88 (0.72-1.09)	0.512	0.963
High	721	1.0	0.80 (0.59-1.08)	0.82 (0.63-1.05)	0.84 (0.66-1.06)	0.84 (0.65-1.07)	0.521	
Red meat intake †								
Low	750	1.0	0.83 (0.63-1.09)	0.82 (0.64-1.04)	0.87 (0.69-1.08)	0.87 (0.67-1.09)	0.642	0.937
High	969	1.0	0.87 (0.69-1.08)	0.93 (0.77-1.13)	0.93 (0.77-1.13)	0.87 (0.69-1.07)	0.396	
Nonalcoholic beverage intake ‡								
Low	751	1.0	0.75 (0.57-0.98)	0.85 (0.67-1.07)	0.90 (0.73-1.12)	0.84 (0.66-1.06)	0.658	0.717
High	968	1.0	0.94 (0.75-1.17)	0.91 (0.65-1.12)	0.91 (0.75-1.11)	0.91 (0.74-1.12)	0.432	
Alcohol use								
No	360	1.0	0.86 (0.58-1.27)	1.10 (0.79-1.53)	1.04 (0.76-1.42)	1.18 (0.86-1.63)	0.219	0.221
Yes	1,359	1.0	0.84 (0.69-1.02)	0.83 (0.69-0.98)	0.86 (0.73-1.02)	0.79 (0.66-0.95)	0.087	
NSAID use§								
No	480	1.0	0.87 (0.62-1.22)	0.96 (0.72-1.28)	0.84 (0.63-1.12)	0.93 (0.69-1.26)	0.652	0.234
Yes	406	1.0	0.77 (0.54-1.11)	0.77 (0.56-1.06)	0.93 (0.69-1.25)	0.70 (0.49-0.98)	0.297	

NOTE: The multivariate models were adjusted for covariates listed in Table 2 footnote. In each case, the stratification variable was excluded from the model. Within each stratum, the category of subjects with a BMI of 18.5 to 24.9 served as the reference group.

*The strata of low and high fruit and vegetable intakes were defined based on the cut point representing the median value of 3.2 servings/1,000 kcal/d.

† The strata of low and high red meat intakes were defined based on the cut point representing the median value of 31.4 g/1,000 kcal/d.

‡ The strata of low and high nonalcoholic beverage intakes were defined based on the cut point representing the median value of 1,782 mL/d.

§The analysis that was stratified by NSAID use was conducted using data from a subcohort of study participants for whom we had collected information regarding NSAID use.

1.68; 95% CI, 1.06-2.65). A third cohort study on bladder cancer mortality found no relation with excess weight (13).

In contrast, two cohort studies (14, 15) documented a statistically nonsignificant inverse association between BMI and bladder cancer, with RRs comparing high with low BMI of 0.74 (95% CI, 0.45-1.22) and 0.63 (95% CI, 0.33-1.19), respectively. As noted by the authors of one of those studies (15), one plausible reason for the inverse relation of BMI to bladder cancer is residual confounding by smoking that may have persisted even after control for smoking intensity and duration.

In a large cohort study (12), the initial modest association between BMI and bladder cancer (RR comparing high versus low BMI, 1.16; 95% CI, 0.89-1.52) was strengthened and became statistically significant (RR, 1.33; 95% CI, 1.01-1.76) after excluding 423 cases diagnosed in the initial years of follow-up. Other than chance, we have no explanation for the attenuation of the BMI and bladder cancer relation after excluding cases diagnosed in the initial years of follow-up in our study.

As opposed to the majority of cohort studies that showed a positive albeit not always statistically significant association between BMI and bladder cancer (6-12, 16), the four available case-control investigations of BMI and bladder cancer (17-20) produced largely divergent findings. Only one case-control study (17) suggested a statistically significant increased RR of bladder cancer comparing high with low BMI of 1.27 (95% CI, 1.01-1.58). One case-control study (18) found a statistically nonsignificant inverse association between BMI and bladder cancer (odds ratio, 0.61; 95% CI, 0.33-1.14), and two additional case-control studies (19, 20) each reported a null association but did not present actual risk estimates.

Our results showed a lack of an independent association between physical activity and bladder cancer, which is compatible with most (12, 15, 21-26) but not all (27, 28) previous studies in this area. One occupational

cohort study (27) reported an increased risk of bladder cancer for sedentary occupations with standardized incidence ratios ranging from 1.10 (95% CI, 1.02-1.18) to 1.33 (95% CI, 1.07-1.61). Those positive associations with sedentary behavior may have been overestimated as a result of confounding by BMI. We found no relation between our measure of sedentary behavior and bladder cancer in the AARP cohort.

In contrast, one cohort study (28) found an increased risk of bladder cancer for high versus low levels of recreational activity (RR, 2.06; 95% CI, 1.08-3.95), although the test for trend did not reach statistical significance (P_{trend} = 0.09). That study (28) evaluated physical activity in relation to a large number of individual cancer sites; multiple comparisons and a small number of bladder cancer cases (n = 92) could have yielded a positive finding for bladder cancer by chance.

Important strengths of our study include its prospective design, a large number of cases, a high follow-up rate, and reasonably detailed information on potential bladder cancer risk factors. In particular, we were able to adjust for cigarette smoking habits, including smoking status, intensity, and time since quitting. BMI was positively associated with former smoking but was inversely related to current smoking in our data, and in analyses that were stratified by smoking status, the relation of BMI to bladder cancer was stronger among former than current smokers. An analysis including only participants who never smoked (n = 283 bladder cancer cases) yielded a stepwise positive association between increasing BMI level and bladder cancer. This observation suggests that smoking did not substantially confound our findings.

Despite numerous advantageous features of our study, one limitation is that weight and height were assessed by self-report, a method that is subject to error; however, self-reported weight and height have been found to be highly accurate (38). Measurement error in assessing physical activity is a more likely issue (39), but the physical activity assessment in the NIH-AARP study is very similar to an instrument with documented reasonable validity and reproducibility (35). Moreover, our physical activity tool predicts decreased cardiovascular mortality in this cohort (36).

Although this study is the largest known prospective investigation to date to examine the relations of BMI and physical activity to bladder cancer risk, our participants are predominantly Caucasians. Thus, we had limited statistical power to evaluate relations among non-White individuals, for whom bladder cancer incidence rates are known to differ from rates among Caucasians (40).

Biological mechanisms underlying the positive association between BMI and bladder cancer are speculative. Excess body fat is associated with elevated production of insulin, and insulin is a mitogenic factor that may also enhance tumor growth by increasing free insulin-like growth factor-I (41), which in turn stimulates cell proliferation and suppresses apoptosis (42) and has been linked to bladder cancer (43). Although hyperinsulinemia per se has not been implicated in bladder carcinogenesis, type 2 diabetes is directly associated with bladder cancer (44). Adiposity is also accompanied by low-grade, systemic inflammation (45), which may play a role in bladder carcinogenesis as suggested by positive relations of circulating levels of inflammatory markers, such as C-reactive protein and interleukin-6, to bladder cancer mortality (46, 47).

We conclude that overweight and obesity are associated with a modest increase in bladder cancer risk. Thus, bladder cancer may be added to the list of cancers potentially related to adiposity. In contrast, physical activity is not independently related to bladder cancer risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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