ORIGINAL ARTICLE

An increase in albuminuria is associated with a higher incidence of malignancies

Li Luo [1], Lyanne M. Kieneker[1], Yuanhang Yang[2], Roemer J. Janse [2,3], Alessandro Bosi[2], Rudolf A. de Boer[4], Priya Vart [5], Juan-Jesus Carrero [2,6,*] and Ron T. Gansevoort [1,*]

[1]Department of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, [2]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, [3]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands, [4]Erasmus MC, Cardiovascular Institute, Thorax Center, Department of Cardiology, Rotterdam, The Netherlands, [5]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands and [6]Division of Nephrology, Department of Clinical Sciences, Karolinska Institutet, Danderyd Hospital, Stockholm, Sweden

*Equal last authors.
Correspondence to: Ron T. Gansevoort; E-mail: r.t.gansevoort@umcg.nl

ABSTRACT

Background. A single albuminuria measurement is reported to be an independent predictor of cancer risk. Whether change in albuminuria is also independently associated with cancer is not known.
Methods. We included 64 303 subjects of the Stockholm CREAtinine Measurements (SCREAM) project without a history of cancer and with at least two urine albumin–creatinine ratio (ACR) tests up to 2 years apart. Albuminuria changes were quantified by the fold-change in ACR over 2 years, and stratified into the absence of clinically elevated albuminuria (i.e. never), albuminuria that remained constant, and albuminuria that increased or decreased. The primary outcome was overall cancer incidence. Secondary outcomes were site-specific cancer incidences.
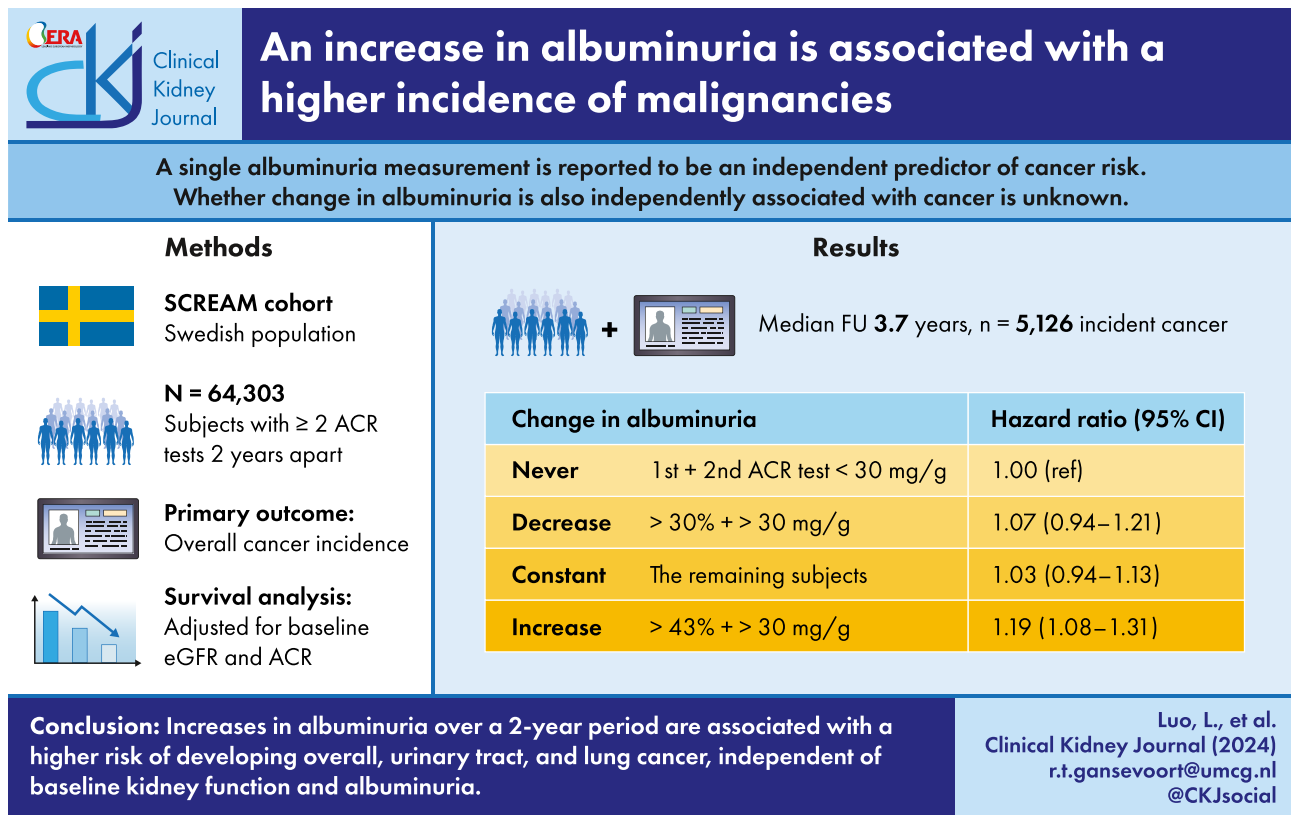**Results.** During a median follow-up of 3.7 (interquartile range 3.6–3.7) years, 5126 subjects developed *de novo* cancer. After multivariable adjustment including baseline estimated glomerular filtration rate and baseline ACR, subjects with increasing ACR over 2 years had a 19% (hazard ratio 1.19; 95% confidence interval 1.08–1.31) higher risk of overall cancer compared with those who never had clinically elevated ACR. No association with cancer risk was seen in the groups with decreasing or constant ACR. Regarding site-specific cancer risks, subjects with increasing ACR or constant ACR had a higher risk of developing urinary tract and lung cancer. No other associations between 2-year ACR changes and site-specific cancers were found.
Conclusions. Increases in albuminuria over a 2-year period are associated with a higher risk of developing overall, urinary tract and lung cancer, independent of baseline kidney function and albuminuria. These data add important weight to the link that exists between albuminuria and cancer incidence.

GRAPHICAL ABSTRACT

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An increase in albuminuria is associated with a higher incidence of malignancies

A single albuminuria measurement is reported to be an independent predictor of cancer risk.
Whether change in albuminuria is also independently associated with cancer is unknown.

Methods

SCREAM cohort
Swedish population

N = 64,303
Subjects with ≥ 2 ACR tests 2 years apart

Primary outcome:
Overall cancer incidence

Survival analysis:
Adjusted for baseline eGFR and ACR

Results

Median FU **3.7** years, n = **5,126** incident cancer

Change in albuminuria		Hazard ratio (95% CI)
Never	1st + 2nd ACR test < 30 mg/g	1.00 (ref)
Decrease	> 30% + > 30 mg/g	1.07 (0.94–1.21)
Constant	The remaining subjects	1.03 (0.94–1.13)
Increase	> 43% + > 30 mg/g	1.19 (1.08–1.31)

Conclusion: Increases in albuminuria over a 2-year period are associated with a higher risk of developing overall, urinary tract, and lung cancer, independent of baseline kidney function and albuminuria.

Luo, L., et al.
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r.t.gansevoort@umcg.nl
@CKJsocial

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KEY LEARNING POINTS

What was known:
- Higher baseline albuminuria is reported to be associated with higher cancer risk, independent of kidney function.
- Previous evidence predominantly focused on the cancer risk associated with a single albuminuria measurement. If change in albuminuria is associated with cancer risk independent of baseline albuminuria, this will add weight to the current evidence on the albuminuria cancer association and possible causality.

This study adds:
- This large cohort study demonstrates that increasing albuminuria over 2 years is associated with higher cancer risk, particularly for urinary tract cancer, independent of baseline kidney function and albuminuria.

Potential impact:
- These data add important weight to the existence of a link between albuminuria and cancer incidence. Studies are warranted to investigate underlying mechanisms.
- Increasing albuminuria may have added predictive values to the existing risk profile used for identifying persons eligible for screening for certain types of cancers, e.g. urinary tract cancer.

INTRODUCTION

Albuminuria, together with estimated glomerular filtration rate (eGFR), is an important indicator to define and stage chronic kidney disease (CKD) [1]. Besides conventional cardio-renal complications [2], these days there is also growing evidence that supports an association of albuminuria with cancer risk independent of kidney function evaluated by eGFR. This as-sociation has been examined in various study populations [3–9].

Of note, these previous studies investigating the association between albuminuria and cancer incidence focused on baseline albuminuria. If change in albuminuria is associated with cancer risk independent of baseline albuminuria, this will add weight to the current evidence on the albuminuria cancer association, suggesting a link between both. Only one study has previously
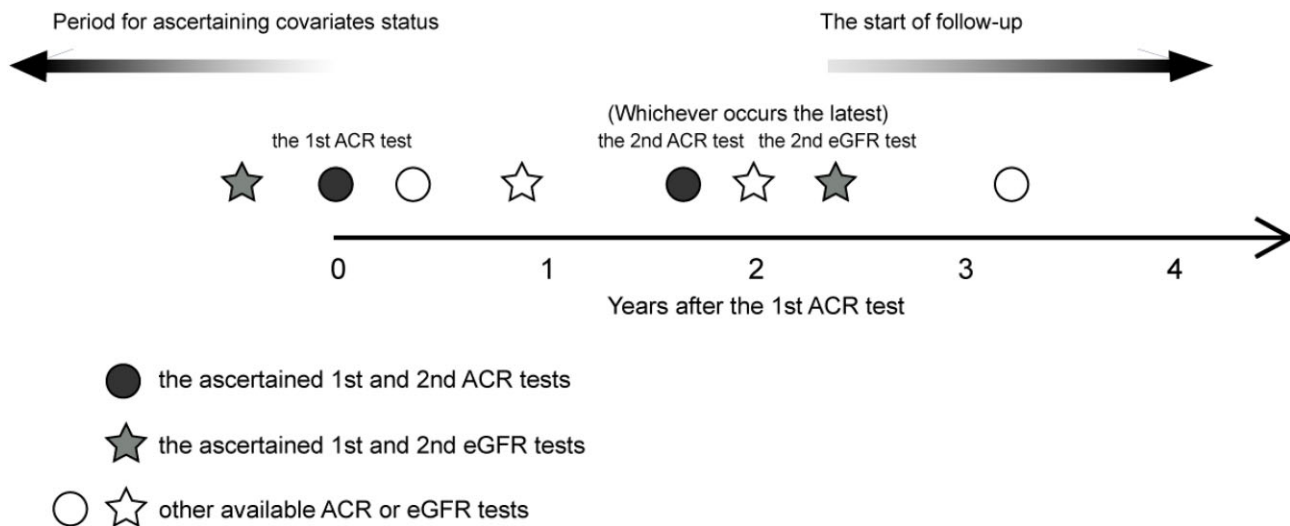
Figure 1: Timeline to define 2-year ACR changes and concomitant eGFR. Circles represent ACR tests and stars represent creatinine tests to calculate eGFR. ACR changes were defined as the fold change between the first and the second ACR tests. An ACR test falling within the period of 2±0.5 years after the first ACR test was chosen as the second ACR test per person. If multiple ACR tests were available to ascertain the second ACR test, the test performed closest to the 2-year landmark was selected. A creatinine-based eGFR value documented 0.5 year before or after the first ACR test was selected as the first eGFR, which was concomitant to the first ACR test. An eGFR value falling within the period of 2±0.5 years after the first ACR test was selected as the second eGFR, which was concomitant to the second ACR test. Similarly, the test performed closest to the index date was chosen if multiple available tests were available to ascertain the first or the second eGFR tests. Study covariates were ascertained before the date of the first ACR test. The start of the follow-up was taken as the date whichever the second ACR test or the second eGFR test occurred latest.

focused on change in albuminuria versus cancer risk, but used albuminuria measurement by semi-quantitative dipsticks. Because dipstick is a less accurate albuminuria measurement technique than the fully quantitative albumin–creatinine ratio (ACR), this study could be hampered in the accuracy of the observed cancer risk associated with albuminuria changes [3].

Taken altogether, this study therefore aimed to investigate whether and how change in albuminuria is associated with cancer incidence, and whether this association is independent of baseline kidney function and albuminuria.

MATERIALS AND METHODS

Study population

We used data from the Stockholm CREAtinine Measurements (SCREAM) project, a healthcare utilization cohort from the region of Stockholm, Sweden that included all residents during 2006–19 [10]. Laboratory data were linked with regional and national administrative databases for complete information on healthcare utilization, dispensed drugs, socioeconomic status, validated kidney replacement therapy endpoints and follow-up for death, with virtually no loss to follow-up. For this study, we included subjects who had at least two ACR tests approximately 2 years apart for our main analyses and similar subjects who had at least two dipstick proteinuria tests 2 years apart for our sensitivity analyses. As a next step, we searched for the presence of a creatinine-based eGFR value concomitant to the selected albuminuria test. The date of the first ACR test was used to ascertain study covariates, and the date of the second ACR test or the second eGFR test, whichever occurred latest, was used to initiate follow-up (Fig. 1). Exclusion criteria were age <18 years old, a history of cancer before the start of follow-up, undergoing kidney replacement therapy and death on the same day as the start of follow-up. After applying the inclusion and exclusion criteria, the study cohort comprised 64 603 subjects

who had at least two ACR tests 2 years apart (Fig. 2). The study was approved by the regional ethics committee in Stockholm, Sweden.

Exposure and covariates

All laboratory measurements were performed using routine methods at the clinical laboratories of the region of Stockholm. Albuminuria changes were quantified by the fold-change in ACR during the 2-year baseline period. A 0.5-year margin was allowed for determining the second available ACR test to calculate the change (i.e. an ACR test between 1.5 and 2.5 years after the first ACR test could be used for the 2-year baseline period analyses) [11]. We chose a 2-year baseline period for our main analyses to be consistent with prior cohort studies that also investigated albuminuria changes as study exposure [11, 12]. We calculated the fold-change in ACR by taking the ratio of the second ACR test to the first ACR test, and then converting this ratio on the log2 scale (i.e. a negative change in ACR of 0.515 on the log2 scale is equivalent to a 30% decrease and a positive change in ACR of 0.515 on the log2 scale to a 43% increase) [12]. The magnitude of the change was further standardized to the time length of 2 years, i.e. divided by the actual time between two ACR tests (years). We then stratified the fold-change in ACR into the absence of clinically elevated albuminuria (i.e. never), albuminuria that remained constant, and albuminuria that increased or decreased. We determined 'never' as the situation in which the first and the second ACR test were both below 30 mg/g. We defined 'decrease' as a >30% decrease in ACR plus a >30 mg/g absolute decrease in ACR. 'Increase' was defined as a >43% increase in ACR plus a >30 mg/g absolute increase in ACR over the 2-year baseline period, leaving the remaining subjects grouped as constant. The never group was a reference in all categorical analyses. We combined a percentage change and an absolute change to stratify albuminuria changes so that such stratification was powered to
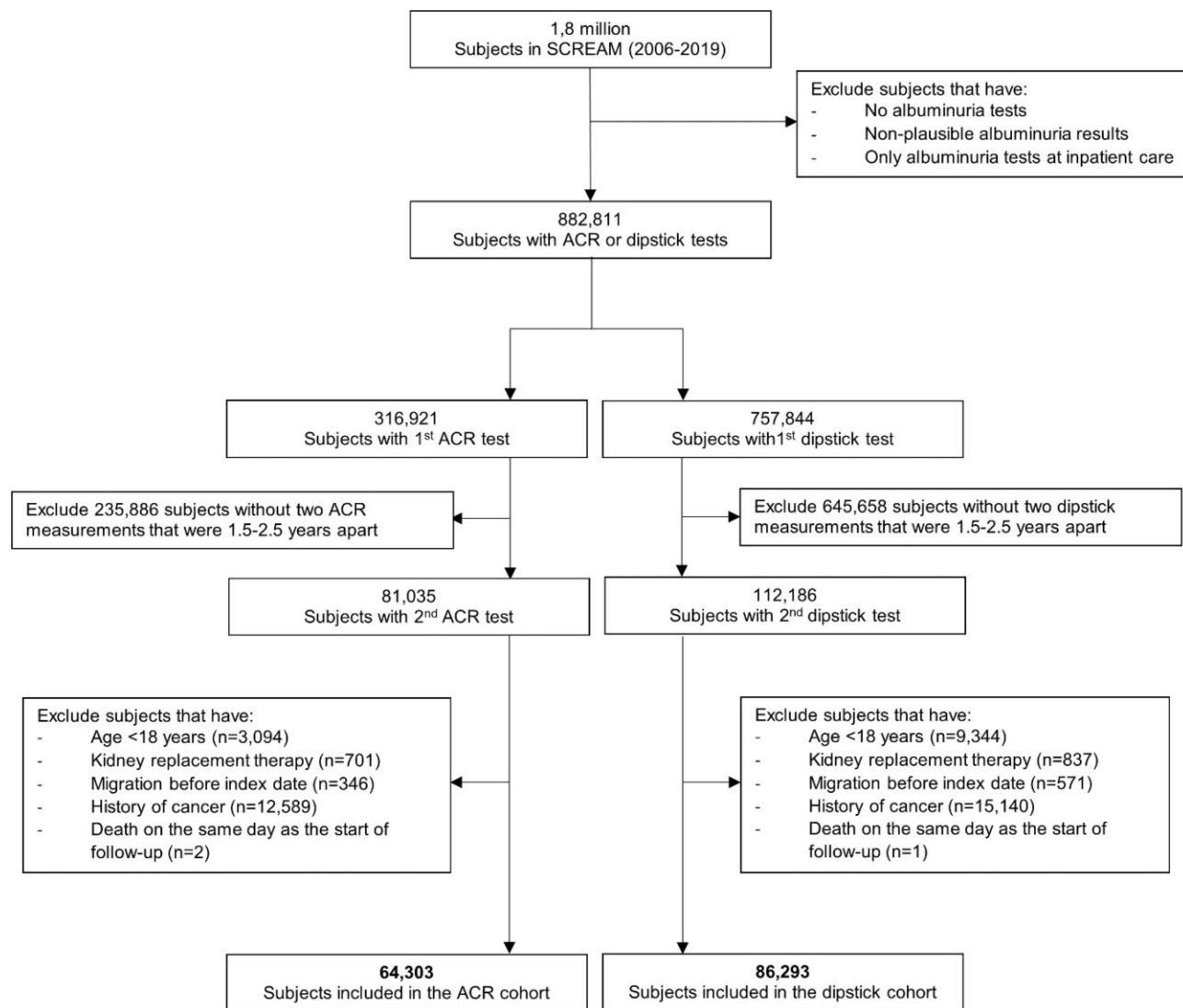
Figure 2: Flow chart of study participants and study design.

indicate clinically significant changes across different baseline albuminuria levels (e.g. a 30% increase in the baseline ACR of 1 mg/g is generally not clinically meaningful).

Baseline covariates included age, sex, highest attained education, hypertension, cardiovascular diseases, diabetes, chronic infections, chronic obstructive pulmonary disease, rheumatic disease, dementia, the use of renin–angiotensin–aldosterone system inhibitors (RAAS-I), statins, non-steroidal anti-inflammatory drugs, diuretics and eGFR, as well as ACR. Highest attained education was categorized into three levels: compulsory school ($\leq$9 years), secondary school (10–12 years) and university (>12 years), obtained from the longitudinal integrated database for health insurance and labor market studies (LISA) register [13]. We used Anatomical Therapeutic Chemical codes to identify ongoing medications and all comorbidities were ascertained with International Classification of Diseases, Tenth Revision (ICD-10) codes (Supplementary data, Table S1). The definition of diabetes was additionally enriched with information on the use of anti-diabetic medications, and the definition of hypertension was additionally enriched with information on the use of anti-hypertensive medications. eGFR

was calculated from serum/plasma creatinine using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation [14]. The 2021 CKD-EPI equation is not in use in Sweden, or elsewhere in Europe [15, 16]. eGFR changes were quantified by eGFR slope, which was calculated by the ratio of the difference of two eGFR tests to the time between these two eGFR tests. We only used creatinine measurements obtained in the outpatient setting to better reflect kidney function, and all creatinine tests were standardized to isotope dilution mass spectrometry standards. Ethnicity data are by law not allowed to be documented in Sweden by law, and all subjects were therefore assumed to be white.

Follow-up and study outcome

The primary outcome was overall cancer incidence. Secondary outcomes were site-specific cancer incidences. We decided *a priori* to report the most common site-specific cancers, defined as those with an incidence of 0.5% or higher in our study population during the total follow-up. Cancer data were ascertained by linkage to the Swedish Cancer Registry, which has high

completeness and reliability [17], and ICD-10 codes were grouped as follows: overall cancer [C00–97, D45–47, excluding non-melanoma skin cancer (C44)], urinary tract (C64–68), gastrointestinal tract (C15–25), lung (C33–34, C39), melanoma (C43), prostate (C61), breast (C50) and hematological cancer (C90–93, C95, C96, D45–47) [18]. Subjects were censored at the end of follow-up (31 December 2018), death or emigration from the region, whichever occurred first. Death data were retrieved from the National Board of Health and Welfare's Cause-of-Death Register (https://www.socialstyrelsen.se).

Statistical analyses

Continuous variables are presented as median with standard deviation or as median with interquartile range in case of skewed distribution. Categorical variables are shown as counts with proportion. Except for eGFR and highest attained education, all covariates were available in all cases. We imputed missing values of highest attained education by adding a category of missing (2%) and imputed missing values of eGFR using the cohort-specific mean values (4%). Incidence rates per 1000 person-years with 95% confidence intervals (95% CIs) were calculated using the exact method. The 10-year crude incidence was calculated by subtracting Kaplan–Meier estimates of the probability of survival at 10 years from 100%. The associations between ACR changes and the risk of overall and site-specific cancer incidence were estimated by Cox proportional hazards regression models. Results are reported as hazard ratios (HRs) with 95% CIs. Models were adjusted for baseline covariates as described above, including the first eGFR and the first log2-transformed ACR. Restricted cubic splines were fitted for the association of overall cancer incidence and ACR changes as a continuous variable to explore nonlinearity.

We conducted several sensitivity analyses. First, to investigate the possible effect of non-cancer death as a competing event, we performed Fine–Gray competing risk analyses [19]. Second, to examine possible reverse causation, we did a 1-year landmark analysis by splitting the follow-up time into two periods (≤1 and >1 year follow-up time) and separately estimating HRs (95% CIs) for these two intervals. Third, to examine whether different albuminuria measurement techniques will influence the association of albuminuria changes with cancer, we replicated the main analyses in subjects with at least two dipstick proteinuria tests 2 years apart. Fourth, to examine the longitudinal effects of eGFR, we additionally adjusted for the eGFR changes (slope) concomitant with the 2-year baseline period. Fifth, we adjusted for the number of ACR tests available per subject because more frequent ACR tests may indicate a worse health condition requiring closer monitoring. Sixth, to assess possible effect modification by baseline age (<65 and ≥65 years old), sex, hypertension, diabetes, eGFR (<60 and ≥60 mL/min/1.73 m^2), and the time-varying use of RAAS-I (not using, using, changing), we fitted Cox models containing both main effects and the cross-product terms with ACR changes. Seventh, to investigate possible attrition bias, we used the date whichever the second ACR test or the second eGFR test occurred latest to determine the study baseline and remodeled the associations. Eighth, to investigate the possible effects of the time length of ACR baseline period on the association between albuminuria changes and cancer, we repeated the analyses for 1- and 3-year ACR baseline periods.

P-values are 2-tailed. A P-value of <.05 is considered statistically significant. Analyses were conducted with R (version 4.1.2, R Foundation for Statistical Computing, Vienna, Austria) and Stata (version 15.0, StataCorp LLC, College Station, TX, USA).

RESULTS

Baseline characteristics

Table 1 presents the baseline characteristics of subjects with data on 2-year ACR changes. The mean age was 61.0 ± 14.4 years and 42.7% were female. At baseline, 76.6% of subjects had an ACR <30 mg/g, 17.4% an ACR of 30–299 mg/g and 6.1% an ACR ≥300 mg/g. The mean eGFR was 83.4 ± 22.5 mL/min/1.73 m^2. The most common comorbidities were hypertension (74.3%) and diabetes (55.8%), and 55.4% of included subjects used RAAS-I.

Albuminuria changes and the risk of overall cancer incidence

During a median follow-up of 3.7 years, 5126 new cases of cancer were detected. The 10-year crude incidence of overall cancer was 17.6% (95% CI 17.0%–18.1%, Table 2). After full adjustment including the first eGFR and the first log2-transformed ACR, subjects with increasing ACR over 2 years had a 19% (HR 1.19; 95% CI 1.08–1.31) higher risk of overall cancer than those who never had clinically elevated ACR. No significant associations between decreasing ACR (HR 1.07; 95% CI 0.94–1.21) and constant ACR (HR 1.03; 95% CI 0.94–1.13) over 2 years with overall cancer incidence were found. When treated as a continuous variable, every fold-change in ACR over 2 years was associated with the risk of overall cancer incidence in a non-linear fashion (Fig. 3, Pnonlinearity = 0.009). The higher risk of overall cancer was observed only for increasing ACR.

Albuminuria changes and the risk of site-specific cancer incidence

HRs (95% CIs) for the association of 2-year ACR changes with the incidence of site-specific cancers are summarized in Table 2. Overall, the 10-year crude incidence for site-specific cancers ranged from 1.0% (95% CI 0.9%–1.1%) for developing hematological cancer to 6.0% (95% CI 5.5%–6.4%) for developing prostate cancer.

Compared with subjects who never had clinically elevated ACR over 2 years, those with increasing ACR displayed a higher risk of developing urinary tract cancer (HR 2.14; 95% CI 1.61–2.83) and lung cancer (HR 1.80; 95% CI 1.30–2.49). Similarly, subjects with constant ACR over 2 years also had a higher risk of developing urinary tract cancer (HR 1.39; 95% CI 1.04–1.87) and lung cancer (HR 1.59; 95% CI 1.17–2.17), while no significant associations of decreasing ACR with the incidences of urinary tract cancer and lung cancer were found. In addition, no associations of 2-year ACR changes with the incidences of melanoma, gastrointestinal tract, breast, prostate and hematological cancer were observed.

Sensitivity analyses

The results of the various sensitivity analyses are provided in Table 2, Supplementary data, Tables S2–S8, Fig. 4, as well as Supplementary data, Figs S1 and S2. The association of 2-year ACR changes with cancer incidence was materially unchanged after we additionally adjusted for the concomitant eGFR changes or the number of ACR tests. We did not find evidence for effect modification by age, sex, hypertension, diabetes, eGFR and

Table 1: Baseline characteristics of eligible subjects overall and stratified by ACR change.

	Overall	Two-year change in ACR			
		Never	Decrease	Constant	Increase
No. of subjects	64 303	44 634	6067	7632	5970
Demographics					
Age, years	61.0 ± 14.4	60.5 ± 14.0	59.2 ± 16.3	63.2 ± 14.4	63.9 ± 14.8
Female, *n* (%)	27 475 (42.7)	19 874 (44.5)	2468 (40.7)	2838 (37.2)	2295 (38.4)
Highest attained education, *n* (%)					
Compulsory school	15 346 (23.9)	9828 (22.0)	1516 (25.0)	2204 (28.9)	1798 (30.1)
Secondary school	27 194 (42.3)	19 114 (42.8)	2504 (41.3)	3126 (41.0)	2450 (41.0)
University	20 577 (32.0)	15 103 (33.8)	1864 (30.7)	2109 (27.6)	1501 (25.1)
Missing	1186 (1.8)	589 (1.3)	183 (3.0)	193 (2.5)	221 (3.7)
Kidney function					
The first ACR, mg/g	8.8 (4.4, 29.2)	5.7 (3.5, 11.4)	175.9 (78.7, 579.9)	38.0 (30.1, 83.3)	32.7 (12.4, 106.1)
<30, *n* (%)	49 225 (76.6)	44 634 (100.0)	0 (0.0)	1878 (24.6)	2713 (45.4)
30–299, *n* (%)	11 187 (17.4)	0 (0.0)	3780 (62.3)	4861 (63.7)	2546 (42.6)
≥300, *n* (%)	3891 (6.1)	0 (0.0)	2287 (37.7)	893 (11.7)	711 (11.9)
The second ACR, mg/g	8.8 (4.4, 29.2)	5.6 (3.5, 10.6)	34.4 (11.5, 113.2)	38.9 (30.1, 84.9)	145.5 (74.2, 406.4)
<30, *n* (%)	49 207 (76.5)	44 634 (100.0)	2790 (46.0)	1783 (23.4)	0 (0.0)
30–299, *n* (%)	11 600 (18.0)	0 (0.0)	2533 (41.8)	4959 (65.0)	4108 (68.8)
≥300, *n* (%)	3496 (5.4)	0 (0.0)	744 (12.3)	890 (11.7)	1862 (31.2)
The first eGFR, mL/min/1.73 m^2	83.4 ± 22.5	86.8 ± 18.9	74.6 ± 29.8	78.6 ± 25.0	73.6 ± 27.9
≥90, *n* (%)	26 836 (41.7)	20 100 (45.0)	2100 (34.6)	2769 (36.3)	1867 (31.3)
60–89, *n* (%)	28 052 (43.6)	20 611 (46.2)	2124 (35.0)	3082 (40.4)	2235 (37.4)
30–59, *n* (%)	7804 (12.1)	3705 (8.3)	1250 (20.6)	1452 (19.0)	1397 (23.4)
<30, *n* (%)	1611 (2.5)	218 (0.5)	593 (9.8)	329 (4.3)	471 (7.9)
Comorbidities, *n* (%)					
Hypertension	47 769 (74.3)	31 457 (70.5)	5029 (82.9)	6263 (82.1)	5020 (84.1)
Cardiovascular disease	12 258 (19.1)	7156 (16.0)	1403 (23.1)	1949 (25.5)	1750 (29.3)
Myocardial infarction	4470 (7.0)	2696 (6.0)	473 (7.8)	682 (8.9)	619 (10.4)
Congestive heart failure	4153 (6.5)	2082 (4.7)	636 (10.5)	713 (9.3)	722 (12.1)
Peripheral vascular disease	2592 (4.0)	1346 (3.0)	341 (5.6)	471 (6.2)	434 (7.3)
Cerebrovascular disease	5038 (7.8)	3040 (6.8)	525 (8.7)	785 (10.3)	688 (11.5)
Diabetes mellitus	35 892 (55.8)	24 482 (54.9)	3015 (49.7)	4689 (61.4)	3706 (62.1)
Chronic infection	1863 (2.9)	1368 (3.1)	177 (2.9)	157 (2.1)	161 (2.7)
COPD	7916 (12.3)	5440 (12.2)	751 (12.4)	933 (12.2)	792 (13.3)
Rheumatic disease	2266 (3.5)	1366 (3.1)	294 (4.8)	304 (4.0)	302 (5.1)
Dementia	346 (0.5)	182 (0.4)	40 (0.7)	69 (0.9)	55 (0.9)
Medication, *n* (%)					
ACEi/ARBs	35 649 (55.4)	22 908 (51.3)	4021 (66.3)	4809 (63.0)	3911 (65.5)
Calcium channel blocker	17 171 (26.7)	10 351 (23.2)	2109 (34.8)	2510 (32.9)	2201 (36.9)
Beta blocker	21 357 (33.2)	13 260 (29.7)	2388 (39.4)	3051 (40.0)	2658 (44.5)
Diuretics	13 476 (21.0)	7755 (17.4)	1810 (29.8)	1914 (25.1)	1997 (33.5)
Statins	25 390 (39.5)	17 023 (38.1)	2324 (38.3)	3347 (43.9)	2696 (45.2)
NSAIDs	22 700 (35.3)	14 973 (33.5)	2107 (34.7)	3119 (40.9)	2501 (41.9)

Continuous variables are reported as mean ± standard deviation or median (interquartile range) and categorical variables as *n* (%).
Regarding the categories of 2-year ACR changes, never was defined as the first and the second ACR test both <30 mg/g. Decrease was defined as a >30% decrease in ACR plus a >30 mg/g absolute decrease in ACR. Increase was defined as a >43% increase in ACR plus a >30 mg/g absolute increase in ACR, leaving the remaining subjects grouped as constant.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; NSAIDs, nonsteroidal anti-inflammatory agent.

the use of RAAS-I in the association of 2-year ACR changes or 2-year dipstick proteinuria changes with overall cancer incidence (Fig. 4, Supplementary data, Figs S1 and S2). In general, the results of all sensitivity analyses were in line with the results of our main analyses. The association of increasing ACR with overall cancer as well as the association of constant ACR with urinary tract cancer were significant, albeit attenuated, in the competing risk analysis (Table 2), the 1-year landmark analysis (Supplementary data, Table S2) and the analysis of redefining the study baseline (Supplementary data, Table S6), respectively. In addition, we no longer found the associated risk of lung cancer among the subjects eligible for analyzing 2-year

dipstick proteinuria changes (Supplementary data, Tables S3 and S4), and in the analyses for 1- and 3-year ACR baseline periods (Supplementary data, Tables S7 and S8).

DISCUSSION

In this large cohort study of Swedes undergoing repetitive ACR tests, we found that increasing albuminuria over 2 years was associated with a higher risk of the incidences of overall, urinary tract and lung cancer, independent of baseline kidney function and albuminuria. The independent associations of increasing albuminuria over 2 years with urinary tract cancer remained

Table 2: Associations of 2-year ACR changes with the overall incidence of cancer and with the incidence of site-specific cancers with an incidence of 0.5% or higher in our study population during the total follow-up.

	No. of events/participants	IR per 1000 PY (95% CI)	10-year crude incidence (%, 95% CI)	Conventional Cox proportional hazards model, HR (95% CI)[a]	Fine–Gray hazards model, sHR (95% CI)[b]
Overall cancer	5126/64 303	18.7 (18.1–19.2)	17.6 (17.0–18.1)		
Never	3196/44 634	17.2 (16.6–17.8)	16.4 (15.8–17.1)	1.00 (ref)	1.00 (ref)
Decrease	531/6067	19.6 (18.0–21.4)	18.4 (16.7–20.1)	1.07 (0.94–1.21)	1.04 (0.91–1.18)
Constant	777/7632	21.2 (19.7–22.7)	19.8 (18.3–21.3)	1.03 (0.94–1.13)	1.01 (0 92–1.11)
Increase	622/5970	24.4 (22.5–26.4)	21.3 (19.4–23.1)	1.19 (1.08–1.31)	1.08 (0.98–1.19)
Urinary tract cancer	469/64 303	1.6 (1.5–1.8)	1.7 (1.5–1.9)		
Never	247/44 634	1.3 (1.1–1.4)	1.4 (1.1–1.6)	1.00 (ref)	1.00 (ref)
Decrease	50/6067	1.8 (1.3–2.3)	1.9 (1.3–2.6)	1.37 (0.91–2.05)	1.33 (0 89–1.99)
Constant	82/7632	2.1 (1.7–2.6)	2.0 (1.5–2.5)	1.39 (1.04–1.87)	1.37 (1.02–1.84)
Increase	90/5970	3.3 (2.7–4.1)	3.4 (2.5–4.2)	2.14 (1.62–2.83)	1.96 (1.45–2.64)
GI tract cancer	1233/64 303	4.3 (4.1–4.6)	4.5 (4.2–4.8)		
Never	791/44 634	4.1 (3.8–4.4)	4.3 (4.0–4.7)	1.00 (ref)	1.00 (ref)
Decrease	127/6067	4.5 (3.8–5.4)	4.3 (3.5–5.2)	0.98 (0.76–1.26)	0.94 (0.73–1.22)
Constant	186/7632	4.8 (4.2–5.6)	5.2 (4.3–6.0)	0.92 (0.76–1.11)	0.89 (0.73–1.08)
Increase	129/5970	4.8 (4.0–5.7)	4.8 (3.8–5.7)	0.92 (0.75–1.13)	0.83 (0.67–1.03)
Lung cancer	397/64 303	1.4 (1.2–1.5)	1.4 (1.2–1.5)		
Never	217/44 634	1.1 (1.0–1.3)	1.1 (0.9–1.2)	1.00 (ref)	1.00 (ref)
Decrease	43/6067	1.5 (1.1–2.0)	1.5 (1.0–2.1)	1.44 (0.93–2.24)	1.41 (0.91–2.20)
Constant	77/7632	2.0 (1.6–2.5)	2.1 (1.6–2.7)	1.58 (1.16–2.16)	1.56 (1.15–2.11)
Increase	60/5970	2.2 (1.7–2.9)	1.9 (1.4–2.5)	1.79 (1.30–2.48)	1.64 (1.18–2.28)
Melanoma	397/64 303	1.4 (1.2–1.5)	1.4 (1.3–1.6)		
Never	273/44 634	1.4 (1.2–1.6)	1.5 (1.2–1.7)	1.00 (ref)	1.00 (ref)
Decrease	41/6067	1.4 (1.0–2.0)	1.7 (1.1–2.3)	1.26 (0.80–1.98)	1.21 (0.78–1.89)
Constant	48/7632	1.2 (0.9–1.6)	1.2 (0.8–1.6)	0.90 (0.63–1.28)	0.87 (0.61–1.24)
Increase	35/5970	1.3 (0.9–1.8)	1.3 (0.8–1.9)	0.92 (0.63–1.36)	0.84 (0.58–1.22)
Breast cancer (in women)	468/27 475	3.8 (3.5–4.2)	3.6 (3.2–4.0)		
Never	341/19 874	4.0 (3.5–4.4)	3.8 (3.3–4.3)	1.00 (ref)	1.00 (ref)
Decrease	48/2468	4.2 (3.1–5.6)	4.1 (2.8–5.4)	1.02 (0.67–1.54)	0.97 (0.62–1.50)
Constant	40/2838	2.7 (1.9–3.7)	2.5 (1.6–3.4)	0.64 (0.44–0.92)	0.60 (0.41–0.88)
Increase	39/2295	3.7 (2.6–5.1)	3.6 (2.1–5.1)	0.90 (0.63–1.28)	0.77 (0.54–1.11)
Prostate cancer (in men)	980/36 828	6.1 (5.7–6.5)	6.0 (5.5–6.4)		
Never	641/24 760	6.1 (5.6–6.6)	6.0 (5.5–6.6)	1.00 (ref)	1.00 (ref)
Decrease	104/3599	6.3 (5.1–7.6)	6.6 (5.1–8.0)	1.03 (0.77–1.37)	0.99 (0.74–1.33
Constant	134/4794	5.8 (4.8–6.8)	5.7 (4.5–6.8)	0.82 (0.66–1.03)	0.81 (0.64–1.01)
Increase	101/3675	6.2 (5.1–7.6)	5.5 (4.3–6.7)	0.90 (0.71–1.14)	0.83 (0.65–1.06)
Hematological cancer	284/64 303	1.0 (0.9–1.1)	1.0 (0.8–1.1)		
Never	188/44 634	1.0 (0.8–1.1)	0.9 (0.8–1.1)	1.00 (ref)	1.00 (ref)
Decrease	23/6067	0.8 (0.5–1.2)	0.8 (0.4–1.1)	0.80 (0.46–1.41)	0.78 (0.45–1.35)
Constant	35/7632	0.9 (0.6–1.3)	0.8 (0.5–1.2)	0.80 (0.53–1.22)	0.78 (0.51–1.21)
Increase	38/5970	1.4 (1.0–1.9)	1.4 (0.9–2.0)	1.28 (0.86–1.91)	1.17 (0.76–1.80)

[a]HRs and 95% CIs were derived from Cox proportional hazards regression models.
[b]sHRs and 95% CIs were derived from Fine and Gray hazards regression models.
Models were adjusted for age, sex, education, hypertension, cardiovascular diseases, diabetes, chronic infection, COPD, rheumatic disease, dementia, RAAS-I, statins, NSAIDs, diuretics, the first eGFR and the first log2-transformed ACR. The Fine and Gray hazards model of breast cancer was adjusted for age, sex, diabetes, RAAS-I, the first eGFR and the first log2-transformed ACR because Loglik converged in the final model.
Regarding the categories of 2-year ACR changes, never was defined as the first and the second ACR test both <30 mg/g. Decrease was defined as a >30% decrease in ACR plus a >30 mg/g absolute decrease in ACR. Increase was defined as a >43% increase in ACR plus a >30 mg/g absolute increase in ACR, leaving the remaining subjects grouped as constant.
COPD, chronic obstructive pulmonary disease; GI tract, gastrointestinal tract; IR, incidence rate; NSAIDs, nonsteroidal anti-inflammatory agents; PY, person-year; sHR, sub-distribution HR.

robust in several sensitivity analyses. No associations of constant or decreasing albuminuria with cancer incidence were found.

To our knowledge, the Korean National Health Insurance System (NHIS) study is the only study that previously investigated the association of albuminuria changes with cancer risk [3]. The NHIS study and our study both document that increasing proteinuria/albuminuria was associated with a higher cancer risk independent of baseline eGFR. Differently, the NHIS study reported persistent proteinuria was associated with the highest
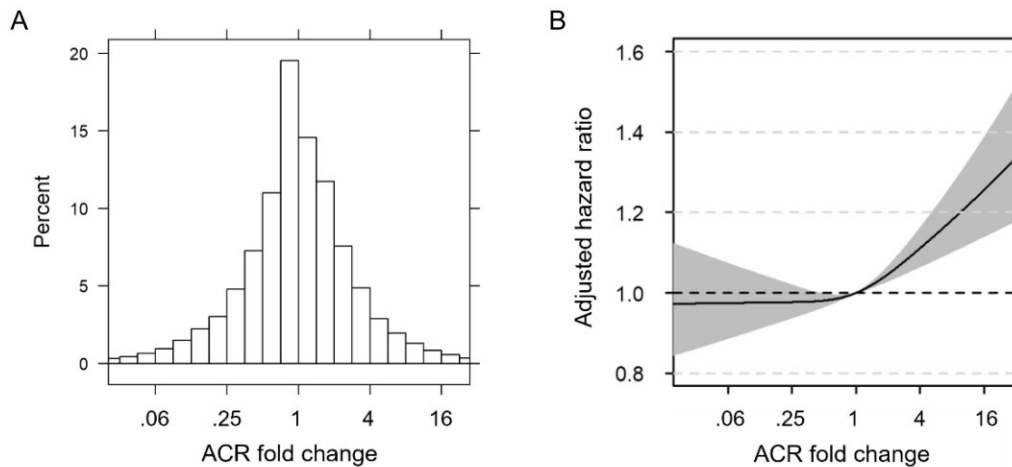
Figure 3: Distribution of 2-year ACR changes (**A**) and adjusted HR of 2-year ACR changes with overall cancer incidence (**B**). The spline shows the association of 2-year ACR changes with the risk of the incidence of overall cancer. Data were fitted by Cox proportional hazards regression models based upon restricted cubic splines with 3 knots at 10.0th and 90.0th percentile of the ACR fold change and adjusted for age, sex, education, hypertension, cardiovascular diseases, diabetes, chronic infection, COPD, rheumatic disease, dementia, RAAS-I, statins, NSAIDs, diuretics, the first eGFR and the first log2-transformed ACR. The spline curves are truncated at the 1.0th and 99.0th percentile of the distribution curve. The reference standard for 2-year ACR changes was 1 (no change). P-value for the nonlinear association is P=0.009.

Figure 4: Subgroup analyses investigating effect modification of the association of 2-year ACR changes (increase versus never) with overall cancer risk by age, sex, hypertension, diabetes and eGFR. HRs and 95% CIs were derived from Cox proportional hazards regression models. HRs were adjusted for age, sex, education, hypertension, cardiovascular diseases, diabetes, chronic infection, COPD, rheumatic disease, dementia, RAAS-I, statins, NSAIDs, diuretics, the first eGFR and the first log2-transformed ACR.

cancer risk after dividing proteinuria changes into four groups (i.e. never, disappearing, new-onset and persistent), while our study documented increasing albuminuria/proteinuria was associated with the highest cancer risk after dividing albuminuria/proteinuria changes into four groups (i.e. never, decrease, constant and increase). These different findings could stem from the discrepant methods to categorize proteinuria changes in the two studies. In the NHIS study an increase in proteinuria among the high-risk subjects with baseline proteinuria 2+ or 3+ was assigned to the persistent group, whereas these subjects were assigned to the increase group in our study. We would suggest assigning these subjects to the increase group rather than the constant group because an increase in albuminuria/proteinuria can have additional predictive value for clinical outcomes even when albuminuria/proteinuria is already high at baseline [12].

Other possible reasons attributed to the discrepant findings between two studies include the lack of adjustment for baseline proteinuria or the use of RAAS-I in the NHIS study [20–22], varied timespan over which proteinuria/albuminuria changes were observed, distinct population sampling strategy (screening versus registry-based cohort) and differences in ethnicity (Asian versus European population).

Of note, the association between increasing albuminuria and cancer risk observed in this study was robust after adjustment for baseline eGFR as well as for eGFR change over the same period. This may support the notion that the pathway linking albuminuria changes to cancer at least in part goes beyond the role of changes in kidney function. Though largely unknown, there are several possible mechanisms explaining the association of increasing albuminuria with cancer. Increasing albu-

minuria likely reflects worsening generalized endothelial dysfunction [23], which can promote angiogenesis predisposing to tumor formation [24]. Another plausible mechanism is that increasing albuminuria may indicate intrarenal RAAS upregulation [25], which itself can stimulate the pre-cancerous microenvironment by inhibiting apoptosis [26]. Conversely, we did not observe our hypothesized association of decreasing albuminuria with lower cancer risk. Nevertheless, given that subjects in the decrease group of our study on average had higher baseline albuminuria (ACR of 175.9 mg/g), and that albuminuria at the second measurement was approximately similar to the ACR value of the reference group who never had clinically elevated ACR (ACR of 34.4 mg/g), it is reasonable to presume that the higher cancer risk associated with the higher baseline albuminuria may cancel out the underlying lower cancer risk associated with decreasing albuminuria.

The reasons why we observed positive associations for change in albuminuria specifically with lung cancer and urinary tract cancer are largely uncharted. Notably, there are several considerations that merit attention. First, although this is the first study to link changes in albuminuria to the incidence of lung cancer and urinary tract cancer, there are several other cohort studies that linked baseline albuminuria to these specific cancer subtypes [3, 7–9]. These observations in combination suggest that the association of (change in) albuminuria with lung cancer and urinary tract cancer is not coincidental. Second, to speculate about possible mechanisms for these specific cancer types, it could be that albuminuria is an indicator of tissue damage due to smoking [8]. It is known that smoking has strong associations with lung and urinary tract cancer, stronger than with, for instance, prostate cancer [27, 28]. This would provide a non-causal mechanism that links albuminuria to some specific cancer subtypes. It could also be speculated that urine albumin irritates urothelial epithelia by direct contact and accelerates oncogenesis in this [29]. This would provide a causal mechanism linking albuminuria to urinary tract cancer. Third, we want to caution that not finding an association between albuminuria and other cancer subtypes does not necessarily deny an association. It could well be that these associations are just less strong and that our study is not sufficiently powered to show them.

Our study suggests an important rationale for examining the possible mechanisms that link albuminuria with cancer risk in future investigations. This is because the positive association of baseline albuminuria and cancer documented in our previous SCREAM study and other studies also holds for albuminuria changes as we observed in the current study [8, 9, 30]. In addition, it may have implications for whom to consider for cancer screening. Albuminuria and especially increasing albuminuria could be added to the list of risk factors that warrant screening for some specific cancer subtypes. This holds true especially for urinary tract cancer. Current guidelines recommend a pre-screening in persons with asymptomatic microscopic hematuria to identify high-risk persons that may have more benefit from cystoscopy and further invasive examinations for diagnosing urinary tract cancer [31]. Cystoscopy is advised especially in subjects of older age, with a smoking history, and with a larger amount of urine red blood cells [32]. Our results support the potential added predictive value of albuminuria and especially increasing albuminuria to such existing pre-screening risk profiles.

As one of the strengths, this study adds weight to the as-yet limited evidence regarding the question of whether and how albuminuria is associated with cancer risk. This is important because the association of change in albuminuria with cancer risk supports the demand and rationale for future investigations into mechanisms underlying the albuminuria cancer association. Another strength of this study is that, different from the NHIS study, we quantified albuminuria changes by ACR which is a more accurate measurement method than the semiquantitative dipstick proteinuria according to the KDIGO guideline [1, 3]. Regarding limitations, selection bias can be introduced due to the clinical indications of ordering repeated albuminuria tests. We would assume that subjects included in this study have more comorbidities requiring albuminuria monitoring than the general Swedish population, and therefore our results should be interpreted with caution when extrapolating them to the general population. Lastly, our data only suggest a link between (change in) albuminuria and cancer risk. As in all observational studies, we cannot infer any causality.

In conclusion, this study shows that increasing albuminuria is associated with a higher risk of overall, urinary tract and lung cancer, and that this association is independent of baseline kidney function and albuminuria. These data strengthen evidence for a link between albuminuria and cancer risk and provide an important rationale for future studies to investigate mechanisms linking albuminuria to cancer incidence.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

L.L., L.M.K., Y.Y, J.-J.C. and R.T.G. conceived and designed the study. J.-J.C. contributed to data acquisition. L.L. conducted data analysis. All authors contributed to the interpretation of the data. L.L. and L.M.K. drafted the manuscript. All authors revised the article. J.-J.C. and R.T.G. supervised the work. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data contain patient-related information and cannot be shared publicly as per European GDPR regulations. The data can be accessed through collaborative research applications address to the Principal Investigator J.-J.C. (juan.jesus.carrero@ki.se), and subjected to data sharing agreements that fulfil institutional and national regulations.

CONFLICT OF INTEREST STATEMENT

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