Association of albuminuria and cancer mortality

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Running title: Albuminuria and cancer death

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ABSTRACT

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

Methods: A total of 6,112 adults aged 50 years and above without a history of cancer at baseline in the Third National Health and Nutrition Examination Survey (NHANES III, 1988-94) 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 of 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 [HR] = 1.20, 95% confidence interval [95% 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 aged 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.

Keywords: Albuminuria; Nutrition Surveys; Neoplasms; Survival Analysis
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 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 intra-renal 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 (CV) 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 CV mortality (10). In the Prevention of Renal and Vascular End Stage Disease (PREVEND) study conducted in the Netherlands, a 2-fold increase of albuminuria was associated with a relative risk of 1.29 and 1.12 for CV and non-CV mortality, respectively (1).

The PREVEND study proposed that albuminuria associated non-CV deaths might represent greater fatalities due to malignant neoplasms, though specific etiologies were not analyzed. Little is known regarding the association of albuminuria with cancer mortality. Since cancer is currently second only to CV disease as a leading cause of death in the US, 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, 1988-94) and its follow up in the NHANES III-linked mortality
dataset (through December 31, 2006) (11, 12).

MATERIALS AND METHODS

Study design and population

The Third National Health and Nutrition Examination Survey (NHANES III) was
conducted by the National Center for Health Statistics (NCHS) 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 website (11). The NHANES III was reviewed and approved
by the NCHS Institutional Review Board. Of 7,593 adults ≥ 50 years of age that com-
pleted 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 aged 50 and older after adjusting for sample
weights.

Baseline demographics

In NHANES III, data were collected at all study sites by trained personnel according

Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.
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to standardized procedures. Information on age, sex, and smoking status was self-reported. Subjects with serum cotinine values greater than 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 ≥ 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 BPs were obtained. Body mass index (BMI) was defined as body weight (kg) divided by the square of the body height (m²). 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-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 eGFR (mL/min/1.73 m²) = 175 x (serum creatinine, mg/dL)^{-1.154} x (Age)^{-0.203} x (0.742 if female) x (1.212 if African American) (19). The presence of chronic kidney disease (CKD) was defined as MDRD eGFR less than 60 ml/min/1.73 m² (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, Tenth 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 (inter-quartile range) and categorical data in percentages. For outcome measurements, the Cox proportional hazard model with the Efron method was used to calculate the relative risk (RR), also known as hazard ratios. Hazard ratios 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, body mass index, hypertension, diabetes, and CKD were added to adjust the association of albuminuria with cancer mortality. Except for age and body mass index, 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-values less than 0.05 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 months). 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 US 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 1000 person-years, respectively (data not shown). As shown in both Kaplan-Meier survival curves (Figure 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-cause cancer, prostate cancer (men only), and the collected cancers other than lung, prostate, and colorectal cancers, as compared to those without albuminuria for both sexes. For instance, the relative risk of all-cause cancer deaths were 83% higher among men with albuminuria than those without it (RR = 1.83, 95% 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 applying the multivariate model that included adjustments for age, race/ethnicity, smoking, body mass index, and hypertension, diabetes, and chronic kidney disease status. However, the resulting hazard ratios were generally reduced by approximately 20-40% 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, \( p <= 0.001 \)) to 1.38 (95% CI= 0.99-1.91, \( p =0.06 \)), and became marginally significant 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 was 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 relative risks were generated from the multivariate-adjusted
analyses using log-transformed UACR as predictor. Logarithmically transformed
UACR was 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 (HR: 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 demonstrated that albuminuria was associated
with increased risk of cancer deaths from all-cause, lung, and prostate cancers in US
men aged 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 5425 participants
without diabetes or previous cancer had the first diagnosis of cancer in 10.3 years of
follow-up. Each standard deviation-higher rise in the log-transformed UACR was
associated with a 1.17 relative risk 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 since inflammation is associated with both increased cancer (26) and cardiovascular risk (4). The rennin-angiotensin system (RAS) 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 can 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 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 relative risk 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 demonstrates a sex difference in the development and prognosis of lung cancer.

Albuminuria is a marker of many underlying diseases, including cardiovascular disease (CVD). In the study group, the estimated prevalence of pre-existing CVD (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 CVD, the associations between albuminuria and cancer deaths were generally reduced 5-10% and there was no positive association between pre-existing CVD 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 risks 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 biologic mechanisms in this regard will determine the prospect of using renal interventions in the management of prostate cancer.
ACKNOWLEDGEMENTS

This work was in part supported by the G62024 Interdisciplinary Research Grant from the University of North Texas Health Science Center at Fort Worth and by the grants from National Taiwan University Hospital Yun-Lin Branch (98.X002 and 99.X004). The authors appreciate the statistical assistance of Dr. Gordon G. Brown from RTI International and Dr. Chia-Hsuin Chang from National Taiwan University Hospital. None of the authors have potential conflicts of interest to disclose. The corresponding author has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DISCLAMERS

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the Centers for Disease Control and Prevention. The corresponding author has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The authors do not have any affiliation with NHANES.
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**FIGURE LEGENDS**

**Figure 1.** Kaplan-Meier curves for men with albuminuria (solid lines) and without albuminuria (dotted lines) in the men aged 50 or older. Panel A: all cancer mortality; Panel B: lung cancer mortality; Panel C: colorectal cancer death; Panel D: prostate cancer death; Panel E: other cancer death. X-axis: survival time (months), Y-axis: cumulative survival. Hazard ratio, 95% confidence interval, and p-value are shown in the corresponding univariate analysis in Table 2.

**Figure 2.** Kaplan-Meier curves for women with albuminuria (solid lines) and without albuminuria (dotted lines) in the women aged 50 or older. Panel A: all cancer mortality; Panel B: lung cancer mortality; Panel C: colorectal cancer death; Panel D: other cancer death. X-axis: survival time (months), Y-axis: cumulative survival. Hazard ratio, 95% confidence interval, and p-value are shown in the corresponding univariate analysis in Table 2.
Table 1. Baseline demographic characteristics for participants in the NHANES III aged 50 years and above (n=6,112)\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
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<th></th>
<th>Women</th>
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<tr>
<td></td>
<td>W/ albuminuria</td>
<td>W/O albuminuria</td>
<td>$p^b$</td>
<td>W/ albuminuria</td>
<td>W/O albuminuria</td>
<td>$p^b$</td>
</tr>
<tr>
<td>n</td>
<td>705</td>
<td>2,291</td>
<td>N/A</td>
<td>592</td>
<td>2,524</td>
<td>N/A</td>
</tr>
<tr>
<td>Percentage (SE) in category</td>
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<td></td>
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<tr>
<td>Chronic kidney disease (yes)</td>
<td>43.8 (3.42)</td>
<td>28.7 (1.51)</td>
<td>0.004</td>
<td>59.5 (3.02)</td>
<td>47.3 (1.32)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypertension (yes)</td>
<td>60.8 (2.82)</td>
<td>42.6 (1.67)</td>
<td>&lt;0.001</td>
<td>51.2 (3.02)</td>
<td>40.7 (1.08)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes (yes)</td>
<td>15.8 (2.15)</td>
<td>5.71 (0.60)</td>
<td>&lt;0.001</td>
<td>24.2 (2.42)</td>
<td>5.13 (0.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoking (yes)</td>
<td>33.3 (2.97)</td>
<td>31.3 (1.69)</td>
<td>0.50</td>
<td>21.1 (2.90)</td>
<td>18.8 (1.28)</td>
<td>0.48</td>
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<td>Race/ethnicity</td>
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<td></td>
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<tr>
<td>Non-Hispanic white</td>
<td>81.3 (1.93)</td>
<td>89.2 (0.70)</td>
<td></td>
<td>80.2 (1.85)</td>
<td>87.9 (0.89)</td>
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<tr>
<td>Non-Hispanic black</td>
<td>14.9 (1.79)</td>
<td>7.64 (0.58)</td>
<td></td>
<td>15.9 (1.72)</td>
<td>9.20 (0.78)</td>
<td></td>
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<tr>
<td>Mexican Americans</td>
<td>3.82 (0.41)</td>
<td>3.12 (0.30)</td>
<td></td>
<td>3.89 (0.41)</td>
<td>2.91 (0.23)</td>
<td></td>
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<tr>
<td>Median (Inter-quartile range)</td>
<td></td>
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<tr>
<td>Age (yrs)</td>
<td>67.2 (58.3-74.1)</td>
<td>60.9 (54.8-68.3)</td>
<td>&lt;0.001</td>
<td>66.8 (59.5-76.2)</td>
<td>62.2 (55.2-70.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m\textsuperscript{2})</td>
<td>26.7 (24.3-30.0)</td>
<td>26.8 (24.4-29.8)</td>
<td>0.59</td>
<td>27.7 (24.0-33.4)</td>
<td>26.4 (23.2-30.6)</td>
<td>0.001</td>
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<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.18 (1.05-1.39)</td>
<td>1.15 (1.04-1.26)</td>
<td>&lt;0.001</td>
<td>0.97 (0.86-1.17)</td>
<td>0.94 (0.84-1.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MDRD eGFR (ml/min/1.73m\textsuperscript{2})</td>
<td>59.9 (50.1-69.9)</td>
<td>62.5 (56.1-69.2)</td>
<td>&lt;0.001</td>
<td>54.8 (44.8-63.2)</td>
<td>57.5 (50.3-64.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>141 (130-156)</td>
<td>131 (120-142)</td>
<td>&lt;0.001</td>
<td>144 (130-161)</td>
<td>130 (119-144)</td>
<td>&lt;0.001</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78.7 (71.4-86.2)</td>
<td>76.6 (70.4-83.0)</td>
<td>0.02</td>
<td>75.2 (69.3-82.6)</td>
<td>73.3 (67.8-79.1)</td>
<td>0.01</td>
</tr>
</tbody>
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\textsuperscript{a} Except for sample size, all of reported values were adjusted for sampling weight.  
\textsuperscript{b} The p-values for demographic comparisons between individuals with and without albuminuria were calculated with log transformed data for continuous variables (t-test) and chi-square test for categorical variables.  
\textsuperscript{c} Smoking defined as serum cotinine values greater than 14 ng/ml.  
Abbreviations: SD, standard deviation; SE, standard error; MDRD: the Modification of Diet in Renal Disease; eGFR: estimated glomerular filtration rate.
Table 2. Hazard ratio between albuminuria status (yes/no) and cancer mortality

<table>
<thead>
<tr>
<th>Mortality cause</th>
<th>Men</th>
<th>Women</th>
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<tbody>
<tr>
<td></td>
<td>Univariate Adjusted&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Univariate Adjusted&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI) &lt;br&gt; p &lt;br&gt; HR (95% CI) &lt;br&gt; p</td>
<td>HR (95% CI) &lt;br&gt; p &lt;br&gt; HR (95% CI) &lt;br&gt; p</td>
</tr>
<tr>
<td>All-cause cancer</td>
<td>1.83 (1.36-2.47) &lt;br&gt; &lt;0.001 &lt;br&gt; 1.38 (0.99-1.91) &lt;br&gt; 0.06</td>
<td>1.56 (1.02-2.39) &lt;br&gt; 0.04 &lt;br&gt; 1.19 (0.73-1.94) &lt;br&gt; 0.48</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1.39 (0.76-2.55) &lt;br&gt; 0.28 &lt;br&gt; 1.13 (0.61-2.09) &lt;br&gt; 0.69</td>
<td>1.00 (0.44-2.29) &lt;br&gt; 0.99 &lt;br&gt; 0.80 (0.32-1.99) &lt;br&gt; 0.62</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>1.99 (0.68-5.77) &lt;br&gt; 0.20 &lt;br&gt; 1.23 (0.39-3.86) &lt;br&gt; 0.71</td>
<td>1.23 (0.29-5.17) &lt;br&gt; 0.77 &lt;br&gt; 0.81 (0.19-3.47) &lt;br&gt; 0.77</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>4.32 (1.60-11.7) &lt;br&gt; 0.005 &lt;br&gt; 2.77 (0.92-8.36) &lt;br&gt; 0.07</td>
<td>- &lt;br&gt; - &lt;br&gt; -&lt;br&gt; -</td>
</tr>
<tr>
<td>Other cancers&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.73 (1.07-2.78) &lt;br&gt; 0.03 &lt;br&gt; 1.31 (0.81-2.11) &lt;br&gt; 0.26</td>
<td>1.92 (1.12-3.30) &lt;br&gt; 0.02 &lt;br&gt; 1.45 (0.77-2.75) &lt;br&gt; 0.25</td>
</tr>
</tbody>
</table>

<sup>a</sup>Hazard ratios adjusted for age, race/ethnicity, cigarette smoking, hypertension, diabetes, chronic kidney disease (defined as MDRD estimated glomerular filtration rate < 60 ml/min/1.73m²), and body mass index. The reference group is the subjects without albuminuria.

<sup>b</sup>Smoking defined as serum cotinine values greater than 14 ng/ml.

Abbreviation: RR, relative risk; 95% CI, 95% confidence interval; MDRD: the Modification of Diet in Renal Disease.
### Table 3. Hazard ratio between log-transformed urinary albumin-creatinine ratio (UACR, mg/mmol) and cancer mortality

<table>
<thead>
<tr>
<th>Mortality cause</th>
<th>Men</th>
<th>Women</th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Univariate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p</td>
<td>HR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>All-cause cancer</td>
<td>1.31 (1.18-1.46)</td>
<td>&lt;0.001</td>
<td>1.20 (1.06-1.36)</td>
<td>0.006</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1.28 (1.12-1.47)</td>
<td>&lt;0.001</td>
<td>1.22 (1.05-1.43)</td>
<td>0.01</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>1.37 (1.06-1.77)</td>
<td>0.02</td>
<td>1.14 (0.88-1.49)</td>
<td>0.31</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>1.60 (1.21-2.11)</td>
<td>0.001</td>
<td>1.40 (1.01-1.95)</td>
<td>0.04</td>
</tr>
<tr>
<td>Other cancers&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.24 (1.00-1.54)</td>
<td>0.05</td>
<td>1.12 (0.90-1.41)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

<sup>a</sup>Hazard ratios adjusted for age, race/ethnicity, cigarette smoking, hypertension, diabetes, chronic kidney disease (defined as MDRD estimated glomerular filtration rate < 60 ml/min/1.73m²), and body mass index.

<sup>b</sup>Smoking defined as serum cotinine values greater than 14 ng/ml.

Abbreviation: RR, relative risk; 95% CI, 95% confidence interval; MDRD: the Modification of Diet in Renal Disease.
Panel A. **All cancer mortality**

Panel B. **Lung cancer mortality**

Panel C. **Colorectal cancer mortality**

Panel D. **Prostate cancer mortality**

Panel E. **Other cancer mortality**