Association of Albuminuria and Cancer Mortality

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Abstract

Background: The objective was to evaluate the association of albuminuria with cancer mortalities in adults ages 50 and older.

Methods: A total of 6,112 adults ages 50 years and above without a history of cancer at baseline in the Third National Health and Nutrition Examination Survey (NHANES III, 1988-1994) were included in the analysis. Albuminuria was measured with urinary albumin-to-creatinine ratio (UACR) in mg/mmol. Cancer mortality was obtained from the NHANES III–linked follow-up database (up to December 31, 2006). Cox-regression models were used to examine the associations of interest.

Results: Albuminuria was present in 705 men (17.5%) and 592 women (14.3%). During an average follow-up of 149 months, 613 subjects died of cancers including 184 lung cancers, 65 colorectal cancers, 55 prostate cancers, and 309 other cancers. There was an increased mortality risk associated with logarithmically transformed UACR for all-cancer [relative risk (RR), 1.20; 95% confidence interval (CI), 1.06-1.36], lung cancer (RR, 1.22; 95% CI, 1.05-1.43), and prostate cancer mortality (RR, 1.40; 95% CI, 1.01-1.95) in men. No associations between UACR and cancer were apparent in women.

Conclusions: The analysis shows that albuminuria is associated with an increased risk of cancer death, specifically for all-cause, lung, and prostate cancers in men ages 50 and above.

Impact: Further studies are needed to explore the relationship between albuminuria and specific cancers. Understanding the biological link between albuminuria and cancer will be critical for determining whether albuminuria represents an early marker or a potential therapeutic target. *Cancer Epidemiol Biomarkers Prev; 19(11); 2950–7. ©2010 AACR.*

Introduction

Albuminuria is an important and independent risk marker for cardiovascular disease in the general population and, more specifically, in patients with hypertension and diabetes mellitus (1-3). Whether albuminuria is a contributory factor in atherothrombosis or merely a marker

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remains unclear. However, evidence suggests that common pathophysiologic processes such as endothelial dysfunction, chronic low-grade inflammation, and transvascular leakage of macromolecules may underlie the association between microalbuminuria and cardiovascular disease (4). Microalbuminuria is also considered an early sign of intrarenal vascular dysfunction and a potent marker for the subsequent development of progressive kidney disease (5-7).

Albuminuria is associated with increases in all-cause and cardiovascular mortality in uncomplicated hypertensives and type 2 diabetics (8, 9). When combined as indicators of renal dysfunction, decreased glomerular filtration rate and albuminuria predict both all-cause and cardiovascular mortality (10). In the Prevention of Renal and Vascular End Stage Disease study conducted in the Netherlands, a 2-fold increase of albuminuria was associated with a relative risk (RR) of 1.29 and 1.12 for cardiovascular and noncardiovascular mortality, respectively (1).

The Prevention of Renal and Vascular End Stage Disease study proposed that albuminuria-associated noncardiovascular deaths might represent greater fatalities due to malignant neoplasms, although specific etiologies were not analyzed. Little is known regarding the association of albuminuria with cancer mortality. Because cancer is currently second only to cardiovascular disease

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as a leading cause of death in the United States, the hypothesis was formulated that albumin in the urine would be associated with an increased risk of cancer mortality. The objective of this study was to test the hypothesis by evaluating the relationship between albuminuria and cancer mortality using the large-scale nationally representative sample from the Third National Health and Nutrition Examination Survey (NHANES III, 1988-1994) and its follow up in the NHANES III–linked mortality data set (through December 31, 2006; refs. 11, 12).

Materials and Methods

Study design and population

NHANES III was conducted by the National Center for Health Statistics from 1988 to 1994 using a stratified, multistage, and cluster sampling design to obtain a representative sample of the non-institutionalized civilian U.S. population. Detailed survey operations manuals, consent documents, and brochures of the NHANES are available on the NHANES web site (11). The NHANES III was reviewed and approved by the National Center for Health Statistics Institutional Review Board. Of 7,593 adults ≥50 years of age that completed the NHANES III interview and examination between 1988 and 1994, the current analysis was limited to non-Hispanic Whites, non-Hispanic Blacks, and Mexican Americans by excluding 266 participants identified as other race. Participants with previous history of malignancy ($n = 547$), missing data for follow-up information ($n = 19$), and other covariates (e.g., urinary albumin measurement, $n = 664$) were also excluded from the cohort. The remaining 6,112 subjects (2,996 men and 3,116 women) in the analyses represent an estimated U.S. non-institutional population of 49,914,220 persons ages 50 and older after adjusting for sample weights.

Baseline demographics

In NHANES III, data were collected at all study sites by trained personnel according to standardized procedures. Information on age, sex, and smoking status was self-reported. Subjects with serum cotinine values >14 ng/mL were classified as current smokers, otherwise as nonsmokers (13). Subjects were classified as diabetic based on a self-reported diagnosis, prescribed medication for diabetes (insulin or oral agents), or a fasting plasma glucose of ≥126 mg/dL (14, 15). A diagnosis of hypertension was assigned if the subjects reported taking prescribed medication for hypertension, a physician diagnosis of hypertension, or if the systolic blood pressure was ≥140 mm Hg and/or diastolic blood pressure was ≥90 mm Hg. Three to four blood pressure (BP) determinations were made using a mercury sphygmomanometer from the right arm by a physician. Averaged systolic and diastolic blood pressure determinations were obtained. Body mass index (BMI) was defined as body weight (kg) divided by the square of the body height (m^2). Blood

was sampled, processed locally, stored, and then shipped to central laboratories for analysis (12).

Definition of albuminuria

A spot urine sample was collected to determine urinary albumin using a solid phase fluorescent immunoassay, capable of measuring values below the limit of detection by the dipstick method (16). Urine creatinine was analyzed using the Jaffé reaction. The urinary albumin-to-creatinine ratio (UACR in mg/mmol) was calculated by dividing the urinary albumin value by the urinary creatinine concentration for each subject. The presence of albuminuria was defined as UACR >2.5 mg/mmol in men and >3.5 mg/mmol in women (17).

Serum creatinine was measured by means of the modified kinetic Jaffé reaction, and standardized serum creatinine values were calibrated by using an enzymatic creatinine assay traceable to a gold standard reference method (18). The glomerular filtration rate was calculated from the modification of diet in renal disease (MDRD) Study equation: MDRD estimated glomerular filtration rate (eGFR; mL/min/1.73 m^2) = 175 × (serum creatinine, mg/dL)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American; ref. 19). The presence of chronic kidney disease was defined as MDRD eGFR <60 mL/min/1.73 m^2 (20).

Cancer mortality follow-up

Several of the most common cancers were selected for analysis. Lung, colorectal and prostate were examined in the current study based on cause of death codes from the International Classification of Diseases, 10th Revision (ICD-10). Cancer mortality was analyzed for all-cause cancer (ICD codes: C00-C95), lung cancer (ICD codes: C33-34), colorectal cancer (ICD codes: C18-21), and prostate cancer (ICD codes: C61). Cancers other than lung cancer, colorectal cancer, or prostate cancer (in men) were defined as other types of cancer. Follow-up for each participant was calculated as the difference between the NHANES III examination date and the end of follow-up (date of death or December 31, 2006, whichever occurred first). Those found alive were right-censored at the last date known alive or at the end of the follow-up. For cancer-specific analysis, those who died from other cancers were also right-censored at the time of death.

Statistical methods

Continuous variables were reported as median (interquartile range) and categorical data in percentages. For outcome measurements, the Cox proportional hazard model with the Efron method was used to calculate the RR, also known as hazard ratio (HR). RRs were determined for mortality risk associated with albuminuria for all-cause and cause-specific cancer (lung, prostate, colorectal, and other types of cancer). Possible confounding factors, such as age, race/ethnicity, smoking, BMI, hypertension, diabetes, and chronic kidney disease were added to adjust the association of albuminuria with cancer

Table 1. Baseline demographic characteristics for participants in the NHANES III ages 50 y and above (n = 6,112)

	Men			Women		
	With albuminuria	**Without albuminuria**	**P***	**With albuminuria**	**Without albuminuria**	**P***
n	705	2,291	N/A	592	2,524	N/A
Percentage (SE) in category						
Chronic kidney disease (yes)	43.8 (3.42)	28.7 (1.51)	0.004	59.5 (3.02)	47.3 (1.32)	0.002
Hypertension (yes)	60.8 (2.82)	42.6 (1.67)	<0.001	51.2 (3.02)	40.7 (1.08)	0.001
Diabetes (yes)	15.8 (2.15)	5.71 (0.60)	<0.001	24.2 (2.42)	5.13 (0.57)	<0.001
Current smoking (yes)	33.3 (2.97)	31.3 (1.69)	0.50	21.1 (2.90)	18.8 (1.28)	0.48
Race/ethnicity			<0.001			<0.001
Non-Hispanic white	81.3 (1.93)	89.2 (0.70)		80.2 (1.85)	87.9 (0.89)	
Non-Hispanic black	14.9 (1.79)	7.64 (0.58)		15.9 (1.72)	9.20 (0.78)	
Mexican Americans	3.82 (0.41)	3.12 (0.30)		3.89 (0.41)	2.91 (0.23)	
Median (Interquartile range)						
Age (y)	67.2 (58.3-74.1)	60.9 (54.8-68.3)	<0.001	66.8 (59.5-76.2)	62.2 (55.2-70.5)	<0.001
BMI (kg/m^2)	26.7 (24.3-30.0)	26.8 (24.4-29.8)	0.59	27.7 (24.0-33.4)	26.4 (23.2-30.6)	0.001
Serum creatinine (mg/dL)	1.18 (1.05-1.39)	1.15 (1.04-1.26)	<0.001	0.97 (0.86-1.17)	0.94 (0.84-1.05)	<0.001
MDRD eGFR (mL/min/1.73 m^2)	59.9 (50.1-69.9)	62.5 (56.1-69.2)	<0.001	54.8 (44.8-63.2)	57.5 (50.3-64.7)	<0.001
Systolic blood pressure (mm Hg)	141 (130-156)	131 (120-142)	<0.001	144 (130-161)	130 (119-144)	<0.001
Diastolic blood pressure (mm Hg)	78.7 (71.4-86.2)	76.6 (70.4-83.0)	0.02	75.2 (69.3-82.6)	73.3 (67.8-79.1)	0.01

NOTE: Except for sample size, all of the reported values were adjusted for sampling weight.

*The P values for demographic comparisons between individuals with and without albuminuria were calculated with log-transformed data for continuous variables (t test) and χ^2 test for categorical variables.

mortality. Except for age and BMI, all variables were fit as categorical terms, which were coded as indicator (dummy) variables. For instance, two indicator variables were created to code for three race/ethnicity categories: non-Hispanic Whites, non-Hispanic Blacks, and Mexican Americans. Statistical analyses were conducted using SUDAAN 10.01 (Research Triangle Institute, 2009) with the Taylor series linearization and were adjusted for sampling weights to obtain unbiased national estimates in all analyses. Two-tailed $P < 0.05$ values were accepted as statistically significant.

Results

The baseline demographics of study subjects (2,996 men and 3,116 women) are presented in Table 1. Except smoking (both men and women) and BMI (men only), all demographic and clinical variables were statistically different between those with and those without albuminuria ($P < 0.05$) for both sexes. In general, albuminuria tended to be more prevalent among the elderly and subjects with chronic kidney disease, hypertension, or diabetes. Albuminuria was also associated with race/ethnicity such that albuminuria was more common in non-Hispanic blacks. Although statistically

different and suggestive of a marginal reduction in renal function, it is unclear whether the higher serum creatinine and lower MDRD eGFR are biologically significant differences.

Between 1988 and 2006, a total of 613 subjects (8.8%) died of cancer (all-cause) in an average follow-up of 149 months (range, 1-217 mo). This included 184 lung cancers (123 men and 61 women), 65 colorectal cancers (48 men and 17 women), 55 prostate cancers, and 309 other cancer deaths (152 men and 157 women). This corresponds to age-adjusted mortality rates (year 2000 U.S. standard population) of 3.2 for lung, 0.94 for colorectal, 1.1 for prostate, and 3.7 for other cancers for men and 1.7 for lung, 0.44 for colorectal, and 4.4 for other cancers for women per 1,000 person-years, respectively (data not shown). As shown in both Kaplan-Meier survival curves (Figs. 1 and 2 for men and women, respectively) and univariate Cox proportional hazard regression (Table 2), subjects with albuminuria are at increased mortality risk from all all-cause cancer, prostate cancer (men only), and the collected cancers other than lung, prostate, and colorectal cancers, as compared with those without albuminuria for both sexes. For instance, the RR of all-cause cancer deaths were 83% higher among men with albuminuria than those without it [RR, 1.83; 95% confidence interval
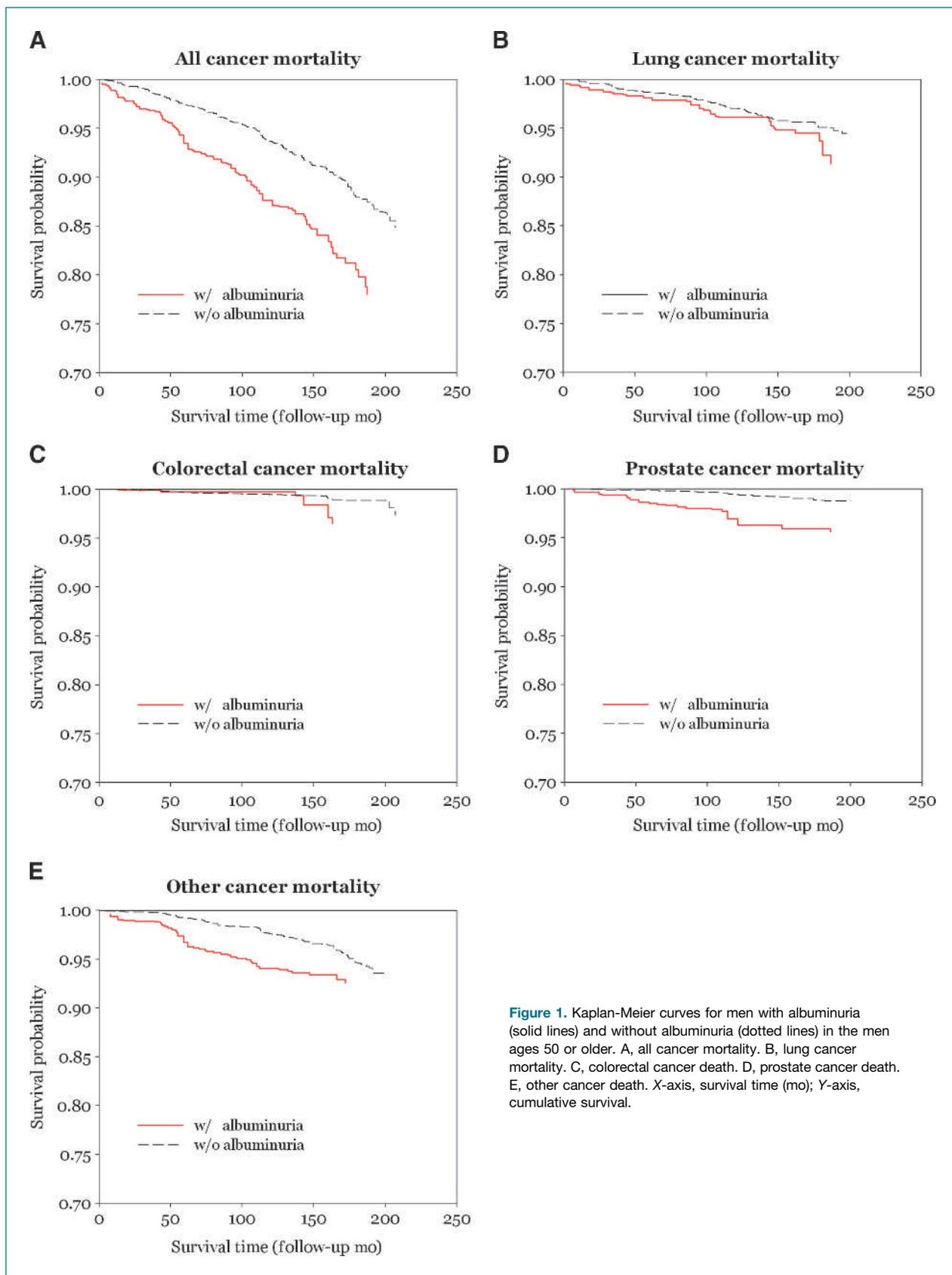
Figure 1. Kaplan-Meier curves for men with albuminuria (solid lines) and without albuminuria (dotted lines) in the men ages 50 or older. A, all cancer mortality. B, lung cancer mortality. C, colorectal cancer death. D, prostate cancer death. E, other cancer death. *X*-axis, survival time (mo); *Y*-axis, cumulative survival.

(CI), 1.36-2.47; $P < 0.001$]. Despite a numerically increased mortality risk for both lung and colorectal cancer deaths in men (RR, 1.39 and 1.99, respectively), these results failed to reach statistical significance. In comparison, there is not even a suggestion of an association of albuminuria with lung and colorectal cancer mortality in women.

Similar results were obtained by applying the multivariate model which included adjustments for age, race/ethnicity, smoking, BMI, and hypertension, diabetes, and chronic kidney disease status. However, the resulting RRs were generally reduced by approximately 20% to 40%, and none of the associations reached statistical significance. For instance, the risk for all-cause cancer mortality associated with albuminuria decreased from RR, 1.83 (95% CI, 1.36-2.47; $P \le 0.001$) to 1.38 (95% CI, 0.99-1.91; $P = 0.06$), and became marginally signifi-

cant in men (Table 2). Indeed, age and smoking are two of the most important factors in cancer deaths. In this cohort, age was significantly associated with increased cancer mortality for all-cause and cause-specific cancers regardless of sex except lung cancer in women ($P = 0.10$; data not shown). On the other hand, smoking is a significant risk factor for all-cause and lung cancer for both sexes, and other types of cancer deaths for men. Of note, neither albuminuria nor smoking were related to colorectal cancer death for men or women. Likewise, no association was found between smoking and prostate cancer death (RR, 1.44; 95% CI, 0.66-3.14; $P = 0.35$; data not shown).

Comparable RRs were generated from the multivariate-adjusted analyses using log-transformed UACR as predictor. Logarithmically transformed UACR was
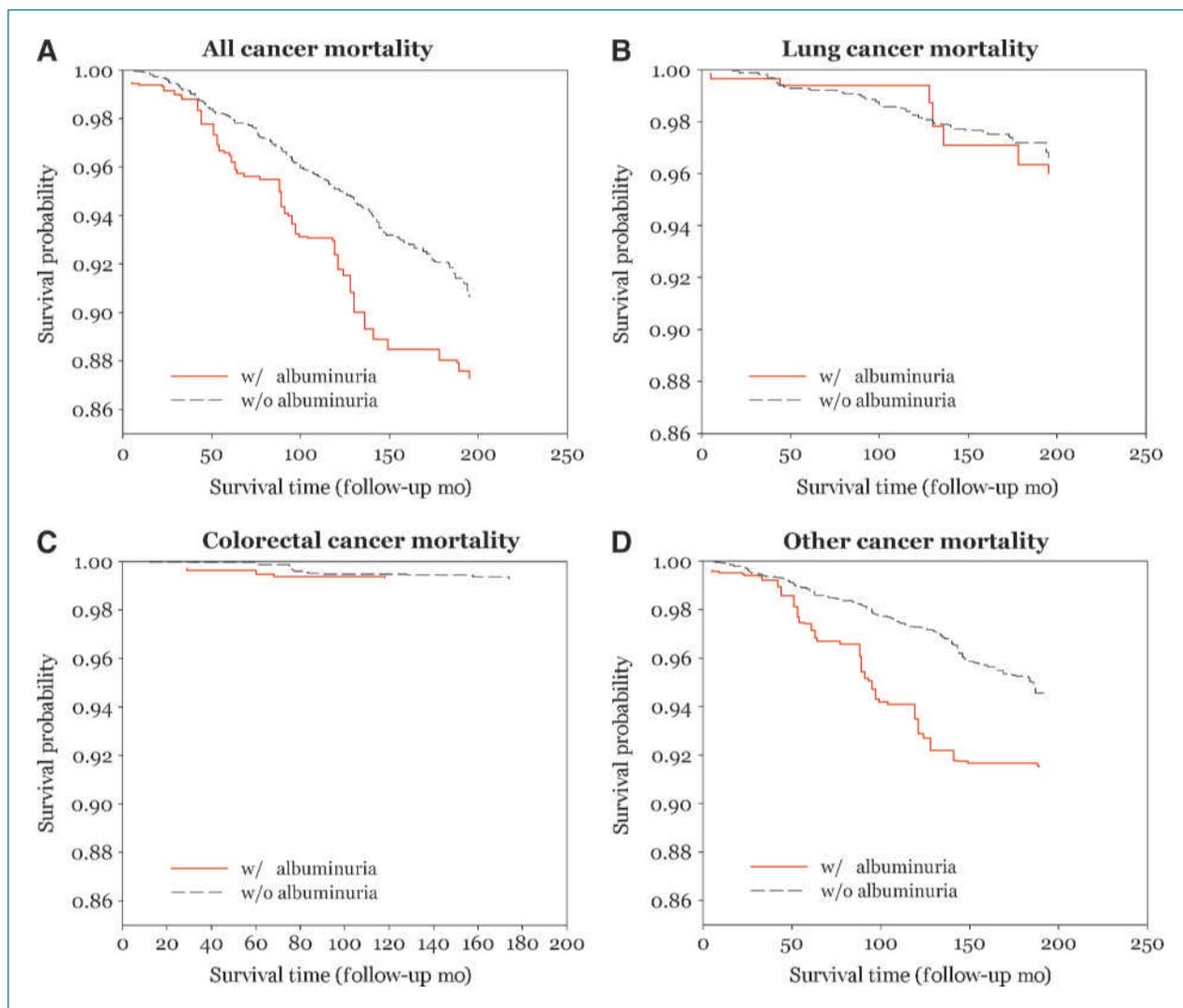

Figure 2. Kaplan-Meier curves for women with albuminuria (solid lines) and without albuminuria (dotted lines) in women ages 50 or older. A, all cancer mortality. B, lung cancer mortality. C, colorectal cancer death. D, other cancer death. X-axis, survival time (mo); Y-axis, cumulative survival.

Table 2. RR between albuminuria status (yes/no) and cancer mortality

Mortality cause	Men				Women			
	Univariate		Adjusted*		Univariate		Adjusted*	
	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
All-cause cancer	1.83 (1.36-2.47)	<0.001	1.38 (0.99-1.91)	0.06	1.56 (1.02-2.39)	0.04	1.19 (0.73-1.94)	0.48
Lung cancer	1.39 (0.76-2.55)	0.28	1.13 (0.61-2.09)	0.69	1.00 (0.44-2.29)	0.99	0.80 (0.32-1.99)	0.62
Colorectal cancer	1.99 (0.68-5.77)	0.20	1.23 (0.39-3.86)	0.71	1.23 (0.29-5.17)	0.77	0.81 (0.19-3.47)	0.77
Prostate cancer	4.32 (1.60-11.7)	0.005	2.77 (0.92-8.36)	0.07	—	—	—	—
Other cancers	1.73 (1.07-2.78)	0.03	1.31 (0.81-2.11)	0.26	1.92 (1.12-3.30)	0.02	1.45 (0.77-2.75)	0.25

*RRs adjusted for age, race/ethnicity, cigarette smoking, hypertension, diabetes, chronic kidney disease (defined as MDRD eGFR <60 mL/min/1.73 m^2), and BMI. The reference group is the subjects without albuminuria.

significantly correlated with all of the outcomes of interest except colorectal cancer in men, suggesting a dose-response relationship between albuminuria and cancer mortality (Table 3). Of note, there is a positive association between log-transformed UACR and prostate cancer in men (RR, 1.40; 95% CI, 1.01-1.95; P = 0.04). Despite the consistent positive associations between log-transformed UACR and cancer deaths observed in women, none of the results are significant (Table 3).

Discussion

The results of the present study showed that albuminuria was associated with increased risk of cancer deaths from all-cause, lung, and prostate cancers in men from the United States ages 50 and older. The association was not significant for any type of cancer in women of the same age group.

One prior report from the Tromsø Study showed that UACR at baseline was correlated with subsequent cancer incidence. A total 590 out of 5,425 participants without diabetes or previous cancer had the first diagnosis of cancer in 10.3 years of follow-up. Each SD-higher rise in the log-transformed UACR was associated with a RR

of 1.17 for cancer (P < 0.001). Participants with UACR in the highest quintile were 8.3- and 2.4-fold more likely to receive a diagnosis of bladder and lung cancer, respectively (6). Our study again examined the relationship between UACR and a variety of cancer mortalities, with similar results.

Despite the growing regard for albuminuria as a paraneoplastic and inflammatory phenomenon, the underlying mechanisms for the association between albuminuria and cancer incidence/mortalities are largely unknown (21-24). Chronic inflammation triggers endothelial dysfunction leading to albuminuria (25) and may provide a common link because inflammation is associated with both increased cancer (26) and cardiovascular risk (4). The renin-angiotensin system may participate in generating the increased cancer risk associated with albuminuria. Angiotensin II has been implicated in the development or invasion of several kinds of cancer (27). Angiotensin could exert mitogenic activity through angiotensin II type I (ATII-I) receptors and ATII-I receptor expression is higher in cancerous prostate (28).

The current data analysis showed a positive association between albuminuria and all-cancer mortality in

Table 3. RR between log-transformed UACR (mg/mmol) and cancer mortality

Mortality cause	Men				Women			
	Univariate		Adjusted*		Univariate		Adjusted*	
	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
All-cause cancer	1.31 (1.18-1.46)	<0.001	1.20 (1.06-1.36)	0.006	1.23 (1.09-1.39)	0.001	1.11 (0.96-1.29)	0.16
Lung cancer	1.28 (1.12-1.47)	<0.001	1.22 (1.05-1.43)	0.01	1.15 (0.88-1.50)	0.29	1.06 (0.77-1.46)	0.73
Colorectal cancer	1.37 (1.06-1.77)	0.02	1.14 (0.88-1.49)	0.31	1.51 (1.19-1.90)	<0.001	1.39 (0.97-2.00)	0.08
Prostate cancer	1.60 (1.21-2.11)	0.001	1.40 (1.01-1.95)	0.04	—	—	—	—
Other cancers	1.24 (1.00-1.54)	0.05	1.12 (0.90-1.41)	0.30	1.23 (1.05-1.43)	0.01	1.10 (0.91-1.34)	0.33

*RRs adjusted for age, race/ethnicity, cigarette smoking, hypertension, diabetes, chronic kidney disease (defined as MDRD eGFR <60 mL/min/1.73 m^2), and BMI.

men, mainly attributed to death from lung and prostate cancer. There was a dose-responsive relationship between albuminuria and prostate cancer death in men. The RR of prostate cancer deaths increased by 1.40-fold when the log-scale of albuminuria increased by 1. In stark contrast with male counterparts, there was no significant association between albuminuria with both all-cause and cause-specific cancer deaths in women. The moderating influence of sex could be attributed to prostate cancer in men and the differential risks of lung cancer between men and women. Although the prevalence of lung cancer in men has been decreasing, it has been increasing in women. The biology of lung cancer differs between the sexes, attributed in part to differences in growth factor receptors, endocrine influences, enzymatic clearance of toxins, the susceptibility to DNA damage, and the capacity for DNA repair, all of which may contribute to the observed differences in treatment outcomes (29). The finding in the current study of an association between albuminuria and lung cancer mortalities in men, but not in women, further shows a sex difference in the development and prognosis of lung cancer.

Albuminuria is a marker of many underlying diseases, including cardiovascular disease. In the study group, the estimated prevalence of pre-existing cardiovascular disease (positive response to the questions: "Doctor ever told you had a heart attack" or "Doctor told: congestive heart failure") was 10.2% (12.8% for men and 8.0% for women). After further adjustment for cardiovascular disease, the associations between albuminuria and cancer deaths were generally reduced 5% to 10% and there was no positive association between pre-existing cardiovascular disease with cancer mortalities. Similarly, although serum cholesterol has been found to be positively associated with albuminuria (30), baseline cholesterol was not associated with cancer mortalities.

One of the major limitations of this study is that despite biological plausibility, the current evidence supports only an association, and not causation, between albuminuria and cancer mortality. In addition, the use of single albumin measurements may not adequately assess normal within-person variations and may bias our findings toward the null (31). The small sample size for many cancer case subpopulations limits the ability to determine whether the association between albuminuria and cancer is a general oncogenic effect or is attributed to one or more specific cancers. Thus, it is also difficult to develop a predictive model based on albuminuria unless other markers (e.g., prostate-specific antigen and serum calcium levels) are also incorporated (32).

In conclusion, the presence of albuminuria increases the risk of cancer death, especially all-cause, lung, and prostate cancer in men over 50 years of age. The association was independent of other conventional risk factors, such as smoking, diabetes, hypertension, and chronic kidney disease. The association was not apparent in women and the sex specificity of the observation clearly needs to be resolved. Further study is also needed to explore whether albuminuria contributes to prostate cancer or is merely a predictive marker of its subsequent incidence and/or progression. Understanding the underlying biological mechanisms in this regard will determine the prospect of using renal interventions in the management of prostate cancer.

Disclosure of Potential Conflicts of Interest

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References

1. Hillege HL, Fidler V, Diercks GF, et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation 2002;106:1777–82.
2. Kshirsagar AV, Bomback AS, Bang H, et al. Association of C-reactive protein and microalbuminuria (from the National Health and Nutrition Examination Surveys, 1999 to 2004). Am J Cardiol 2008;101:401–6.
3. Wu CK, Yang CY, Tsai CT, et al. Association of low glomerular filtration rate and albuminuria with peripheral arterial disease: the National Health and Nutrition Examination Survey, 1999-2004. Atherosclerosis 2010;209:230–4.
4. Sasaki A, Horiuchi N, Hasegawa K, Uehara M. Mortality and causes of death in type 2 diabetic patients. A long-term follow-up study in Osaka District, Japan. Diabetes Res Clin Pract 1989;7:33–40.
5. Astor BC, Hallan SI, Miller ER III, Yeung E, Coresh J. Glomerular filtration rate, albuminuria, and risk of cardiovascular and all-cause mortality in the US population. Am J Epidemiol 2008;167:1226–34.
6. Jorgensen L, Heuch I, Jenssen T, Jacobsen BK. Association of albuminuria and cancer incidence. J Am Soc Nephrol 2008;19:992–8.
7. Wen CP, Cheng TY, Tsai MK, et al. All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. Lancet 2008;371:2173–82.
8. Astor BC, Levey AS, Stevens LA, Van Lente F, Selvin E, Coresh J. Method of glomerular filtration rate estimation affects prediction of mortality risk. J Am Soc Nephrol 2009;20:2214–22.
9. Viazzi F, Leoncini G, Ratto E, Pontremoli R. Serum uric acid as a risk factor for cardiovascular and renal disease: an old controversy revived. J Clin Hypertens (Greenwich) 2006;8:510–8.
10. Sattar N, Murray HM, Welsh P, et al. Are markers of inflammation

more strongly associated with risk for fatal than for nonfatal vascular events? PLoS Med 2009;6:e1000099.

11. Centers for Disease Control and Prevention (CDC)National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Questionnaire (or Examination Protocol, or Laboratory Protocol). Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 1996, Available from: http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm [last retrieved on 8 January 2010].

12. Gunter EW, Lewis BL, Koncikowski SM. Laboratory methods used for the Third National Health and Nutrition Examination Survey (NHANES III), 1988-1994. Included in CD-ROM 6-0178, NHANES III reference manuals and reports. Hyattsville, MD: Centers for Disease Control and Prevention; 1996.

13. Wei W, Kim Y, Boudreau N. Association of smoking with serum and dietary levels of antioxidants in adults: NHANES III, 1988-1994. Am J Public Health 2001;91:258–64.

14. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.

15. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735–52.

16. Eknoyan G, Hostetter T, Bakris GL, et al. Proteinuria and other markers of chronic kidney disease: a position statement of the National Kidney Foundation (NKF) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Am J Kidney Dis 2003;42:617–22.

17. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. JAMA 2007;298:2038–47.

18. Selvin E, Manzi J, Stevens LA, et al. Calibration of serum creatinine in the National Health and Nutrition Examination Surveys (NHANES) 1988-1994, 1999-2004. Am J Kidney Dis 2007;50:918–26.

19. Pedersen LM, Terslev L, Sørensen PG, Stokholm KH. Urinary albumin excretion and transcapillary escape rate of albumin in malignancies. Med Oncol 2000;17:117–22.

20. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39:S1–266.

21. McCarthy ET, Sharma R, Sharma M, et al. TNF-alpha increases albumin permeability of isolated rat glomeruli through the generation of superoxide. J Am Soc Nephrol 1998;9:433–8.

22. Mahmud N, O'Connell MA, Stinson J, Goggins MG, Weir DG, Kelleher D. Tumour necrosis factor-α and microalbuminuria in patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol 1995;7:215–9.

23. Pollock CA, Poronnik P. Albumin transport and processing by the proximal tubule: physiology and pathophysiology. Curr Opin Nephrol Hypertens 2007;16:359–64.

24. Gekle M, Knaus P, Nielsen R, et al. Transforming growth factor-β1 reduces megalin- and cubilin-mediated endocytosis of albumin in proximal-tubule-derived opossum kidney cells. J Physiol 2003;552: 471–81.

25. Stehouwer CD, Gall MA, Twisk JW, Knudsen E, Emeis JJ, Parving HH. Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes: progressive, inter-related, and independently associated with risk of death. Diabetes 2002;51:1157–65.

26. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420: 860–7.

27. Heffelfinger SC. The renin angiotensin system in the regulation of angiogenesis. Curr Pharm Des 2007;13:1215–29.

28. Uemura H, Ishiguro H, Kubota Y. Pharmacology and new perspectives of angiotensin II receptor blocker in prostate cancer treatment. Int J Urol 2008;15:19–26.

29. Rivera MP. Lung cancer in women: the differences in epidemiology, biology and treatment outcomes. Expert Rev Respir Med 2009;3: 627–34.

30. Tseng CH. Differential dyslipidemia associated with albuminuria in type 2 diabetic patients in Taiwan. Clin Biochem 2009;42:1019–24.

31. Baron JA, Beach M, Wallace K, et al. Risk of prostate cancer in a randomized clinical trial of calcium supplementation. Cancer Epidemiol Biomarkers Prev 2005;14:586–9.

32. Skinner HG, Schwartz GG. Serum calcium and incident and fatal prostate cancer in the National Health and Nutrition Examination Survey. Cancer Epidemiol Biomarkers Prev 2008;17:2302–5.

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