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Original Article

ORIGINAL ARTICLE

Albuminuria and the risk of cancer: the Stockholm CREAtinine Measurements (SCREAM) project

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ABSTRACT

Background. Studies investigating the association of chronic kidney disease and cancer have focused on estimated glomerular filtration (eGFR) rather than on albuminuria. This study aimed to examine whether albuminuria is associated with cancer incidence, and whether this association is independent of eGFR.

Methods. We included subjects of the Stockholm Creatinine Measurements (SCREAM) project without a history of cancer—250 768 subjects with at least one urine albumin–creatinine ratio (ACR) test (primary cohort) and 433 850 subjects with at least one dipstick albuminuria test (secondary cohort). Albuminuria was quantified as KDIGO albuminuria stages. The primary outcome was overall cancer incidence. Secondary outcomes were site-specific cancer incidence rates. Multivariable Cox proportional hazards regression models adjusted for confounders including eGFR to calculate hazard ratios and 95% confidence intervals (HRs, 95% CIs).

Results. During a median follow-up of 4.3 (interquartile range 2.0–8.2) years, 21 901 subjects of the ACR cohort developed *de novo* cancer. In multivariable analyses, adjusting among others for eGFR, subjects with an ACR of 30–299 mg/g or ≥300 mg/g had a 23% (HR 1.23; 95% CI 1.19–1.28) and 40% (HR 1.40; 95% CI 1.31–1.50) higher risk of developing cancer, respectively, when compared with subjects with an ACR <30 mg/g. This graded, independent association was also observed for urinary tract, gastrointestinal tract, lung and hematological cancer incidence (all $P < .05$). Results were similar in the dipstick albuminuria cohort.

Conclusions. Albuminuria was associated with the risk of cancer independent of eGFR. This association was primarily driven by a higher risk of urinary tract, gastrointestinal tract, lung and hematological cancers.

LAY SUMMARY

Previous studies investigating the association of chronic kidney disease with cancer risk predominantly focused on decreased estimated glomerular filtration rate (eGFR) rather than increased albuminuria. This cohort study therefore

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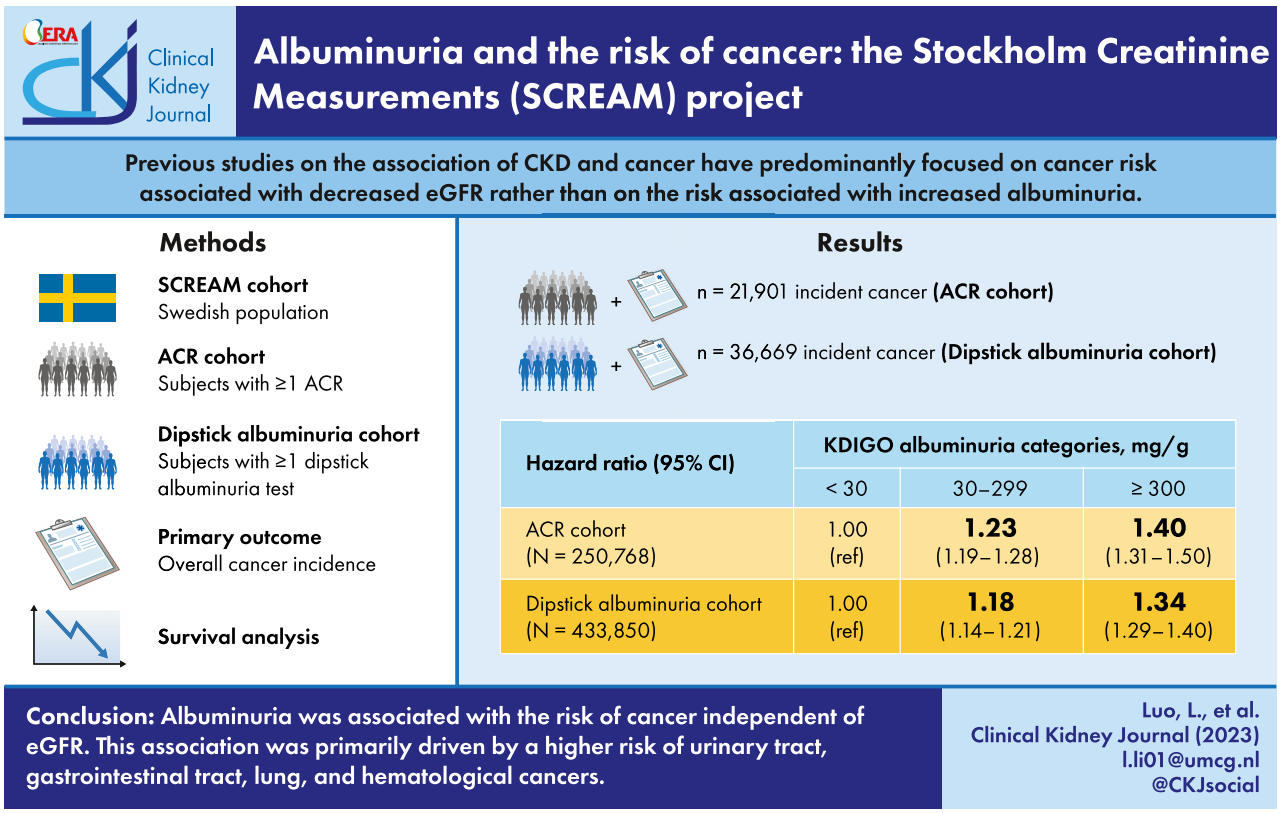
aimed to investigate whether albuminuria is associated with cancer incidence, and whether this association is independent of kidney function. The results showed that higher albuminuria was associated with an increased risk of cancer independent of eGFR. This study may have practical consequences in that albuminuria could be a potential marker to add value when identifying subjects eligible for the screening programs of certain cancer types, e.g. urinary tract cancer.

GRAPHICAL ABSTRACT



Keywords: albuminuria, cancer, chronic kidney disease, cohort study, SCREAM

INTRODUCTION

Chronic kidney disease (CKD) is defined as decreased kidney function [estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2] and/or increased albuminuria [1]. CKD is prevalent among about 11% of the adult population in developed countries [2]. In these countries cancer is considered one of the leading causes of death [3]. Accumulating research has shown that CKD predisposes to developing cancer [4]. Observational evidence in this field has predominantly investigated the excess risk of cancer incidence in persons with decreased eGFR. Possible cancer risks associated with increased levels of albuminuria are less studied [5–9].

The few studies exploring this association provide results that vary considerably [10–17]. This might be attributable among other things to a lack of consideration of eGFR, their limited sample sizes and the fact that different albuminuria measurement techniques were used, including semi-quantitative dipstick techniques and fully quantitative assessment of urine albumin–creatinine ratio (ACR). Of note, the dipstick technique is less accurate to quantify albuminuria levels when compared with the assessment of ACR, owing to the indirect estimate of albuminuria derived from a semi-quantitative colorimetric measurement method and the lack of correction for the degree of urine dilution–concentration [1].

To fill these gaps in previous studies, this study therefore aimed to explore the eGFR-independent risk of cancer incidence associated with albuminuria in a large Swedish population, and separately examined this association with ACR and dipstick albuminuria measurements.

MATERIALS AND METHODS

Study population

We analyzed data from the Stockholm CREAtinine Measurements (SCREAM) project, a healthcare utilization cohort from the region of Stockholm, Sweden that includes information on all residents seeking healthcare during 2006–19 [18]. 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 without a history of cancer who had at least one ACR test as our primary cohort and similar subjects who had at least one dipstick albuminuria test as our secondary cohort. The date of the first-encountered ACR or dipstick test per patient (if more than one was available) was considered for patient selection. As a next step, we searched for the presence of a creatinine-based eGFR value in the 6 months before or after the selected albuminuria test. This was considered as concomitant eGFR and the latest of both tests (either albuminuria or eGFR) was set as the baseline (index) date of the cohorts. At this index date, we assessed exclusion criteria, calculated study covariates and initiated follow-up. Exclusion criteria were age <18 years old, lack of concurrent eGFR test, a history of cancer, undergoing kidney replacement therapy and death on the same day as the baseline assessment. 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. ACR was calculated by taking the ratio between urinary albumin and urinary creatinine and expressed in mg/mmol (to convert to mg/g multiply by 8.84). Dipstick albuminuria was estimated by dipstick proteinuria. Dipstick proteinuria was assessed by an automated urine analyzer and recorded as negative, 1+, 2+ and 3+ [19]. Dipstick albuminuria values were converted into KDIGO albuminuria categories by the Chronic Kidney Disease Prognosis Consortium (CKD-PC) equation with the principle of negative to A1 (<30 mg/g), 1+ to A2 (30–299 mg/g), and 2+ and 3+ to A3 (≥300 mg/g) [20].

Baseline covariates included age, sex, highest attained education, hypertension, cardiovascular diseases, diabetes, chronic infections, chronic obstructive pulmonary disease, rheumatic disease and dementia, as well as the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARBs), statins, non-steroidal anti-inflammatory drugs, diuretics and eGFR. Highest attained education was categorized into three levels: compulsory school (≤9 years), secondary school (10–12 years) and university (>12 years), and obtained from the longitudinal integrated database for health insurance and labor market studies (LISA) register [21]. We used Anatomical Therapeutic Chemical codes to identify ongoing medications and all comorbidities were ascertained with International Classification of Diseases (ICD)-10 codes (Supplementary data, Table S1). The definition of diabetes was additionally enriched with information on the use of anti-diabetic medications. eGFR was calculated from serum/plasma creatinine using the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine equation [22]. 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 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 [23], and ICD-10 codes were grouped as follows: overall cancer [C00-C97, D45-D47, 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, C95-96, D45-47) [24]. 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).

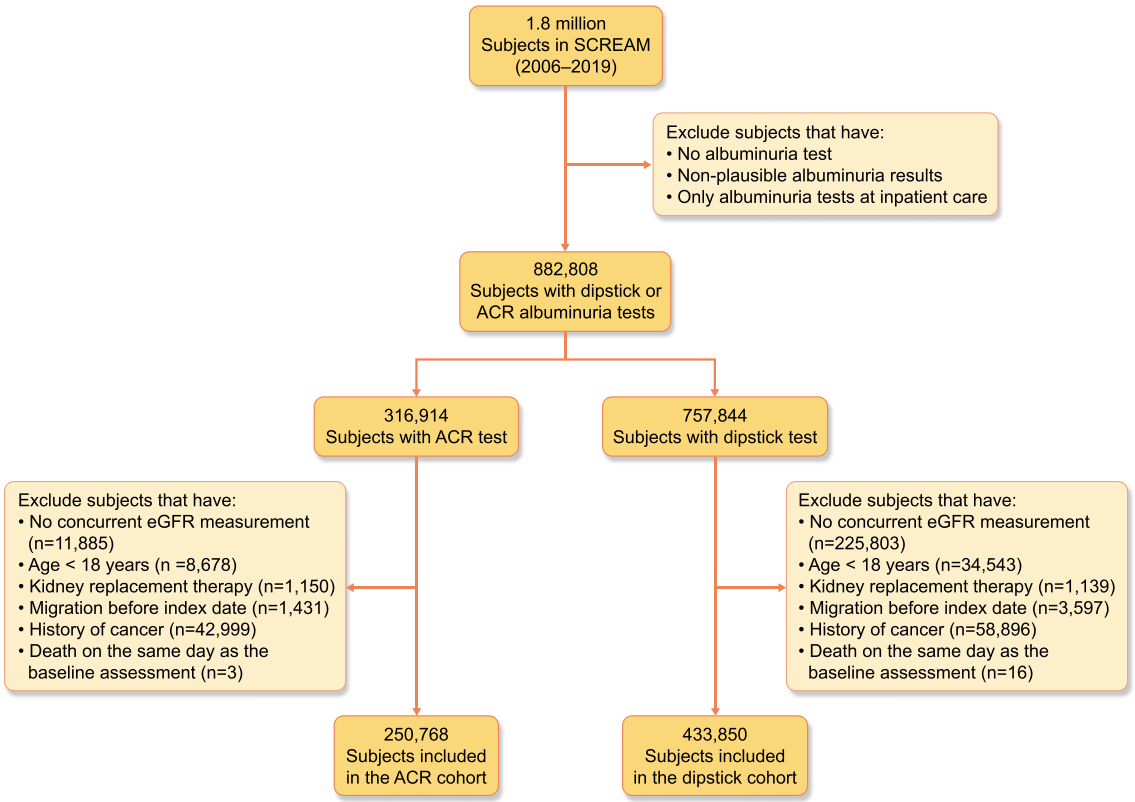
Statistical analyses

Continuous variables are presented as median with standard deviation (SD) or as median with interquartile range (IQR) in case of skewed distribution. Categorical variables are shown as counts with proportion.

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 cancer-free survival at 10 years from 100%. Cox proportional hazards regression models were used to estimate the association between baseline albuminuria KDIGO categories and the risk of overall and site-specific cancer incidence. Results are reported as hazard ratios (HRs) with 95% CIs. Models were adjusted for baseline covariates as described above, including baseline eGFR. HRs (95% CIs) for overall cancer incidence according to KDIGO combined albuminuria and eGFR global risk strata were also calculated using Cox regression models, in which the reference group comprised the subjects with ACR <30 mg/g and eGFR ≥90 mL/min/1.73 m^2 [1]. Kaplan–Meier curves were plotted for overall cancer incidence by KDIGO albuminuria categories in the dipstick albuminuria cohort and graphs showing restricted cubic splines were made for the ACR cohort.

We conducted several sensitivity analyses. First, to investigate the possible effect of non-cancer death on the association of albuminuria with cancer incidence, we performed Fine and Gray competing risk proportional hazards regression to estimate subdistribution hazard ratios with 95% CIs [25]. 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 detect possible effect modification by baseline age (<65 and ≥65 years old), sex, hypertension, diabetes and eGFR (<60 and ≥60 mL/min/1.73 m^2), we fitted Cox models containing both main effects and the cross-product terms with albuminuria. Fourth, to explore the possible effect of glycemic control on the association of albuminuria with cancer, we additionally adjusted for glycosylated hemoglobin (HbA1c) in the final model. Fifth, to investigate whether the overlap in the subjects of the ACR and the dipstick albuminuria cohorts will influence the estimated associations, we excluded subjects among the dipstick albuminuria cohort who were also in the ACR cohort (24.7%) and remodeled the associations.

P-values are two-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).



Abbreviations: ACR, urine albumin-creatinine ratio; eGFR, estimated glomerular filtration rate; SCREAM, the Stockholm Creatinine project

Figure 1: Flow chart of study participants and study design.

RESULTS

Baseline characteristics

After applying the inclusion and exclusion criteria, we identified 250 768 and 433 850 subjects that underwent at least one ACR test and one dipstick albuminuria test, respectively (Fig. 1). The baseline characteristics of the subjects of the ACR cohort are presented in Table 1. Their mean age was 60.1 ± 15.8 years and 48% were female. Some 81.3% of subjects had an ACR <30 mg/g, 14.9% had an ACR of 30–299 mg/g and 3.8% had an ACR ≥300 mg/g. The mean eGFR was 89.1 ± 21.8 mL/min/1.73 m^2. The most common comorbidities were hypertension (55%) and diabetes (33%). Subjects included in the dipstick albuminuria cohort were slightly younger, more often female, had higher eGFR and a lower prevalence of hypertension and diabetes, and less often used ACEi/ARBs when compared with subjects of the ACR cohort (Supplementary data, Table S2).

Albuminuria and the risk of overall cancer incidence

During a median follow-up of 4.3 (IQR 2.0–8.2) years, 21 901 new cases of cancer were recorded in the ACR cohort. The 10-year crude incidence of overall cancer was 16.2% (95% CI 16.0%–16.5%, Table 2). Higher albuminuria categories were associated with a higher risk of developing overall cancer. After full adjustment including eGFR, subjects with an ACR of 30–299 mg/g and subjects with an ACR ≥300 mg/g had a 23% (HR 1.23; 95% CI 1.19–1.28) and 40% (HR 1.40; 95% CI 1.31–1.50) higher risk of overall cancer incidence, respectively, when compared with subjects with an ACR <30 mg/g. Every doubling of ACR was linearly associated with the risk of overall cancer incidence (Fig. 2, $P_{\text{non-linearity}} = .78$). These results were similar in the dipstick albuminuria cohort (Table 2).

We explored cancer risks in individuals with differing KDIGO eGFR and albuminuria categories (Table 3, Supplementary data, Table S3). Within each eGFR stratum, cancer risk generally increased across worsening ACR categories.

Albuminuria and the risk of site-specific cancer incidence

HRs (95% CIs) for the association of albuminuria with site-specific cancers are shown in Tables 2 and 4. The 10-year crude incidence rate of site-specific cancers in the subjects of the ACR cohort ranged from 1.0% (95% CI 1.0%–1.1%) for developing hematological cancer to 6.1% (95% CI 5.9%–6.3%) for developing prostate cancer. Subjects with an ACR ≥300 mg/g had a higher risk to develop urinary tract cancer (HR 2.33; 95% CI 1.94–2.80), gastrointestinal tract cancer (HR 1.30; 95% CI 1.13–1.49), lung cancer (HR 1.35; 95% CI 1.05–1.73) and hematological cancer (HR 1.64; 95% CI 1.30–2.06), when compared with subjects with an ACR <30 mg/g. No significant associations of albuminuria with the risk of melanoma, breast and prostate cancers were observed. In general we observed a similar association pattern in the dipstick albuminuria cohort (Tables 2 and 4).

Table 1: Baseline characteristics of the 250 768 subjects of the ACR cohort, overall and according to KDIGO albuminuria categories.

		KDIGO albuminuria categories (mg/g)		
	Overall	A1 <30	A2 30–299	A3 ≥300
No. of subjects	250 768	203 754	37 410	9604
Demographics				
Age, years	60.1 ± 15.8	59.6 ± 15.3	63.5 ± 16.9	57.9 ± 19.3
Female	119 426 (48)	98 566 (48)	16 600 (44)	4260 (44)
Highest attained education				
Compulsory school	54 336 (22)	41 387 (20)	10 373 (28)	2576 (27)
Secondary school	103 241 (41)	84 495 (41)	14 943 (40)	3803 (40)
University	88 368 (35)	74 541 (37)	10 944 (29)	2883 (30)
Missing	4823 (2)	3331 (2)	1150 (3)	342 (4)
Kidney function				
Albuminuria, mg/g	8.0 (3.9, 24.8)	6.1 (3.5, 11.5)	60.1 (38.9, 109.6)	731.1 (430.5, 1494.2)
eGFR, ml/min/1.73 m^2	89.1 ± 21.8	91.0 ± 19.3	83.2 ± 26.6	71.1 ± 35.6
eGFR category, ml/min/1.73 m^2				
≥90	138 659 (55)	117 551 (58)	17 651 (47)	3457 (36)
60–89	86 781 (35)	72 197 (35)	12 273 (33)	2311 (24)
30–59	21 375 (9)	13 166 (6)	5962 (16)	2247 (23)
<30	3953 (2)	840 (0)	1524 (4)	1589 (17)
Comorbidities				
Hypertension	137 537 (55)	109 149 (54)	22 959 (61)	5429 (57)
Cardiovascular disease	45 458 (18)	32 299 (16)	10 404 (28)	2755 (29)
Myocardial infarction	15 513 (6)	11 189 (5)	3463 (9)	861 (9)
Congestive heart failure	16 378 (7)	10 217 (5)	4750 (13)	1411 (15)
Peripheral vascular disease	9412 (4)	6189 (3)	2454 (7)	769 (8)
Cerebrovascular disease	19 475 (8)	14 113 (7)	4295 (11)	1067 (11)
Diabetes mellitus	83 171 (33)	63 635 (31)	15 851 (42)	3685 (38)
Chronic infection	5011 (2)	3944 (2)	771 (2)	296 (3)
COPD	34 147 (14)	27 209 (13)	5594 (15)	1344 (14)
Rheumatic disease	9586 (4)	7267 (4)	1821 (5)	498 (5)
Dementia	2523 (1)	1666 (1)	700 (2)	157 (2)
Medication				
ACEi/ARBs	117 364 (47)	90 903 (45)	20 750 (55)	5711 (59)
Calcium channel blocker	58 189 (23)	43 195 (21)	11 398 (30)	3596 (37)
Beta-blocker	74 336 (30)	55 047 (27)	14 909 (40)	4380 (46)
Diuretics	44 942 (18)	32 174 (16)	9460 (25)	3308 (34)
Statins	75 301 (30)	59 236 (29)	12 823 (34)	3242 (34)
NSAIDs	78 741 (31)	61 592 (30)	13 783 (37)	3366 (35)

Continuous variables are reported as mean ± SD or median (IQR), and categorical variables as *N* (%).
COPD, chronic obstructive pulmonary disease; NSAIDs, nonsteroidal anti-inflammatory agent.

Sensitivity analyses

Results in our sensitivity analyses were in general compatible with our main analysis with a few exceptions. First, the associations of albuminuria with gastrointestinal tract and lung cancers were attenuated to null in competing risk models (Table 2). Second, elevated albuminuria categories were no longer significantly associated with a higher risk of developing gastrointestinal tract, lung and hematological cancers when excluding the first year of follow-up, suggesting the possibility of reverse causation bias (Supplementary data, Tables S4 and S5). In subgroup analyses we found in the ACR cohort as well as the dipstick albuminuria cohort, a suggestion of heterogeneity by baseline eGFR ($P_{interaction} < .05$, Fig. 3); however, the magnitude of the differences in the estimates of different eGFR subgroups was only minor. We did not find evidence for effect modification by age, sex or hypertension status in either cohort ($P_{interaction} > .05$). In addition, the associations of albuminuria with cancer were generally unchanged when we additionally adjusted for HbA1c in the final models (Supplementary data, Table S6). Lastly, we found the associations of albuminuria with overall and urinary tract cancers were robust after we excluded the overlapped subjects in the dipstick albuminuria cohort (Supplementary data, Table S7).

DISCUSSION

In this large cohort study of persons tested for albuminuria and eGFR in routine care, we observed consistent and dose-dependent associations between increased levels of albuminuria and risk of overall, urinary tract, gastrointestinal tract, lung and hematological cancers, independent of eGFR. The associations of albuminuria with overall and urinary tract cancer remained significant in our sensitivity analyses. These findings were in general consistent between the primary study cohort, in which albuminuria was determined as ACR on a continuous scale, and the secondary cohort, in which albuminuria was determined as dipstick on a semi-quantitative scale.

Prior studies have provided results on the association between albuminuria and cancer risk that varied considerably [10, 12–15, 17, 26]. One of the possible explanations might be the difference in covariates for which the associations are adjusted, especially eGFR. For example, results of the Atherosclerosis Risk

Table 2: Associations of albuminuria categories with the overall incidence of cancer and with incidence of site-specific cancers with an incidence of 0.5% or higher in the ACR and dipstick albuminuria cohorts during follow-up.

KDIGO albuminuria categories, mg/g	No. of events/participants	IR per 1000 PY (95% CI)	10-year crude incidence (%, 95% CI)	Conventional Cox proportional hazards model, crude HR (95% CI)[a]	Conventional Cox proportional hazards model, adjusted HR (95% CI)[a]	Fine and Gray hazards model, adjusted sHR (95% CI)[b]
ACR cohort (n = 250 768)						
Overall cancer	21 901/250 768	18.1 (17.8–18.3)	16.2 (16.0–16.5)			
<30	16 403/203 754	16.8 (16.5–17.1)	15.4 (15.1–15.6)	1.00 (ref)	1.00 (ref)	1.00 (ref)
30–299	4429/37 410	23.8 (23.1–24.5)	20.2 (19.5–20.8)	1.42 (1.38–1.47)	1.23 (1.19–1.28)	1.15 (1.11–1.19)
≥300	1069/9604	21.8 (20.5–23.1)	17.8 (16.6–18.9)	1.30 (1.22–1.38)	1.40 (1.31–1.50)	1.19 (1.12–1.27)
Urinary tract cancer	1834/250 768	1.4 (1.4–1.5)	1.4 (1.3–1.5)			
<30	1148/203 754	1.1 (1.1–1.2)	1.2 (1.1–1.2)	1.00 (ref)	1.00 (ref)	1.00 (ref)
30–299	541/37 410	2.7 (2.5–3.0)	2.3 (2.1–2.5)	2.45 (2.21–2.71)	1.91 (1.72–2.12)	1.79 (1.60–1.99)
≥300	145/9604	2.8 (2.4–3.3)	2.3 (1.8–2.7)	2.49 (2.09–2.96)	2.33 (1.94–2.80)	2.00 (1.64–2.42)
GI tract cancer	4777/250 768	3.8 (3.7–3.9)	3.7 (3.6–3.8)			
<30	3605/203 754	3.5 (3.4–3.6)	3.5 (3.4–3.7)	1.00 (ref)	1.00 (ref)	1.00 (ref)
30–299	945/37 410	4.8 (4.5–5.1)	4.7 (4.4–5.1)	1.35 (1.26–1.46)	1.09 (1.02–1.18)	1.02 (0.94–1.09)
≥300	227/9604	4.4 (3.8–5.0)	3.9 (3.3–4.5)	1.24 (1.08–1.41)	1.30 (1.13–1.49)	1.10 (0.96–1.27)
Lung cancer	1641/250 768	1.3 (1.2–1.3)	1.3 (1.2–1.4)			
<30	1189/203 754	1.2 (1.1–1.2)	1.2 (1.1–1.3)	1.00 (ref)	1.00 (ref)	1.00 (ref)
30–299	382/37 410	1.9 (1.7–2.1)	1.9 (1.7–2.2)	1.66 (1.48–1.86)	1.40 (1.25–1.58)	1.30 (1.15–1.47)
≥300	70/9604	1.3 (1.0–1.7)	1.3 (1.0–1.7)	1.15 (0.91–1.47)	1.35 (1.05–1.73)	1.13 (0.88–1.45)
Dipstick albuminuria cohort (n = 433 850)						
Overall cancer	36 669/433 850	14.9 (14.7–15.1)	13.4 (13.3–13.6)			
<30	29 089/353 442	14.1 (13.9–14.3)	12.9 (12.8–13.1)	1.00 (ref)	1.00 (ref)	1.00 (ref)
30–299	4471/49 757	17.4 (16.9–17.9)	15.0 (14.5–15.4)	1.22 (1.19–1.26)	1.18 (1.14–1.21)	1.12 (1.08–1.16)
≥300	3109/30 651	22.0 (21.2–22.8)	17.4 (16.8–18.1)	1.53 (1.48–1.59)	1.34 (1.29–1.40)	1.21 (1.16–1.27)
Urinary tract cancer	3087/433 850	1.2 (1.2–1.2)	1.1 (1.1–1.1)			
<30	2050/353 442	0.9 (0.9–1.0)	0.9 (0.9–1.0)	1.00 (ref)	1.00 (ref)	1.00 (ref)
30–299	467/49 757	1.7 (1.6–1.9)	1.5 (1.3–1.6)	1.79 (1.62–1.98)	1.55 (1.40–1.72)	1.48 (1.33–1.63)
≥300	570/30 651	3.8 (3.5–4.1)	2.7 (2.4–3.0)	3.87 (3.53–4.25)	2.84 (2.58–3.13)	2.58 (2.34–2.85)
GI tract cancer	7162/433 850	2.8 (2.7–2.8)	2.7 (2.6–2.8)			
<30	5716/353 442	2.7 (2.6–2.7)	2.6 (2.5–2.7)	1.00 (ref)	1.00 (ref)	1.00 (ref)
30–299	879/49 757	3.2 (3.0–3.5)	3.1 (2.9–3.3)	1.21 (1.13–1.30)	1.11 (1.04–1.19)	1.05 (0.98–1.13)
≥300	567/30 651	3.8 (3.5–4.1)	3.4 (3.1–3.7)	1.39 (1.28–1.52)	1.12 (1.03–1.22)	1.00 (0.92–1.10)
Lung cancer	2475/433 850	1.0 (0.9–1.0)	1.0 (0.9–1.0)			
<30	1958/353 442	0.9 (0.9–0.9)	0.9 (0.9–0.9)	1.00 (ref)	1.00 (ref)	1.00 (ref)
30–299	322/49 757	1.2 (1.1–1.3)	1.2 (1.0–1.3)	1.31 (1.16–1.47)	1.23 (1.09–1.38)	1.15 (1.02–1.30)
≥300	195/30 651	1.3 (1.1–1.5)	1.3 (1.1–1.5)	1.43 (1.23–1.66)	1.23 (1.06–1.43)	1.08 (0.93–1.26)

[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, ACEi/ARB, statins, NSAIDs, diuretics and eGFR.
COPD, chronic obstructive pulmonary disease; GI tract, gastrointestinal tract; IR, incidence rate; NSAIDs, nonsteroidal anti-inflammatory agents; PY, person-years.

in Communities study from the USA, in which the investigators adjusted for eGFR, showed that albuminuria was associated with an increased risk of prostate cancer, while the Norwegian Tromsø study, in which the investigators did not adjust for eGFR, did not show an association between albuminuria and prostate cancer [10, 14]. Another possible explanation for the variation in results between studies is the difference in albuminuria measurement techniques that were used. For instance, the Korean National Health Insurance System study reported that dipstick proteinuria was associated with the incidence of several gastrointestinal tract cancers, while the UK Biobank study did not find an association between continuously measured ACR and these cancers [12, 16]. We tried to resolve these discrepancies by adjusting for eGFR and separating the albuminuria methods in two parallel cohorts. When doing so, we found that associations in general were stronger in the ACR cohort. This is in line with our hypothesis that because ACR is more accurate to quantify albuminuria when compared with the measurement of dipstick albuminuria, it may also be more accurate to predict risk. Furthermore, our findings suggest that the association of albuminuria with cancer incidence is independent of eGFR, meaning that albuminuria captures risk not captured by eGFR, or that the mechanism connecting albuminuria to cancer risk may, at least in part, go beyond the role of kidney function. Of note, although we found significant interaction by baseline eGFR, the albuminuria cancer risk association was significant in subjects with impaired as well as preserved kidney function, and the strength of the association differed only slightly in these two subgroups.

To date, mechanisms underlying the association of albuminuria with the risk of cancer independent of eGFR are largely unknown, although several hypotheses have been proposed. First, chronic inflammation can lead to not only increased glomerular albumin permeability [27], but also to carcinogenesis and tumor growth [28]. Second, albuminuria is considered a sign of endothelial dysfunction, which can stem from increased reactive oxygen species (ROS) production. ROS-induced DNA damage

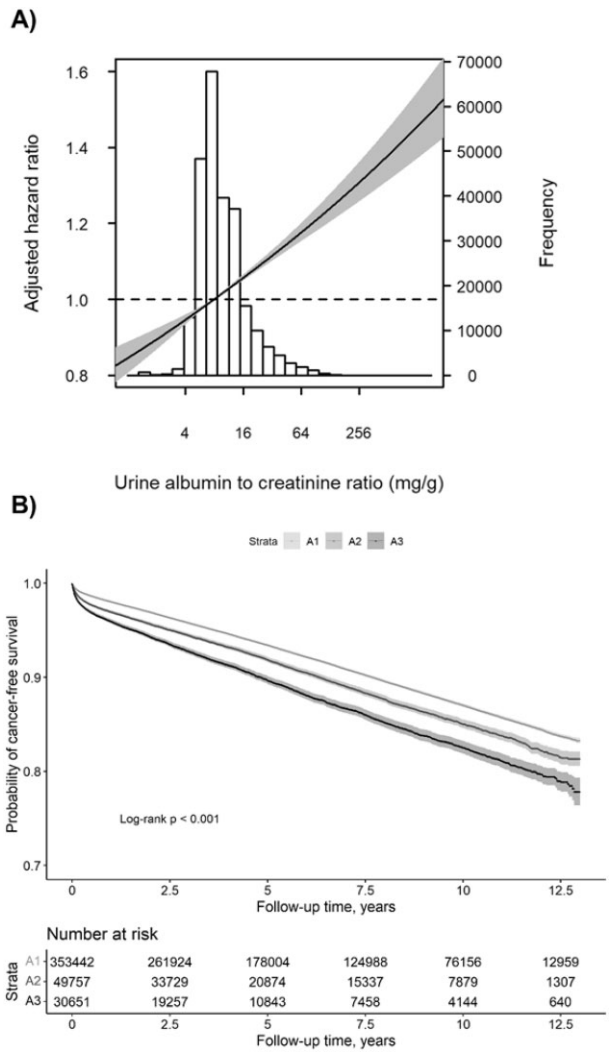


Figure 2: Associations of albuminuria with overall cancer risk in subjects from the ACR cohort (A) and the dipstick albuminuria cohort (B).
The spline (A) shows the association of albuminuria with the risk of overall cancer in 250 768 subjects from the ACR cohort. Data were fitted by Cox proportional hazards regression models based upon restricted cubic splines with 3 knots and adjusted for age, sex, education, hypertension, cardiovascular disease, diabetes, chronic infection, COPD, rheumatic disease, dementia, ACEi/ARB, statins, NSAIDs, diuretics and eGFR. The histogram represents the albuminuria distribution. The spline curve is truncated at the 1.0th and 99.0th percentile of the distribution curve. Data are reported as HRs and 95% CIs (shaded in gray). The reference standard for albuminuria is 8.0 mg/g. P-value for nonlinear association is $P = 0.78$. The Kaplan Meier curve (B) presents the survival function of 433 850 subjects of the dipstick albuminuria cohort. Abbreviations: COPD, chronic obstructive pulmonary disease; NSAIDs, nonsteroidal anti-inflammatory agent.

and apoptosis are crucial to the development of cancer [29]. Third, albuminuria *per se* can reflect activation of the renin–angiotensin system, which can stimulate pro-cancerous milieus through tissue remodeling, angiogenesis and apoptosis [30]. Future studies are warranted to verify these hypotheses. Fourth, several medications (e.g. erythropoiesis-stimulating agents and immunosuppressive drugs) can be prescribed to patients with higher albuminuria if they progressed to advanced CKD. These medications are reported to be associated with cancer risk [31, 32] and may mediate the albuminuria cancer association. Future studies are warranted to verify these possible mechanisms.

An important addition of our study to the field is the ability to consider potential bias relevant to observational studies when interpreting these associations. For example, competing risk analyses suggested that persons with increased albuminuria are more likely to die than to develop gastrointestinal tract and lung cancers, in line with studies linking albuminuria with non-cancer mortality risk [33]. The cause-specific hazard for non-cancer mortality associated with increased albuminuria can also lead to an evident decrease in the cumulative incidence for melanoma, breast cancer and prostate cancer even when albuminuria has no effect on the cause-specific hazard for these cancer incidences (Table 4 and Supplementary data, Table S8) [34]. Second, the associations of albuminuria with some cancers were not robust in our 1-year landmark analysis, suggesting potential reverse causation bias (i.e. that the testing is related to the processes of investigation leading to a diagnosis). Third, we were able to study the choice of the albuminuria measurement technique as a possible source of selection bias in healthcare-based databases. Dipstick albuminuria is mainly indicated for initial screening in primary care, and ACR is often for the confirmatory quantification of urinary albumin in persons with a positive dipstick test or in persons at high risk for albuminuria [1]. We argue that the indications for these tests and hence the type of population selected differ, justifying our decisions to separate in our study these methods in two parallel cohorts. Although the albuminuria–cancer risk association was quantitatively stronger in the ACR cohorts compared with the dipstick cohorts, the qualitatively consistent results in the ACR and dipstick albuminuria cohorts indicate that the albuminuria–cancer associations are robust among persons with different overall risks for albuminuria.

Notably, urinary tract cancer was the only site-specific cancer that is persistently observed to be associated with albuminuria. In another study from the SCREAM project eGFR was also found to be associated with a higher risk of urinary tract cancer [5]. These findings may have practical consequences. In patients with microscopic hematuria, it is currently recommended to first conduct a risk evaluation to select persons at high risk for cystoscopy and imaging examinations, as such to reduce invasive and costly screening for urinary tract cancer [35]. Given our findings, albuminuria and eGFR can be added to the list of possible risk factors predisposing for urinary tract cancer. Whether and how much albuminuria and eGFR can independently or multiplicatively add to this pre-screening risk profile should be a topic of future research.

Our study has additional strengths, including a large sample size and general population representativeness, which allows us to examine the association of albuminuria with the risk of site-specific cancers that have a low incidence. Our unique study setting, involving real-world patients from a country with universal free healthcare, minimizes selection bias caused by disparate access to healthcare across population subgroups. Limitations of our study include the inability to disentangle causality because of its observational nature. Our median follow-up of 4.3 years might be considered too short to investigate some cancer outcomes due to the possible latency period of cancer development. We were unable to adjust for some confounders (e.g. alcohol, smoking and blood pressure) that were not available in the SCREAM project. Lastly, we acknowledge that there may be overlap in the subjects included in both cohorts (i.e. the same patient may have been tested for dipstick and for ACR throughout the course of their disease). However, given the essentially unchanged results of the sensitivity analysis excluding the overlapped subjects in the dipstick albuminuria cohort,

Table 3: Adjusted HRs (and 95% CIs) for overall cancer incidence by KDIGO albuminuria and eGFR cross categories.

	KDIGO albuminuria categories (mg/g)		
eGFR, mL/min/1.73 m^2	A1 <30	A2 30–299	A3 ≥300
ACR cohort (n = 250 768)			
>90	1.00 (ref)	1.21 (1.14–1.27)	1.35 (1.20–1.53)
60–89	0.92 (0.89–0.95)	1.13 (1.07–1.19)	1.38 (1.23–1.54)
30–59	0.88 (0.83–0.93)	1.12 (1.04–1.20)	1.30 (1.16–1.46)
<30	0.96 (0.79–1.17)	1.40 (1.22–1.61)	1.20 (1.03–1.39)
Dipstick albuminuria cohort (n = 433 850)			
>90	1.00 (ref)	1.17 (1.12–1.23)	1.37 (1.28–1.46)
60–89	0.94 (0.92–0.97)	1.08 (1.03–1.14)	1.24 (1.17–1.32)
30–59	0.88 (0.84–0.93)	1.12 (1.03–1.22)	1.28 (1.18–1.38)
<30	1.10 (0.97–1.25)	1.38 (1.16–1.65)	1.17 (1.02–1.35)

HRs and 95% CIs were derived from Cox proportional hazards regression models.
HRs and 95% CIs of the combined albuminuria and eGFR categories were calculated by models adjusted for age, sex, education, hypertension, cardiovascular diseases, diabetes, chronic infection, COPD, rheumatic disease, dementia, ACEi/ARB, statins, NSAIDs and diuretics.
COPD, chronic obstructive pulmonary disease; NSAIDs, nonsteroidal anti-inflammatory agents.

Table 4: Associations of albuminuria categories with the incidence of other site-specific cancers with an incidence of 0.5% or higher in the ACR and dipstick albuminuria cohort during the total follow-up.

KDIGO albuminuria categories, mg/g	No. of events/ participants	IR per 1000 PY (95% CI)	10-year crude incidence (%, 95% CI)	Conventional Cox proportional hazards model, crude HR (95% CI)[a]	Conventional Cox proportional hazards model, adjusted HR (95% CI)[a]	Fine and Gray hazards model, adjusted sHR (95% CI)[b]
ACR cohort (n = 250 768)						
Melanoma	1570/250 768	1.2 (1.2–1.3)	1.3 (1.2–1.3)			
<30	1279/203 754	1.2 (1.2–1.3)	1.3 (1.2–1.4)	1.00 (ref)	1.00 (ref)	1.00 (ref)
30–299	244/37 410	1.2 (1.1–1.4)	1.3 (1.1–1.5)	0.98 (0.86–1.13)	0.90 (0.78–1.03)	0.83 (0.73–0.96)
≥300	47/9604	0.9 (0.7–1.2)	0.9 (0.6–1.2)	0.72 (0.54–0.96)	0.80 (0.59–1.08)	0.68 (0.50–0.92)
Breast cancer (in women)	2116/119 426	3.5 (3.3–3.6)	3.5 (3.3–3.6)			
<30	1776/98 566	3.6 (3.4–3.8)	3.5 (3.3–3.7)	1.00 (ref)	1.00 (ref)	1.00 (ref)
30–299	288/16 600	3.3 (3.0–3.7)	3.4 (3.0–3.9)	0.93 (0.82–1.05)	0.92 (0.81–1.04)	0.85 (0.75–0.96)
≥300	52/4260	2.2 (1.7–2.9)	2.4 (1.7–3.2)	0.62 (0.47–0.82)	0.81 (0.61–1.07)	0.69 (0.52–0.92)
Prostate cancer (in men)	4160/131 342	6.4 (6.2–6.6)	6.1 (5.9–6.3)			
<30	3284/105 188	6.4 (6.2–6.6)	6.1 (5.9–6.4)	1.00 (ref)	1.00 (ref)	1.00 (ref)
30–299	722/20 810	6.6 (6.1–7.1)	6.1 (5.6–6.7)	1.04 (0.96–1.12)	0.90 (0.82–0.97)	0.85 (0.78–0.92)
≥300	154/5344	5.4 (4.6–6.3)	5.2 (4.3–6.2)	0.85 (0.72–1.00)	0.86 (0.73–1.02)	0.74 (0.63–0.88)
Hematological cancer	1534/250 768	1.2 (1.1–1.3)	1.0 (1.0–1.1)			
<30	1085/203 754	1.1 (1.0–1.1)	1.0 (0.9–1.0)	1.00 (ref)	1.00 (ref)	1.00 (ref)
30–299	359/37 410	1.8 (1.6–2.0)	1.4 (1.2–1.5)	1.74 (1.54–1.96)	1.53 (1.35–1.73)	1.44 (1.27–1.64)
≥300	90/9604	1.7 (1.4–2.1)	1.2 (0.9–1.5)	1.66 (1.34–2.06)	1.64 (1.30–2.06)	1.44 (1.14–1.83)
Dipstick albuminuria cohort (n = 433 850)						
Melanoma	2659/433 850	1.0 (1.0–1.1)	1.1 (1.0–1.1)			
<30	2239/353 442	1.0 (1.0–1.1)	1.1 (1.0–1.1)	1.00 (ref)	1.00 (ref)	1.00 (ref)
30–299	259/49 757	1.0 (0.8–1.1)	1.0 (0.8–1.1)	0.93 (0.82–1.06)	0.92 (0.81–1.04)	0.87 (0.76–0.99)
≥300	161/30 651	1.1 (0.9–1.2)	1.1 (0.9–1.3)	1.05 (0.90–1.24)	0.97 (0.82–1.14)	0.86 (0.72–1.02)
Breast cancer (in women)	4109/237 490	2.9 (2.8–3.0)	2.8 (2.7–2.9)			
<30	3540/198 001	2.9 (2.8–3.0)	2.9 (2.8–3.0)	1.00 (ref)	1.00 (ref)	1.00 (ref)
30–299	364/25 042	2.7 (2.4–3.0)	2.6 (2.3–2.9)	0.93 (0.83–1.03)	0.97 (0.87–1.08)	0.92 (0.82–1.02)
≥300	205/14 447	2.9 (2.5–3.3)	2.9 (2.4–3.3)	1.00 (0.87–1.15)	1.04 (0.90–1.20)	0.94 (0.81–1.09)
Prostate cancer (in men)	6985/196 360	6.3 (6.1–6.4)	5.7 (5.6–5.9)			
<30	5599/155 441	6.2 (6.0–6.3)	5.7 (5.6–5.9)	1.00 (ref)	1.00 (ref)	1.00 (ref)
30–299	843/24 715	6.4 (6.0–6.9)	5.7 (5.3–6.1)	1.03 (0.96–1.11)	0.96 (0.89–1.03)	0.92 (0.85–0.99)
≥300	543/16 204	7.0 (6.5–7.6)	5.9 (5.3–6.5)	1.11 (1.02–1.21)	0.92 (0.84–1.01)	0.83 (0.76–0.91)
Hematological cancer	1973/433 850	0.8 (0.7–0.8)	0.7 (0.7–0.8)			
<30	1490/353 442	0.7 (0.7–0.7)	0.7 (0.6–0.7)	1.00 (ref)	1.00 (ref)	1.00 (ref)
30–299	280/49 757	1.0 (0.9–1.2)	0.9 (0.8–1.1)	1.48 (1.30–1.68)	1.35 (1.18–1.53)	1.28 (1.12–1.45)
≥300	203/30 651	1.3 (1.2–1.5)	1.1 (0.9–1.3)	1.90 (1.64–2.20)	1.51 (1.30–1.75)	1.36 (1.17–1.58)

[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, ACEi/ARB, statins, NSAIDs, diuretics and eGFR. Models analyzing breast and prostate cancers were not adjusted for sex.
COPD, chronic obstructive pulmonary disease; GI tract, gastrointestinal tract; IR, incidence rate; NSAIDs, nonsteroidal anti-inflammatory agents; PY, person-years.

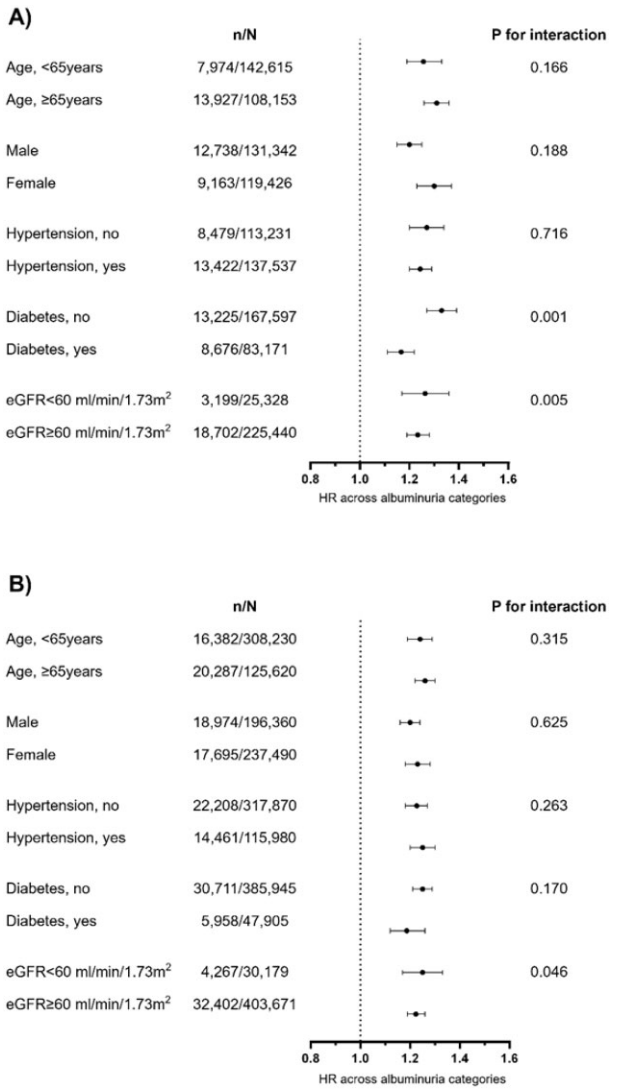


Figure 3: Subgroup analyses investigating effect modification of the association of albuminuria (<30 versus ≥30 mg/g) with overall cancer risk by age, sex, hypertension, diabetes and eGFR, for subjects of the ACR cohort (**A**) and subjects of the dipstick albuminuria cohort (**B**).
HRs and 95% CIs 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, ACEi/ARB, statins, NSAIDs, diuretics and eGFR. COPD, chronic obstructive pulmonary disease; NSAIDs, nonsteroidal anti-inflammatory agent.

we feel that overlapping cannot fully explain the consistency of findings.

In conclusion, this study shows that increased albuminuria is associated with a higher risk of overall cancer independently of eGFR, and the risk association is mainly attributable to the risk of the urinary tract, gastrointestinal tract, lung and hematological cancers.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

L.L., Y.Y., L.M.K., R.T.G. and J.-J.C. conceived and designed the study. J.-J.C. contributed to data acquisition. L.L. and Y.Y. 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. R.T.G. and J.-J.C. 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 General Data Protection Regulation. 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

None declared.

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