Hypertension, diuretics and antihypertensives in relation to bladder cancer

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The aim of this study is to investigate the relationships between hypertension, hypertension medication and bladder cancer risk in a population-based case–control study conducted in Los Angeles. Non-Asians between the ages of 25 and 64 years with histologically confirmed bladder cancers diagnosed between 1987 and 1996 were identified through the Los Angeles County Cancer Surveillance Program. A total of 1585 cases and their age-, gender- and race-matched neighborhood controls were included in the analyses. Conditional logistic regression models were used to examine the relationship between history of hypertension, medication use and bladder cancer risk. A history of hypertension was not related to bladder cancer; however, among hypertensive individuals, there was a significant difference in bladder cancer risk related to the use of diuretics or antihypertensive drugs (P for heterogeneity = 0.004). Compared with individuals without hypertension, hypertensive individuals who regularly used diuretics/antihypertensives had a similar risk [odds ratio (OR) 1.06; 95% confidence interval (CI) 0.86–1.30], whereas untreated hypertensive subjects had a 35% reduction in risk (OR: 0.65; 95% CI: 0.48–0.88). A greater reduction in bladder cancer risk was observed among current-smokers (OR: 0.43; 95% CI: 0.27–0.71) and carriers of GSTM1-null (homozygous absence) genotypes (OR: 0.43; 95% CI: 0.22–0.85). Similarly, among smokers with GSTM1-null genotype, levels of 4-aminobiphenyl-hemoglobin adducts were significantly lower among untreated hypertensive individuals (45.7 pg/g Hb) compared with individuals without hypertension (79.8 pg/g Hb) (P = 0.009). In conclusion, untreated hypertension was associated with a reduced risk of bladder cancer.

Materials and methods

Study population

The design of the Los Angeles Bladder Cancer Study was described previously (18). Briefly, cases were non-Asians between the ages of 25 and 64 years with histologically confirmed bladder cancer diagnosed between January 1987 and April 1996. All cases were identified through the Los Angeles County Cancer Surveillance Program (19). For each enrolled case, a standard procedure was followed to recruit a control subject from the neighborhood of residence of the case at the time of cancer diagnosis, with the control subject matched to the case by age (±5 years), sex and race/ethnicity (non-Hispanic white, Hispanic white or African–American) (18). We attempted to identify the age, sex and race of all inhabitants of each housing unit; ‘not at home’ units were systematically revisited to complete the census. The first resident along this defined route who satisfied all eligibility criteria for controls was asked to participate in the study (i.e. first eligible control). If that individual refused, the next eligible control (i.e. second eligible control) in the sequence was asked and so on until we located an eligible control who agreed to be interviewed. When we failed to find any resident who met our matching criteria after canvassing 150 housing units, we excluded race from the matching criteria. If a matched control subject based on this relaxed criterion could not be found within a maximum of 300 housing units, the case was dropped from the study. We interviewed 1671 eligible cases (70% of eligible cases identified). A matched control was found for 95% (1586) of the interviewed cases. After exclusion of one pair in which the case failed to answer the question on physician-diagnosed hypertension, a total of 1585 matched pairs of cases and controls were included in the current analyses. All study subjects signed informed consent forms approved by the Institutional Review Board at the University of Southern California.
Hypertension and bladder cancer

Data gathering and exposure definitions

All study cases and controls were interviewed at home by trained interviewers using a structured questionnaire. The questionnaire requested information up to a reference date: 2 years prior to the diagnosis of cancer for cases and 2 years prior to the diagnosis of cancer of the index case for matched controls. Each subject was asked to report information on demographic characteristics, height and weight, lifetime use of tobacco products and alcohol, usual adult dietary habits, lifetime occupational history, history of physician-diagnosed hypertension and other selected medical conditions and use of medications. We defined hypertension status according to the subject’s answer to the question, ‘Did a doctor ever tell you that you had hypertension or high blood pressure’. Subjects who answered ‘yes’ were classified as hypertensive. We explicitly listed 21 brand name diuretics/antihypertensive drugs in the questionnaire; these drugs listed represented all the common prescription medications in these respective categories marketed in the USA since the 1950s (20). Diuretics included were aldactazide, aldactone, diuril, dyazide, endurone, diuril, hydrochlorothiazide, hydroinduri, hygroton, lasix, metahydrin, oretic and zaroxylin. Non-diuretic antihypertensives included were aludomet, aludron, lopressor, minipres, rau-sed, reserpine and serpasil. Adoril was also included as a diuretic/antihypertensive combination drug.

Regular use was defined as taking a listed brand name drug twice or more times a week for >1 month. We asked regular users the ages at first and last use, duration of use, usual frequency and dosage of use and the primary reason for such use. Aside from the 21 brand name diuretics/antihypertensives listed, the subject was asked if they had taken any other drug regularly. If the answer was yes, the names of the drugs were recorded and ages at first and last use, duration of use, usual frequency and dosage of use and the primary reason for use were similarly asked. Regular use of the following diuretics/antihypertensives was reported by a few subjects: apresoline, capoten, catapres, corgard, hyrdalazine, furosemide, procdura, tenormin, hydrepore and scrapes.

The formulations of each of the listed drugs as well as those volunteered by the study subjects were established through numerous pharmaceutical sources, including the annually updated Physician’s Desk Reference. Each class of drugs was then placed into a major formulation category. For example, diuretics were grouped as thiazides, furosemides or potassium-sparing diuretics. Antihypertensives were grouped as beta blockers, central anti-adrenergic agents, neuronal depleting agents, angiotensin-converting enzyme inhibitors or vasodilators. Age-specific exposure to a given drug was estimated from the subject’s reported dose and duration of use at that age. Lifetime cumulative exposure to a specific class of compounds (in grams) was computed by summing age-specific exposures across all brand name drugs belonging to that class of compounds. Cumulative exposures were grouped into tertiles according to their distributions among control subjects.

Clinical characteristics of the tumors were obtained from pathology reports. Consistent with Kienemey et al. (21), tumors with tumor-node-metastasis stage pTa and grade 1 or 2 were classified as having low risk of progression and the rest tumors as having high risk of progression.

Blood sample collection, GST enzymes genotyping and 4-aminobiphenyl-hemoglobin measurements

Beginning in January 1992, all case patients (n = 972) and control subjects (n = 973) were asked to donate a blood sample. Seventy-four percent (720/972) of the case patients and 79% (770/973) of the control subjects donated blood. Plasma, buffy coat and red blood cells were isolated from heparinized whole blood and stored at −80°C before analysis.

Genomic DNA was isolated from blood lymphocytes. The presence or absence of the GSTM1 and GSTT1 and GSTP1 105 Ile/Val polymorphism (GSTP1 A/G GSTP1 B) were genotyped, as described in detail previously (22). Among subjects who donated blood samples (720 cases and 770 controls), information on GSTM1, GSTT1 and GSTP1 genotypes were obtained in 708 (98.3%), 704 (97.8%) and 703 (97.6%) case patients and 761 (98.8%), 754 (97.7%) and 758 (98.4%) control subjects, respectively.

De-identified red blood cell samples were sent on dry ice to the Massachusetts Institute of Technology for quantitative analysis of 4-aminobiphenyl-hemoglobin (4-ABP-Hb) adducts as described previously (23). Index cases and their individually matched controls were always tested in a single laboratory. For cases without matched controls or controls without matched cases, the number of cases was comparable with the number of controls in any given laboratory batch (24). Level of 4-ABP-Hb adducts was measured in 765 (99.4%) of the 770 controls who donated a blood sample.

Statistical analysis

The associations of bladder cancer with medical history, diuretics use and antihypertensive drug use were measured by ORs and their corresponding 95% CIs and P-values. Conditional logistic regression models were used to examine the relationship between history of hypertension, medication use and bladder cancer risk with adjustment for other risk/protective factors for bladder cancer: level of education (high school or less, some college and college or above) (25), lifetime use of ‘non-steroidal anti-inflammatory drugs’ (NSAIDs) (non/irregular use, <1441 pills and ≥1441 pills over lifetime) (26), intake of carotenoids (quintiles) (27), ever held a high-risk occupation (truck, bus or taxi driver, officer, truck or barber or aluminum product worker) (no and yes) (28), average number of cigarettes smoked per day, number of years of smoking and smoking status in reference year (smoker or nonsmoker) (18). We also examined the possibility that the hypertension–bladder cancer association was modified by factors such as age, gender, cigarette smoking, use of NSAIDs, body mass index (BMI), consumptions of fluids and genetic variations in genes including GSTM1, GSTT1 and GSTP1 (29). To test this hypothesis, dummy variables representing stratum-specific exposure were created for estimating stratum-specific results in one single conditional logistic regression model. The analyses by genotypes of GSTM1, GSTT1 and GSTP1 were limited to the 545 pairs of individually matched cases and controls with complete data on genotypes for all three genes. P-values for interactions were estimated from likelihood ratio tests. Results were materially unchanged when unconditional logistic regression involving all eligible subjects was used.

The analysis of covariance method was used to compare levels of 4-ABP-Hb adducts by history of hypertension. The distribution of 4-ABP-Hb adducts was markedly skewed; therefore, their values were logarithmically transformed before statistical analysis and geometric mean levels of 4-ABP-Hb adducts were presented.

Statistical analyses were performed using the SAS version 9.1 (SAS Institute, Cary, NC) statistical software package. All P values are two sided. P < 0.05 was considered statistically significant.

Results

Table I summarizes the baseline characteristics of the study subjects by their history of hypertension and use of antihypertensive medications. In the present study, 25% cases and 27% of controls reported being diagnosed with hypertension before the reference date. These hypertensive subjects reported significantly higher BMI and were more probably to be diabetic and have smoked cigarettes, regardless of their disease status. When asked about use of antihypertensive medications, 74% of hypertensive cases and 65% of hypertensive controls reported regular use diuretics or antihypertensives.

The absence of treatment among hypertensive subjects was significantly associated with ethnic minority, younger age, male gender, less use of NSAIDs and higher consumption of alcoholic beverages. In addition, compared with treated hypertensive subjects, untreated hypertensive subjects were slightly more probably to be current-smokers (P(2) = 0.001 and 0.14 among controls and cases, respectively), but no significant differences in number of cigarettes smoked, number of years of smoking or pack-years of smoking were observed.

A history of hypertension was not associated with risk of bladder cancer (OR: 0.92; 95% CI: 0.77–1.11; Table II). However, among hypertensive individuals, there was a significant difference in bladder cancer risk associated with the use of diuretics/antihypertensives (P for heterogeneity = 0.004). Compared with individuals without hypertension, hypertensive individuals who regularly used diuretics or antihypertensives had a similar risk (OR: 1.06; 95% CI: 0.86–1.30), whereas hypertensive individuals who did not use antihypertensives had a 35% reduction in risk (OR: 0.65; 95% CI: 0.48–0.88). Among hypertensive subjects, the main reason for using antihypertensive and/or diuretics (96%) was to lower blood pressure. Other reasons included weight reduction, heart problems, anxiety/depression control and trembling. When we limited our analysis to those who took these medications for lowering blood pressure, the associations between hypertension and bladder cancer risk did not change substantially (data not shown). Among subjects without hypertension, fluid/weight loss was the primary reason for using diuretics (26 cases and 30 controls) and anxiety/depression control was the primary reason for using antihypertensives (28 cases and 24 controls), and there was no significant difference in bladder cancer risk by diuretics/antihypertensives use. For simplicity, hypertensive individuals who reported regular use of diuretics or antihypertensives were considered as having treated hypertension, and hypertensive individuals who did not use antihypertensive drugs were considered as having untreated hypertension.

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We also examined the hypertension–bladder cancer associations by type of medication (for diuretics or antihypertensive users only), age at the diagnosis of hypertension and duration between the diagnosis of hypertension and the diagnosis of bladder cancer (Table II). No significant difference was observed by any of these factors. When the above analyses were limited to non-Hispanic white subjects, our observations did not change materially.

Table III shows the hypertension–bladder cancer association stratified by potential effect modifiers. The inverse association between untreated hypertension and bladder cancer was greater among men (OR: 0.59; 95% CI: 0.42–0.82) than among women (OR: 1.18; 95% CI: 0.51–2.76); however, this difference in ORs did not reach statistical significance (P for interaction = 0.17). The effect of untreated hypertension was different by cigarette smoking status (P for interaction = 0.11), number of cigarettes smoked per day (P for interaction = 0.072) and number of years of smoking (P for interaction = 0.030). In general, the inverse association between untreated hypertension and bladder cancer risk seemed stronger with increasing categories of smoking. The effect of untreated hypertension was not statistically different by age, use of NSAIDs, BMI, consumption of fluids (alcoholic beverages, coffee and water), urination frequency, dietary intake of carotenoids (data not shown) and diabetes (data not shown). We also assessed the effect of untreated hypertension within tumors with different risk of progression and did not find any significant differences (P = 0.18). The OR (95% CI) associated with untreated hypertension was 0.53 (0.36–0.78) and 0.69 (0.49–0.96) for tumors with low and high risk of progression, respectively.

As GST enzymes, which play important roles in the metabolism of a broad range of ROS and xenobiotics, have been implicated in the pathogenesis of both hypertension and bladder cancer, we examined whether genetic variations in three GST enzymes modified the hypertension–bladder cancer association (Table IV). A significant interaction was observed between GSTM1 genotype and untreated hypertension (P for interaction = 0.014) with the effect of untreated hypertension being confined to carriers of the GSTM1-null (homozygous absence of the GSTM1 gene) genotype (OR: 0.43; 95% CI: 0.22–0.85). A similar but non-significant effect modification by GSTT1 genotype was also observed. We further examined the combined modifying effect of GSTM1 genotype and cigarette smoking (data not shown). The inverse association between untreated hypertension and bladder cancer risk was limited to carriers of the GSTM1-null genotype, regardless of their smoking status, suggesting that GSTM1 genotype may be the main modifier in this association.

To explore potential mechanisms for the observed reduction in bladder cancer risk, we examined whether hemoglobin adducts of 4-ABP, an established bladder carcinogen, differed by hypertension status and GSTM1 genotype (Table V). The level of 4-ABP-Hb adducts was slightly lower among untreated hypertensive controls than among controls without hypertension, after controlling for cigarette smoking status at blood draw (P = 0.56). The hypertension-associated...
Among untreated hypertensive subjects

Type of medication

- Diuretics only: 73/70, OR = 0.93 (0.64–1.37)
- Antihypertensives only: 96/87, OR = 1.10 (0.79–1.54)
- Both: 128/121, OR = 1.11 (0.83–1.50)

Age at diagnosis of hypertension

- <50 years old: 184/171, OR = 1.08 (0.84–1.39)
- ≥50 years old: 106/102, OR = 1.02 (0.74–1.40)

Duration between the diagnosis of hypertension and the diagnosis of bladder cancer

- <5 years: 34/27, OR = 1.05 (0.59–1.86)
- 5–14 years: 142/137, OR = 0.98 (0.74–1.30)
- ≥15 years: 114/109, OR = 1.15 (0.84–1.57)

Among treated hypertensive subjects

Age at diagnosis of hypertension

- <50 years old: 75/104, OR = 0.67 (0.47–0.97)
- ≥50 years old: 29/41, OR = 0.66 (0.38–1.16)

Duration between the diagnosis of hypertension and the diagnosis of bladder cancer

- <5 years: 14/25, OR = 0.46 (0.22–0.96)
- 5–14 years: 48/80, OR = 0.85 (0.54–1.33)
- ≥15 years: 42/60, OR = 0.60 (0.37–0.97)

Discussion

Our study found a reduced risk of bladder cancer among hypertensive subjects who did not use antihypertensives or diuretics regularly and this reduction in risk was limited to smokers and carriers of the GSTM1-null genotype. Consistent with these results, untreated hypertensive control subjects exhibited a lower level of hemoglobin adducts (45.7 pg/g Hb; 95% CI: 32.6–64.0 pg/g Hb) than controls without hypertension (79.8 pg/g Hb; 95% CI: 67.1–95.0 pg/g Hb), even though, on average, they smoked more cigarettes per day. Results were similar when our analyses were restricted to non-Hispanic white subjects, male subjects (data not shown) or hypertensive subjects who were diagnosed within 10 years of blood draw.

Our observation of a lower level of 4-ABP-Hb adducts among untreated hypertensive healthy subjects may indicate a possible connection between hypertension and metabolism of 4-ABP. Arylamines, such as 4-ABP, are present in tobacco smoke and are the leading putative carcinogens responsible for bladder cancer development in smokers (54). One could hypothesize that if the mechanism of protection involves reducing exposure to cigarette-derived carcinogens, smokers would have benefited more from untreated hypertension than non-smokers. Consistent with this hypothesis, our study found that untreated hypertension appeared most protective among smokers. However, no direct evidence for this proposed mechanism is currently available. In addition, the interpretation of the 4-ABP-Hb adducts results needs to be cautious since the blood samples used to measure the 4-ABP-Hb adducts were collected at the time of study recruitment, whereas the hypertension and treatment status were lifetime histories. It is also possible that factors associated with the decision of treatment for hypertensive patients may explain the association between untreated hypertension and bladder cancer risk. In our study, untreated hypertensive subjects were relatively young with a mean age of 56 years. To achieve blood pressure control, these individuals may have adopted healthy lifestyles, such as eating more fruits and vegetables and engaging in regular aerobic physical activity (55), instead of taking antihypertensive medications. Information on physical (OR: 0.89; 95% CI: 0.60–1.31) (33). Similarly, no significant association with bladder cancer risk was found for history of hypertension in a Korean case–control study (OR: 1.63; 95% CI: 0.79–3.34) (34). Interestingly, a case–control study conducted in Japan found a significantly lower risk for bladder cancer in men who had a past history or complications of hypertension (35). As for antihypertensive drugs, an elevated risk of bladder cancer was observed in a Danish cohort among men who received diiltiazem (a class of calcium channel blocker used in the treatment of hypertension) exclusively (standardized incidence ratio = 2.1; 95% CI: 1.2–3.4) or combined with other calcium channel blockers (36).

The precise mechanism whereby hypertension reduces the risk of bladder cancer is unclear. We speculate that one mechanism could be related to the oxidative stress-induced apoptosis pathway, although the underlying biological basis of this pathway as an anticancer mechanism is still unclear and controversial. Damage to DNA by ROS has been widely accepted as a major cause of cancer (7). However, evidence is also accumulating that ROS are essential mediators of apoptosis, which eliminates precancerous and cancerous, virus-infected and otherwise damaged cells (37,38). Thus, it seems that ROS may have divergent cellular effects depending on their origin, extent of their production and the enzymatic or nonenzymatic mechanisms available for their disarmament in a given cell type. It has been shown that untreated hypertensive subjects have significantly increased levels of ROS (6,39–44), and this increase is reversible upon treatment with antihypertensive medications (45). In bladder cancer, the generation of ROS and oxidative stress have been proposed as the major mechanism for the induction of apoptosis and inhibition of cancer growth by the cancer chemopreventive or chemotherapeutic agents N-(4-hydroxyphenyl) retinamide (46), isothiocyanates (37,47), arsenic trioxide (48), interferon-γ (49–51) and cis-dichlorodiammineplatinum (52). In light of this evidence, it is plausible that increased ROS from untreated hypertension may induce apoptosis of bladder cancer cells and thus reduce bladder cancer risk. However, as expressed above, despite these experimental data, the underlying biological basis of this pathway as an anticancer mechanism is still uncertain.

Because glutathione-associated metabolism is a major mechanism against agents that generate oxidative stress by eliminating ROS, we hypothesized that individuals possessing the low activity genotypes of antioxidant GSTM1, GSTT1 and or GSTP1 (i.e. the GSTM1 null, GSTT1 null and GSTP1 AB/BB genotypes, respectively) may exhibit a stronger untreated hypertension–bladder cancer inverse association than those possessing the high-activity genotypes (53). This hypothesis is supported by our results that the reduction in bladder cancer risk from untreated hypertension was mostly confined to carriers of the GSTM1-null genotype. An association with bladder cancer risk was found for history of hypertension in a Korean case–control study (OR: 1.63; 95% CI: 0.79–3.34) (34). Interestingly, a case–control study conducted in Japan found a significantly lower risk for bladder cancer in men who had a past history or complications of hypertension (35). As for antihypertensive drugs, an elevated risk of bladder cancer was observed in a Danish cohort among men who received diiltiazem (a class of calcium channel blocker used in the treatment of hypertension) exclusively (standardized incidence ratio = 2.1; 95% CI: 1.2–3.4) or combined with other calcium channel blockers (36).
Alcoholic beverages
Use of NSAIDs
Years of smoking
Cigarettes/day
Smoking status
Non-smokers
Former-smokers
Current-smokers
P for interaction
Age
< Median (58 yrs)
≥ Median
P for interaction
Sex
Males
Females
P for interaction
Sex
Males
Females
P for interaction
Sex
Males
Females
P for interaction
Smoking status
Non-smokers
Former-smokers
Current-smokers
P for interaction
Years of smoking
Never
< 20
20 – 39
40+
P for interaction
Use of NSAIDs
Nonusers
≥ 1441 pills over lifetime
P for interaction
BMI
< 25
25 – < 30
≥ 30
P for interaction
Alcoholic beverages
Nondrinkers
< 3 drinks/day
≥ 3 drinks/day
P for interaction

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<td>293/240</td>
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*Results were estimated from conditional logistic regression. Smoking status was missing for one case; use of NSAIDs was missing for 13 cases and 13 controls; BMI was missing for two cases and one control; consumption level of alcohol was missing for 13 cases and 9 controls.

P values were estimated from likelihood ratio tests of conditional logistic regressions with effect modifiers modeled as continuous variables (except that smoking status was modeled as a categorical variable).

Activity was not collected in our study. Nonetheless, physical activity is not an established risk/protective factor for bladder cancer with most studies showing a lack of association (56). We did collect information on dietary intake of fruits and vegetables and found that dietary intake of carotenoids was associated with reduced risk of bladder (27). Similarly, we previously reported on inverse association between alcohol intake and bladder cancer (25). In our study, hypertensive control subjects, especially those who did not regularly use diuretics or antihypertensives, reported a significantly higher dietary intake of carotenoids and a significantly higher consumption of alcoholic beverages than control subjects without hypertension, therefore it is possible that the association between hypertension and bladder cancer was confounded by one of these two factors. However, the hypertension–bladder cancer association remained unchanged after we adjusted our analyses for dietary intake of carotenoids and alcohol consumption, and the untreated hypertension-associated reduction in risk was also observed among subjects with low intake of carotenoids and alcohol nondrinkers. It is possible that people who were not treated for hypertension may have been different in many aspects from people who were, including in hypertension itself. According to the Third National Health and Nutrition Examination Survey (NHANES III), in the 45- to 64-year-old age group (to which majority of our study subjects belonged), untreated hypertensive patients had a mean blood pressure of 152/89, with 54% having isolated systolic hypertension (systolic blood pressure ≥ 140 mm Hg and diastolic blood pressure < 90 mm Hg) (57). For a long time, guidelines, clinical trials and clinical practice on blood pressure control have placed greater importance on diastolic blood pressure levels (58) (the first Joint National Committee report in 1977 (59) defined diastolic blood pressure, not systolic blood pressure, as the basis for detection and treatment), so it is possible that an individual with isolated systolic hypertension may have not been eligible for treatment under the old guidelines. Consistent with this notion, studies that documented physicians’ behavior have also confirmed that physicians are unlikely to diagnose isolated systolic hypertension as hypertension or to treat this condition aggressively (57). We did not directly measure the
study participants’ blood pressure and hence were unable to quantitatively measure the effect of hypertension by its severity and different types, so it is still possible that confounding by indication may have risen due to different prognostic factors that have influenced treatment decisions.

Our study has limitations. One important limitation is the relatively small sample size of untreated hypertensive subjects (104 cases and 150 controls), particularly in the subgroup analyses and 4-ABP-Hb analyses, increasing thus the likelihood of spurious associations and precluding firm conclusions. Large studies are needed to confirm these findings. In addition, the diagnosis of hypertension was self-reported and the retrospective nature of our case–control design did not allow us to obtain accurate and complete history of hypertension and use of medications over long periods, leading to potential misclassification. However, we believe the misclassification is non-differential for cases and controls, therefore unlikely to explain our findings. Hypertension is often associated with other medical conditions such as central obesity, diabetes mellitus and hyperlipidemia. Some of these conditions (56,60) and their associated medications such as statin (61) have been associated with bladder cancer risk in some studies. Our study did not collect detailed information on all these conditions and their associated medications; therefore, it is possible that our observed associations may be confounded by these factors. However, we did obtain some information on diabetes and BMI and these two factors did not seem to affect the inverse association between untreated hypertension and bladder cancer risk.

Untreated or poorly treated hypertension is associated with increased mortality and stroke (62), indicating the possibility that untreated hypertensive subjects may be more probably to die from competing risks and therefore less probably to live long enough to develop bladder cancer. However, such possibility is most probably to be low since the NHANES III found that subjects with acknowledged untreated hypertension were more probably to be young male current-smokers (average age: 55.3 years old), similar to the findings from our study.
(average age among controls: 56.1 years old), and majority of them were subjects who had access to medical care (57). In addition, our observation of a similar effect of untreated hypertension for bladder cancer diagnosed at different stages indicates that survival bias is unlikely. Finally, there is also the possibility that the GSTM1 genotyping method that we used, which did not distinguish between homozygous wild-type ++/+, and heterozygous ++/− individuals, may have led to an underestimation of the genetic effect.

In summary, we observed a statistically significant inverse association between untreated hypertension and bladder cancer risk. Future studies are needed to confirm our findings and explore possible mechanisms.

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References


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