Research paper

Kidney function and cancer risk: An analysis using creatinine and cystatin C in a cohort study

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A B S T R A C T

Background: We examined whether an increased risk of cancer incidence and death is associated with kidney function and albuminuria and whether the risk is more readily identified when kidney function is estimated using cystatin C.

Methods: Participants were from UK Biobank (recruitment spanning 2007−2010), excluding those with a prior diagnosis of cancer. Estimated glomerular filtration rate (ml/min/1.73m^2) was calculated using creatinine (eGFRcr), cystatin C (eGFRcys) and creatinine-cystatin C (eGFRcr-cys). Cox proportional hazards models tested associations between eGFR, urinary albumin:creatinine ratio (uACR) and cancer incidence and death.

Findings: In 431,263 participants over median follow-up of 11.3 (IQR 10.6−12.0) years, there were 41,745 incident cancers and 11,764 cancer deaths. eGFRcys was most strongly associated with cancer incidence and death (HR 1.04 (95% CI 1.03−1.04) and 1.06 (1.05−1.07) per 10 ml/min/1.73m^2 decline, respectively). eGFRcr was not associated with either outcome (incidence: HR 1.00 (1.00−1.01); death: HR 0.99 (0.98−1.01) per 10 ml/min/1.73m^2 decline). Relative to eGFRcys>90 or uACR<3 mg/mmol, eGFRcys60−89 (HR 1.04 (95% CI 1.02−1.07)), eGFRcys<60 (HR 1.19 (1.14−1.24)) and uACR≥3 mg/mmol (HR 1.09 (1.06−1.12)) were associated with higher risk of incident cancer. eGFRcys60−89 (HR 1.15 (1.10−1.21)); eGFRcys<60 (HR 1.48 (1.38−1.59) and uACR≥3 mg/mmol (HR 1.17 (1.11−1.24)) were associated with cancer death.

Interpretation: Excess risk of cancer incidence and cancer death is more readily captured in early chronic kidney disease by eGFRcys than by current measures. The association between kidney function, uACR and cancer death in particular is concerning and warrants further scrutiny.

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1. Introduction

Cancer is more common in people with advanced chronic kidney disease (CKD) and/or kidney failure requiring kidney replacement therapy (KRT) [1]. It is unclear when higher cancer risk begins in relation to the CKD life course.

As kidney function, defined by estimated glomerular filtration rate (eGFR), falls below 60 ml/min/1.73m^2, there is a well described increased risk of cardiovascular disease [2] but this is less clear for cancer risk. Several studies have demonstrated a potential association between markers of CKD (below eGFR 60 ml/min/1.73m^2, alone or in combination with albuminuria) with higher risk of incidence and

death from overall [3−6] and site-specific urinary [3,7−9], lung[3] and haematological [10] cancers. However, the data are inconsistent [1,4,7,11], possibly as most studies have assessed associations with eGFR calculated from serum creatinine [1,3,5,7−12], which has been shown to have a U-shaped relationship with cancer risk [12]. Independent of the effect of eGFR and diabetes, albuminuria has been associated with higher risk of cancer overall [4,5,13], and particularly site-specific lung [4,5,13,14] and urinary tract [4,14] cancers.

Compared with creatinine, cystatin C is not influenced by muscle mass, age, ethnicity and gender and, combined in an equation with creatinine, affords more accurate estimation of kidney function than creatinine alone [15]. For cardiovascular disease, risk prediction in CKD is enhanced when cystatin C is used to estimate kidney function [2,16]. This has not previously been explored for cancer outcomes.

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Research in context

Evidence before the study

Cancer is more common in people with kidney failure, especially in people requiring dialysis or a kidney transplant. Although kidney failure is relatively uncommon, mild kidney disease (estimated glomerular filtration rate 60−89 ml/min/1.73m^2) may be present in one third of the population, is usually asymptomatic, is not routinely diagnosed and is monitored infrequently. Using sensitive markers of kidney dysfunction (cystatin C), mild kidney disease is associated with 20−30% increase in risk of cardiovascular disease and early death, and this heightened risk is more pronounced in people with more advanced kidney disease (estimated glomerular filtration rate <60 ml/min/1.73m^2). This may also be true for some forms of cancer, as kidney disease, cardiovascular disease and cancer share common risk factors. The presence of albuminuria (urine albumin:creatinine ratio >3 mg/mmol) is abnormal, and has been shown previously to be associated with higher risk of cancer incidence and cancer death for some cancer subtypes.

Added value of this study

Using a more sensitive and intuitively linear marker of kidney disease (cystatin C), we show that even mild kidney disease is associated with a 4% increased risk of developing cancer and a 15% risk in dying from cancer. In people with more advanced kidney disease, there is a 19% increased risk in developing cancer and a 48% increased risk in dying from cancer. This heightened risk of developing and dying from cancer is not identified when kidney function is estimated using serum creatinine, the marker most commonly used to estimate kidney function. Albuminuria is associated with 9% increased risk of developing cancer and 17% risk of dying from cancer, independently of the association between estimated glomerular filtration rate and cancer risk.

Implications of the available evidence

Our results show that mild kidney disease is clinically important in predicting cancer risk (and risk of cardiovascular disease and early death) but identifying this excess risk requires measurement of more sensitive markers of kidney dysfunction such as cystatin C. Greater uptake of cystatin C testing is clinically warranted for risk stratification of cancer, cardiovascular disease and early death. Though cystatin C testing is available in most developed countries, it is more expensive than creatinine in many laboratories; however, more widespread use could drive down the costs of testing and aid further research into identifying and addressing the factors responsible for worse cancer outcomes in people with kidney disease.

The UK Biobank has over 500,000 participants and nearly 5 million participant-years of follow-up. Using UK Biobank, we tested the hypothesis that CKD markers (eGFR and albuminuria) are associated with increased risk of overall and site-specific cancer incidence, cancer death, and that these risks are independent of known risk factors for cancer. Additionally, we hypothesised that kidney function estimates incorporating cystatin C, compared with creatinine alone, would be more strongly associated with cancer incidence and cancer-specific outcomes.

2. Methods

2.1. Participants and baseline data collection

Data were collected from 502,536 participants of the UK Biobank from 2007 to 2010 across assessment centres in the UK as previously described [17,18]. All participants provided written informed consent for baseline phenotyping and follow-up (with data linkage to electronic health records) until death or withdrawal of consent. The UK Biobank obtained ethical approval from the North West Multi-Centre Research Ethics Committee (REC reference 11/NW/03/820). The study was conducted under UK Biobank project code 7155 and reported according to STROBE principles.

Participants with available biochemistry at baseline and who provided ongoing consent for follow-up were included. Participants were excluded if they had a pre-existing diagnosis of cancer at the first UK Biobank assessment or if they did not have baseline biochemistry measurements.

Biochemical sampling processes have been described and validated previously [19−22]. In brief, serum and spot urine samples were collected and analysed at a central laboratory. eGFR was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations using serum creatinine (eGFRcr), cystatin C (eGFRcys) or a combination of creatinine and cystatin C (eGFRcr-cys) [15]. CKD stage was categorised according to the Kidney Disease: Improving Global Outcomes standard classification [23]: ≥90 (Reference: eGFR≥90), >60−89 (eGFR60−89), >30−60, >15−30-, ≤15 ml/min/1.73m^2. Participants with eGFR <60 ml/min/1.73m^2 were combined into one group for analysis (eGFR<60) due to small numbers with eGFR <30 ml/min/1.73m^2. Albuminuria was calculated as urine albumin:creatinine ratio (uACR) and categorised as <3 mg/mmol (normal) and ≥3 mg/mmol (abnormal) owing to small numbers of participants with uACR >30 mg/mmol.

Age was calculated from dates of birth and baseline assessment. Body mass index (BMI) was calculated from weight(kg)/height(m)^2. Ethnicity, smoking and alcohol history were self-reported. Townsend deprivation index [24] was calculated from the residential postcode.

Follow-up was recorded from first UK Biobank assessment date until date of the relevant outcomes. The end of follow-up was defined as the sooner of date of death, first diagnosis of cancer or the end of data collection (1st June 2020 for death (all centres), 1st June 2020 for hospital admissions in England; 31st March 2017 for hospital admissions in Scotland and Wales).

2.2. Outcomes of interest

(i) Cancer incidence: via linkage to national cancer registries, relevant cancer diagnoses were obtained using current ICD10 code classifications and grouped as follows: overall cancer (C00-C97, excluding non-melanoma skin cancer (D44)), digestive system (oesophagus, stomach, small intestine, colon, rectosigmoid, rectum and anal: C15−21), head and neck cancers (lip, tongue, gum, mouth, palate, parotid, salivary glands, tonsil, oropharynx, nasopharynx, sinus, hypopharynx, other oral; C00−14), respiratory system (trachea, bronchus and lung: C33−34), abdominal solid organs (liver, gallbladder, biliary tract, pancreas, other digestive: C22−25), haematological cancers (lymphoma, leukaemia, multiple myeloma, immunoproliferative diseases and other malignant haematological conditions (C81−96), renal tract cancers (kidney, renal pelvis, ureter, bladder: C64−67), female cancers (breast, vulva, vagina, cervix, uterus, ovary: C50−56), male cancers (penis, prostate, testis: C60−62) and malignant melanoma (C43).

(ii) Cancer death: cause and date of death were obtained from death certificates (National Health Service Information Centre for England and Wales or the NHS Central Register for Scotland).

2.3. Statistical analysis

For all analyses, results were obtained for eGFR categories using eGFRcr, eGFRcys, eGFRcr-cys. Distribution of baseline risk factors and missing data were displayed overall and by eGFR categories.

Continuous variables were displayed as mean (standard deviation; SD) or median (interquartile range) if non-normally distributed. Normality was tested by visual inspection of histograms and quantile-quantile plots for the full cohort and across eGFR categories. Categorical risk factors were displayed as number (%). Tests for trends across categories were assessed by ANOVA, chi-squared tests or Wilcoxon rank-sum tests as appropriate.

Missing data were multiply imputed by chained equations, using the average of five separately imputed datasets, assuming the data were missing at random and that the proportion of missing data was <10%.

Cancer event rates were described in the whole cohort per 100,000 participants and per 100,000 person-years. Furthermore, cancer incidence by cancer subtype was also described using the same approach per 100,000 participants and per 100,000 person-years.

To assess the relationship between each eGFR measure and cancer incidence and cancer death (overall), penalised splines of eGFR against hazard ratios of each outcome were plotted, after adjustment for age, sex, smoking and alcohol history, BMI, ethnicity, deprivation index, C-reactive protein, uACR, systolic and diastolic blood pressure, total and low-density lipoprotein (LDL) cholesterol, use of antihypertensive medications, use of cholesterol-lowering medications, baseline hypertension, diabetes and cardiovascular disease. eGFR 90 ml/min/1.73m^2 was considered the reference value for all outcomes.

Cox proportional hazards models were constructed to assess the association between eGFR measures and risk of cancer incidence (overall and by subtype) and cancer death (overall and by subtype) by 10 ml/min/1.73m^2 reduction in eGFR, by one standard deviation reduction in eGFR, and across eGFR categories (eGFR≥90, eGFR60−89, eGFR<60). Similar models were conducted to assess the effect of uACR on cancer incidence and death (overall and by subtype) in those with uACR <3 versus ≥3 mg/mmol. Proportional hazard assumptions were checked by plotting Schoenfeld residuals. Cox models were adjusted for known risk factors for cancer development as above. Models to assess the impact of uACR category were adjusted for eGFRcys. Evidence of multiplicative interaction effects were sought between age, sex, eGFR, uACR and type 2 diabetes for all outcomes using all eGFR measures. To attenuate the possibility of any observed associations between eGFR and cancer outcomes being linked to reverse causality, we conducted exploratory analyses for cancer incidence and cancer death overall: (i) excluding participants who developed multiple myeloma and renal tract cancers; (ii) 1-year landmark analysis, excluding participants who developed cancer or died within 1 year of enrolment. All survival models were censored for the competing risk of non-cancer death.

Model fit of Cox proportional hazards models to predict cancer incidence and death (overall and by subtype) was assessed by C-statistics with the addition of each eGFR measure as above, Akaike and Bayesian Information Criteria (AIC and BIC respectively; significance testing by log-likelihood ratios).

The rate advancement period (RAP): the time by which the risk is advanced compared to 1 year of ageing) was estimated from the regression coefficients (β) in fully-adjusted Cox proportional hazards models using methods described previously [25]: RAP = β_E/β_A, where β_E represents the adjusted coefficient of the exposure variable, and β_A represents the regression coefficient for age. Confidence intervals were estimated as follows [25]: $\beta_E/\beta_A \pm 1.96 \sqrt{\text{var}(\beta_E/\beta_A)}$. For RAP analyses, BMI and deprivation index were assessed according to the impact of a 5-unit increment.

Analyses were conducted using *tidyverse, finalfit, ggplot2, Hmisc, nephro, survival, survminer* and *tableone* packages for R statistical software (version 4.0.3) [26].

3. Role of funding

4. Results

There were 502,493 participants available in the full dataset: 33,484 had missing biochemical data and 37,746 had a diagnosis of cancer at baseline: 431,263 participants were included in the analyses. Over median follow-up of 11.3 (IQR 10.6−12.0) years, there were 41,745 new diagnoses of cancer, 23,525 deaths from any-cause of which 11,674 were cancer deaths.

4.1. Distribution of baseline risk factors according to eGFR categories

Baseline data by CKD stage can be found in Table 1 (eGFRcys), Supplementary Data Tables 1 (eGFRcr) and 2 (eGFRcr-cys). Overall, 53.4% were female, median age overall was 57.0 (IQR 50.0−63.0) years and 94.2% were of White ethnicity (2.0% South Asian and 1.6% Black). With declining eGFR, cardiometabolic risk factors tended to increase: compared to the reference group, participants with CKD G3−5 were older (median age 64 (IQR 61−67) versus 52 (IQR 46−59) years, *p*<0.001), with higher BMI (29.9 (IQR 26.6−34.1) versus 25.7 (IQR 23.4- 28.5) kg/m^2, *p*<0.001) and systolic blood pressure (142 (SD 20) versus 135 (SD 18) mmHg, *p*<0.001). Participants with eGFRcys<60 had a greater burden of cardiometabolic comorbidity at baseline compared to the reference group (hypertension 58.1 versus 18.3%, *p*<0.001; type 2 diabetes 14.9 versus 3.2%, *p*<0.001; cardiovascular disease 20.6 versus 3.6%, *p*<0.001).

4.2. Cancer event rates by eGFR category

Cancer event rates and incidence per 100,000 participants and per 100,000 person-years are displayed overall, by cancer subtype, and by eGFR categories in Supplementary Tables 3 (eGFRcys), 4 (eGFRcr) and 5 (eGFRcr-cys). Across all three measures, the rate of cancer incidence-overall and across cancer subtypes-increased with reduction in eGFR. This was more pronounced for eGFRcys and eGFRcr-cys.

4.3. Survival analysis

Risk of cancer incidence and cancer death are displayed graphically across the spectrum of eGFRcr, eGFRcys and eGFRcr-cys (Fig. 1). The relationship between eGFR and both cancer outcomes were largely linear and negative below ~90 ml/min/1.73m^2 for eGFRcys and eGFRcr-cys, and below ~75 ml/min/1.73m^2 for eGFRcr, suggesting that eGFRcys and eGFRcr-cys can detect heightened risk of cancer at an earlier stage. However, there was a J-shaped relationship for eGFRcr and eGFRcr-cys, with elevated risk of cancer incidence and death >90 ml/min/1.73m^2. This was more pronounced for eGFRcr. For each reduction in eGFR by 10 ml/min/1.73m^2 or by one standard deviation, there was a stronger association between cancer incidence and death overall with eGFRcys than with eGFRcr or eGFRcr-cys (Table 2). Increasing uACR was positively associated with risk of both cancer outcomes, plateauing at uACR ~90 mg/mmol for cancer incidence and ~80 mg/mmol for cancer death (Fig. 1).

4.3.1. Cancer incidence-overall

On multivariable analysis, increasing age, male sex, higher BMI, C-reactive protein, smoking and alcohol history, ethnicity, increasing deprivation, total and LDL cholesterol, cholesterol-lowering and antihypertensive medications and history of type 2 diabetes were all

Table 1
Baseline characteristics across eGFRcys categories.

Baseline characteristics		Overall	REF eGFR $\geq$90 ml/min/1.73m^2	eGFR 60−89 ml/min/1.73m^2	eGFR <60 ml/min/1.73m^2	p
N=		431,263	212,516	200,067	18,680	
Age (years): Median [IQR]		57.00 [50.00, 63.00]	52.00 [46.00, 59.00]	61.00 [55.00, 65.00]	64.00 [61.00, 67.00]	<0.001
Sex: N(%)	Female	230,374 (53.4)	118,681 (55.8)	101,900 (50.9)	9793 (52.4)	<0.001
	Male	200,889 (46.6)	93,835 (44.2)	98,167 (49.1)	8887 (47.6)	
Deprivation index*: Median [IQR]		−2.15 [−3.65, 0.51]	−2.20 [−3.69, 0.38]	−2.16 [−3.64, 0.53]	−1.32 [−3.22, 1.89]	<0.001
	Missing: N(%)	531 (0.12)	268 (0.13)	247 (0.12)	16 (0.09)	
Body mass index: Median [IQR]		26.74 [24.14, 29.88]	25.74 [23.38, 28.52]	27.64 [24.99, 30.86]	29.90 [26.57, 34.05]	<0.001
	Missing: N(%)	1450 (0.34)	584 (0.27)	699 (0.35)	167 (0.89)	
Ethnicity: N(%)	White	406,242 (94.2)	198,171 (93.2)	190,579 (95.3)	17,492 (93.6)	<0.001
	Black	6929 (1.6)	4635 (2.2)	2085 (1.0)	209 (1.1)	
	Chinese	1375 (0.3)	1060 (0.5)	303 (0.2)	12 (0.1)	
	Mixed	2587 (0.6)	1672 (0.8)	855 (0.4)	60 (0.3)	
	South Asian	8703 (2.0)	3876 (1.8)	4130 (2.1)	697 (3.7)	
	Any other	3951 (0.9)	2415 (1.1)	1398 (0.7)	138 (0.7)	
	Missing	1476 (0.3)	687 (0.3)	717 (0.4)	72 (0.4)	
Smoking status: N(%)	Never	236,745 (55.1)	125,099 (59.0)	103,451 (51.9)	8195 (44.2)	<0.001
	Previous	147,456 (34.3)	68,646 (32.4)	71,548 (35.9)	7262 (39.1)	
	Current	45,477 (10.6)	18,181 (8.6)	24,200 (12.1)	3096 (16.7)	
	Missing: N(%)	0 (0)	0 (0)	0 (0)	0 (0)	
Alcohol intake (units/week)		16.47 (19.00)	17.49 (18.98)	15.82 (19.04)	11.72 (17.77)	<0.001
	Missing: N(%)	37,455 (8.7)	17,332 (8.2)	18,265 (9.1)	1858 (9.9)	
Systolic blood pressure (mmHg)		137.68 (18.60)	134.60 (18.07)	140.56 (18.52)	141.85 (19.62)	<0.001
	Missing: N(%)	24,394 (5.7)	11,905 (5.6)	18,265 (9.1)	1120 (6.0)	
Diastolic blood pressure (mmHg)		82.22 (10.12)	81.35 (10.05)	83.16 (10.07)	81.93 (10.60)	<0.001
	Missing: N(%)	37,269 (8.6)	18,047 (8.5)	17,424 (8.7)	1798 (9.6)	
Medications for cholesterol: N(%)	Yes	74,026 (17.2)	23,738 (11.2)	42,544 (21.3)	7744 (41.5)	<0.001
	Missing: N(%)	0 (0)	0 (0)	0 (0)	0 (0)	
Medications for hypertension: N(%)	Yes	88,399 (20.5)	26,749 (12.6)	51,268 (25.6)	10,382 (55.6)	<0.001
	Missing: N(%)	0 (0)	0 (0)	0 (0)	0 (0)	
Total cholesterol (mmol/l)		5.69 (1.14)	5.67 (1.08)	5.74 (1.18)	5.32 (1.28)	<0.001
	Missing: N(%)	131 (0.03)	67 (0.03)	57 (0.03)	7 (0.04)	
LDL cholesterol (mmol/l)		3.55 (0.87)	3.52 (0.83)	3.61 (0.89)	3.33 (0.96)	<0.001
	Missing: N(%)	844 (0.21)	446 (0.21)	359 (0.18)	39 (0.21)	
uACR (mg/mmol): Median [IQR]		1.09 [0.69, 1.85]	1.14 [0.70, 1.92]	1.05 [0.67, 1.75]	1.22 [0.74, 2.36]	<0.001
	Missing: N(%)	12,214 (2.8)	5515 (2.6)	5867 (2.9)	832 (4.5)	
uACR category: N(%)	<3 mg/mmol	377,618 (90.1)	186,068 (89.9)	177,151 (91.2)	14,399 (80.7)	<0.001
	>=3 mg/mmol	41,431 (9.9)	20,933 (10.1)	17,049 (8.8)	3449 (19.3)	
C-reactive protein (ng/ml): Median [IQR]		1.31 [0.65, 2.73]	0.99 [0.51, 2.04]	1.63 [0.84, 3.24]	2.81 [1.43, 5.64]	<0.001
	Missing: N(%)	687 (0.16)	334 (0.16)	324 (0.16)	29 (0.16)	
Type 1 diabetes: N(%)	Yes	1388 (0.3)	671 (0.3)	520 (0.3)	197 (1.1)	<0.001
	Missing	0 (0)	0 (0)	0 (0)	0 (0)	
Type 2 diabetes: N(%)	Yes	19,900 (4.6)	6848 (3.2)	10,269 (5.1)	2783 (14.9)	<0.001
	Missing	0 (0)	0 (0)	0 (0)	0 (0)	
Hypertension: N(%)	Yes	112,955 (26.2)	38,938 (18.3)	63,173 (31.6)	10,844 (58.1)	<0.001
	Missing	0 (0)	0 (0)	0 (0)	0 (0)	
Cardiovascular disease: N(%)	Yes	28,239 (6.5)	7631 (3.6)	16,756 (8.4)	3852 (20.6)	<0.001
	Missing	0 (0)	0 (0)	0 (0)	0 (0)	

* Townsend deprivation index: each participant was assigned a numerical score corresponding to their postcode (range −6.26 − 11.00) with higher number representing greater deprivation. Data are presented as mean (standard deviation) unless otherwise indicated.

independently associated with higher risk of cancer incidence (p<0.05 for all).

After multivariable adjustment, there was a small but detectable increase in cancer incidence in people with eGFRcys60−89 (HR 1.04 (95% CI 1.02−1.07), p<0.001) and a higher increase in risk in people with eGFRcys<60 (HR 1.19 (1.14−1.24), p<0.001). This increase in risk was not detected by eGFRcr. uACR$\geq$3 mg/mmol was independently associated with increased risk of cancer incidence (HR 1.09 (1.06−1.12), p<0.001).

4.3.2. Cancer death-overall

Increasing age, male sex, higher BMI, C-reactive protein, smoking and alcohol history, ethnicity, increasing deprivation, uACR, C-reactive protein, systolic blood pressure, medications for cholesterol and blood pressure, total and LDL cholesterol and history of type 2 diabetes and cardiovascular disease were all independently associated with higher risk of cancer death (p<0.05 for all).

After adjustment, there was a moderate increase in cancer death in people with eGFRcys60−89 (HR 1.15 (1.10−1.21), p<0.001) and a more pronounced increase in risk in people with eGFRcys<60 (HR 1.48 (1.38−1.59), p<0.001). This increase in risk was not detected by eGFRcr. uACR$\geq$3 mg/mmol was independently associated with increased risk of cancer death (HR 1.17 (1.11−1.24), p<0.001).

There was a multiplicative interaction detected between age and sex for all eGFR measures with both cancer incidence and cancer death (p<0.001), with older men demonstrating highest increase in cancer risk. Statistical interactions between eGFR and uACR, type 2 diabetes, age and sex were variable according to the eGFR measure and cancer outcome (Supplementary Table 6). Exploratory analyses (Tables 3 and 4) suggest that eGFRcys<60 may be more strongly associated with cancer outcomes in those without type 2 diabetes (incidence: HR 1.20 (1.14−1.25) versus 1.14 (1.01−1.30); death: 1.53 (1.41−1.65) versus 1.28 (1.04−1.57)). uACR $\geq$3 mg/mmol may be more strongly associated with cancer death in younger compared with older participants (Table 4). Similar associations between eGFR
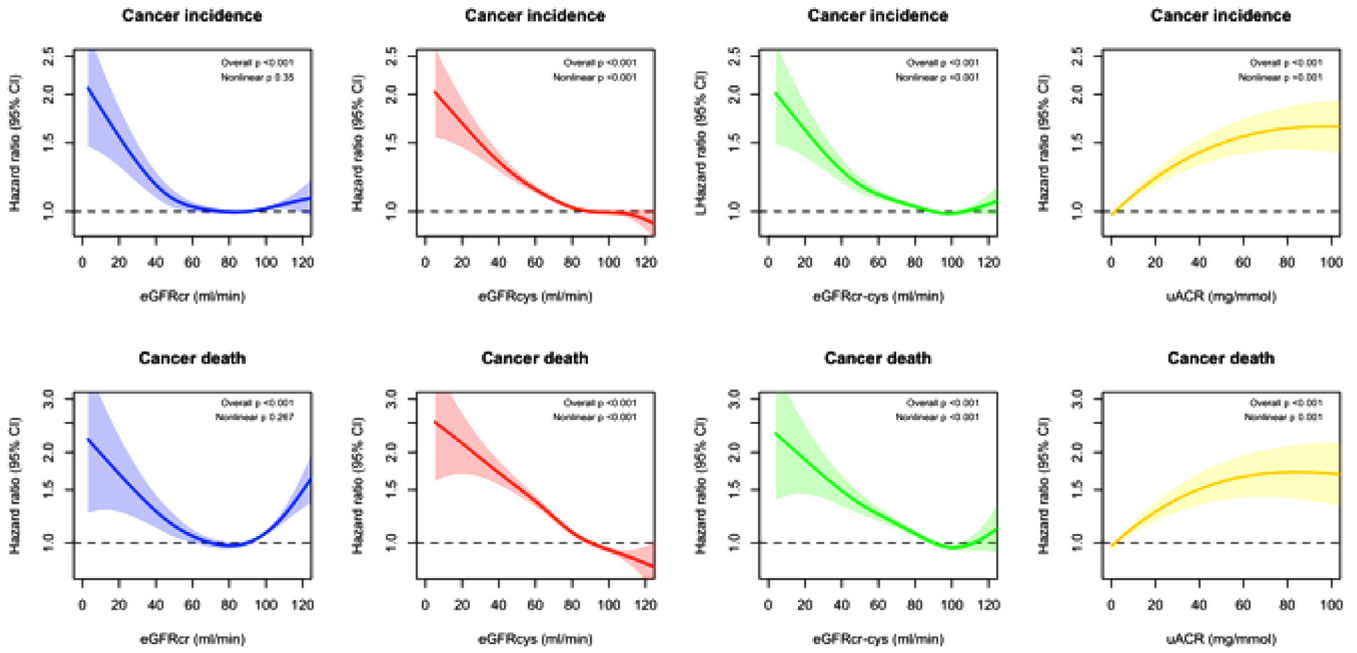
Fig. 1. *Adjusted penalised splines of risk of cancer incidence and cancer death across the spectrum of eGFRcr, eGFRcys, eGFRcr-cys and uACR.* Penalised splines of hazard ratios (95% confidence intervals) of each outcome were plotted for all eGFR measures and for uACR, after adjustment for known risk factors for cancer development: age, sex, smoking and alcohol history, BMI, ethnicity, deprivation index, C-reactive protein, uACR (for all eGFR splines), eGFRcys (for uACR splines only), systolic and diastolic blood pressure, total and LDL cholesterol, use of antihypertensive medication, use of cholesterol-lowering medication, baseline diabetes, hypertension and cardiovascular disease. eGFR 90 ml/min/1.73m^2 was considered the reference value for all outcomes. P nonlinear: likelihood-ratio test for addition of eGFR as a continuous variable to adjusted Cox proportional hazards model adjusted for other variables as above. P Overall: likelihood-ratio test for addition of eGFR as a spline term to Cox proportional hazards model adjusted for other variables as above.

Table 2
Hazard ratios for cancer incidence and cancer death for each eGFR measure and displayed per 10 ml/min/1.73m^2 and per one standard deviation reduction in eGFR. Hazard ratios were estimated from Cox proportional hazards models adjusted for age, sex, smoking and alcohol history, BMI, ethnicity, deprivation index, C-reactive protein, uACR, systolic and diastolic blood pressure, total and LDL cholesterol, use of antihypertensive medication, use of cholesterol-lowering medication, baseline diabetes, hypertension and cardiovascular disease.

	Per 10 ml/min/1.73m^2 reduction in eGFR	Per 1 SD reduction in eGFR	
	Adjusted HR (95% CI, *p* value)	1 SD (ml/min/1.73m$^{2)}$)	Adjusted HR (95% CI, *p* value)
Cancer incidence (41,745 incident cancers/431,263 participants)			
eGFRcr	1.00 (1.00−1.01, *p* = 0.303)	13.4	1.01 (0.99−1.02, *p* = 0.303)
eGFRcys	1.04 (1.03−1.04, *p*<0.001)	16.1	1.06 (1.05−1.07, *p*<0.001)
eGFRcr-cys	1.03 (1.02−1.03, *p*<0.001)	14.2	1.04 (1.03−1.05, *p*<0.001)
Cancer death (11,764 cancer deaths/431,263 participants)			
eGFRcr	0.99 (0.98−1.01, *p* = 0.288)	13.4	0.99 (0.97−1.01, *p* = 0.288)
eGFRcys	1.10 (1.08−1.11, *p*<0.001)	16.1	1.16 (1.13−1.18, *p*<0.001)
eGFRcr-cys	1.06 (1.05−1.08, *p*<0.001)	14.2	1.09 (1.07−1.11, *p*<0.001)

and risk of cancer incidence were observed between younger men and women (Table 4). eGFRcys<60 may be associated with higher incidence in cancer death in younger compared with older women (HR 1.49 (1.27−1.75) versus HR 1.34 (1.12−1.60); Table 4).

The addition of eGFRcys and eGFRcr-cys, but not eGFRcr, improved model fit for cancer incidence overall (Supplementary Tables 7 and 8). The greatest improvement was observed with eGFRcys.

4.3.3. Cancer incidence-subtypes
eGFRcys60−89 was associated with increased risk of haematological malignancies (HR 1.24 (1.14−1.33): 25.1% multiple myeloma) and cancers of the abdominal solid organs (HR 1.12 (1.01−1.25)), renal (HR 1.11 (1.01−1.21)) and respiratory tracts (HR 1.11 (1.03−1.20)), and this risk was augmented for each of these cancer subtypes when eGFRcys<60 (Fig. 2). eGFRcr60−89 was not associated with increased risk of any of these cancer subtypes but eGFRcr<60 was associated with increased risk of haematological (HR 1.19 (1.00−1.41)) and renal (HR 1.30 (1.10−1.53)) cancers. uACR ≥3 mg/mmol was convincingly associated

with increased risk of haematological (HR 1.13 (1.02−1.24)), abdominal (HR 1.40 (1.23−1.58)), renal (HR 1.40 (1.27−1.54)) and respiratory (HR 1.20 (1.09−1.32)) cancers, with weaker associations with digestive and head and neck cancers (Fig. 2).

The addition of eGFRcys improved model fit for cancer incidence in the respiratory and renal tracts, abdominal solid organs and haematological cancers but not head and neck, digestive tract, male/female-specific cancers or melanoma (Supplementary Table 7).

4.3.4. Cancer death-subtypes
eGFRcys60−89 was associated with increased risk of death from haematological malignancies (HR 1.40 (1.20−1.64): 20.8% deaths from multiple myeloma), digestive (HR 1.22 (1.10−1.35) and respiratory cancers (HR 1.15 (1.03−1.27)) with stronger associations detected for eGFRcys<60 (Fig. 3). eGFRcys<60 was further associated with risk of death from abdominal solid organ (HR 1.36 (1.11−1.66)), head and neck (HR 2.50 (1.40−4.47)), male-specific (HR 1.46 (1.08−1.96)) and renal (HR 1.77 (1.34−2.35)) cancers. eGFRcr<60 was associated with increased risk of death from renal tract cancers

Table 3
Hazard ratios and 95% confidence intervals for cancer incidence: model adjusted for age, sex, smoking and alcohol history, BMI, ethnicity, deprivation index, C-reactive protein, uACR (for eGFR categories), eGFRcys (for uACR categories), systolic and diastolic blood pressure, total and LDL cholesterol, use of antihypertensive medication, use of cholesterol-lowering medication, baseline diabetes, hypertension and cardiovascular disease.

	REF eGFR ≥90 ml/min/1.73m² Reference HR	eGFR 60−89 ml/min/1.73m² Adjusted HR (95% CI, p value)	eGFR <60 ml/min/1.73m² Adjusted HR (95% CI, p value)	REF uACR <3 mg/mmol Reference HR	uACR normal ≥3 mg/mmol Adjusted HR (95% CI, p value)
Older Men ≥ 65 years (7598 incident cancers/39,345 participants)					
eGFRcr	1	1.03 (0.98−1.08, p = 0.261)	1.08 (0.97−1.20, p = 0.153)		
eGFRcys	1	1.06 (1.00−1.13, p = 0.043)	1.24 (1.14−1.35, p<0.001)	1	1.13 (1.05−1.22, p = 0.001)
eGFRcr-cys	1	1.04 (0.98−1.10, p = 0.212)	1.18 (1.07−1.31, p = 0.001)		
Younger Men < 65 years (14,381 incident cancers/161,544 participants)					
eGFRcr	1	0.98 (0.95−1.01, p = 0.245)	1.09 (0.96−1.23, p = 0.174)		
eGFRcys	1	1.06 (1.02−1.09, p = 0.003)	1.25 (1.15−1.36, p<0.001)	1	1.13 (1.06−1.20, p<0.001)
eGFRcr-cys	1	1.04 (1.00−1.08, p = 0.028)	1.30 (1.16−1.45, p<0.001)		
Older Women ≥ 65 years (4989 incident cancers/38,978 participants)					
eGFRcr	1	1.01 (0.95−1.07, p = 0.783)	1.02 (0.90−1.16, p = 0.752)		
eGFRcys	1	1.09 (1.01−1.18, p = 0.021)	1.19 (1.07−1.32, p = 0.002)	1	1.08 (1.00−1.17, p = 0.066)
eGFRcr-cys	1	1.09 (1.02−1.17, p = 0.012)	1.14 (1.01−1.29, p = 0.039)		
Younger Women < 65 years (14,777 incident cancers/191,396 participants)					
eGFRcr	1	0.99 (0.96−1.03, p = 0.629)	1.06 (0.94−1.20, p = 0.321)		
eGFRcys	1	1.02 (0.98−1.06, p = 0.254)	1.23 (1.13−1.35, p<0.001)	1	1.09 (1.04−1.14, p<0.001)
eGFRcr-cys	1	1.03 (1.00−1.07, p = 0.063)	1.17 (1.04−1.31, p = 0.009)		
Type 2 diabetes (2748 cases/19,901 participants)					
eGFRcr	1	0.97 (0.89−1.05, p = 0.418)	1.04 (0.89−1.21, p = 0.611)		
eGFRcys	1	1.07 (0.97−1.18, p = 0.159)	1.14 (1.01−1.30, p = 0.041)	1	1.11 (1.01−1.22, p = 0.030)
eGFRcr-cys	1	1.03 (0.94−1.12, p = 0.525)	1.14 (0.99−1.31, p = 0.069)		
No type 2 diabetes (38,991 cases/411,309 participants)					
eGFRcr	1	1.00 (0.98−1.02, p = 0.899)	1.03 (0.97−1.10, p = 0.352)		
eGFRcys	1	1.04 (1.02−1.06, p = 0.001)	1.20 (1.14−1.25, p<0.001)	1	1.09 (1.05−1.12, p<0.001)
eGFRcr-cys	1	1.04 (1.02−1.07, p<0.001)	1.16 (1.09−1.23, p<0.001)		

Table 4
Hazard ratios and 95% confidence intervals for cancer death: model adjusted for age, sex, smoking and alcohol history, BMI, ethnicity, deprivation index, C-reactive protein, uACR (for eGFR categories), eGFR (for uACR categories), systolic and diastolic blood pressure, total and LDL cholesterol, use of antihypertensive medication, use of cholesterol-lowering medication, baseline diabetes, hypertension and cardiovascular disease.

	REF eGFR ≥90 ml/min/1.73m² Reference HR	eGFR 60−89 ml/min/1.73m² Adjusted HR (95% CI, p value)	eGFR <60 ml/min/1.73m² Adjusted HR (95% CI, p value)	REF uACR <3 mg/mmol Reference HR	uACR normal ≥3 mg/mmol Adjusted HR (95% CI, p value)
Older Men ≥ 65 years (2759 cancer deaths/39,345 participants)					
eGFRcr	1	1.00 (0.92−1.09, p = 0.953)	1.20 (1.02−1.41, p = 0.027)		
eGFRcys	1	1.13 (1.01−1.25, p = 0.026)	1.53 (1.33−1.76, p<0.001)	1	1.14 (1.01−1.28, p = 0.029)
eGFRcr-cys	1	1.08 (0.98−1.19, p = 0.103)	1.39 (1.19−1.63, p<0.001)		
Younger Men < 65 years (3966 cancer deaths/161,544 participants)					
eGFRcr	1	0.95 (0.89−1.01, p = 0.115)	1.11 (0.90−1.37, p = 0.328)		
eGFRcys	1	1.19 (1.11−1.28, p<0.001)	1.54 (1.34−1.77, p<0.001)	1	1.26 (1.14−1.40, p<0.001)
eGFRcr-cys	1	1.12 (1.05−1.20, p = 0.001)	1.49 (1.23−1.79, p<0.001)		
Older Women ≥ 65 years (1717 cancer deaths/38,978 participants)					
eGFRcr	1	0.97 (0.87−1.07, p = 0.505)	1.03 (0.84−1.27, p = 0.772)		
eGFRcys	1	1.11 (0.97−1.27, p = 0.123)	1.34 (1.12−1.60, p = 0.001)	1	1.13 (0.99−1.28, p = 0.080)
eGFRcr-cys	1	1.10 (0.97−1.24, p = 0.137)	1.22 (1.00−1.50, p = 0.054)		
Younger Women < 65 years (3322 cancer deaths/191,396 participants)					
eGFRcr	1	0.94 (0.88−1.02, p = 0.124)	1.05 (0.83−1.32, p = 0.677)		
eGFRcys	1	1.13 (1.05−1.23, p = 0.002)	1.49 (1.27−1.75, p<0.001)	1	1.21 (1.10−1.33, p<0.001)
eGFRcr-cys	1	1.10 (1.02−1.19, p = 0.010)	1.28 (1.03−1.59, p = 0.023)		
Type 2 diabetes (1073 cancer deaths/19,901 participants)					
eGFRcr	1	0.89 (0.78−1.02, p = 0.091)	1.09 (0.86−1.37, p = 0.477)		
eGFRcys	1	1.16 (0.99−1.35, p = 0.065)	1.28 (1.04−1.57, p = 0.020)	1	1.18 (1.02−1.37, p = 0.027)
eGFRcr-cys	1	1.18 (1.02−1.36, p = 0.026)	1.29 (1.03−1.61, p = 0.027)		
No type 2 diabetes (10,689 cancer deaths/411,309 participants)					
eGFRcr	1	0.97 (0.93−1.01, p = 0.153)	1.09 (0.98−1.21, p = 0.131)		
eGFRcys	1	1.15 (1.10−1.21, p<0.001)	1.53 (1.41−1.65, p<0.001)	1	1.17 (1.11−1.24, p<0.001)
eGFRcr-cys	1	1.10 (1.05−1.15, p<0.001)	1.37 (1.24−1.51, p<0.001)		

only (HR 1.50 (1.06−2.12)), though eGFRcr60−89 was associated with a reduced risk of death from abdominal solid organ and male-specific cancers (Fig. 3). uACR ≥3 mg/mmol was associated with increased risk of death from abdominal (HR 1.22 (1.06−1.41)), digestive (HR 1.14 (1.01−1.30), renal (HR 1.73 (1.42−2.11) and respiratory (HR 1.19 (1.06 − 1.34) cancers (Fig. 3).

The addition of eGFRcys improved model fit for death from digestive, respiratory, abdominal, head and neck, haematological and renal tract cancers (Supplementary Table 8).

4.3.5. Outcomes excluding participants with multiple myeloma or renal tract cancers

After exclusion of 4524 participants diagnosed with multiple myeloma or renal tract cancers, eGFRcys remained associated with increased risk of cancer incidence (eGFRcys 60−89: HR 1.03 (1.01−1.05), p = 0.016); eGFRcys<60: HR 1.15 (1.10−1.20), p<0.001) and cancer death (eGFRcys60−89: HR 1.14 (1.09−1.20), p<0.001); eGFRcys<60 HR 1.44 (1.34−1.56), p<0.001; Supplementary Table 9).
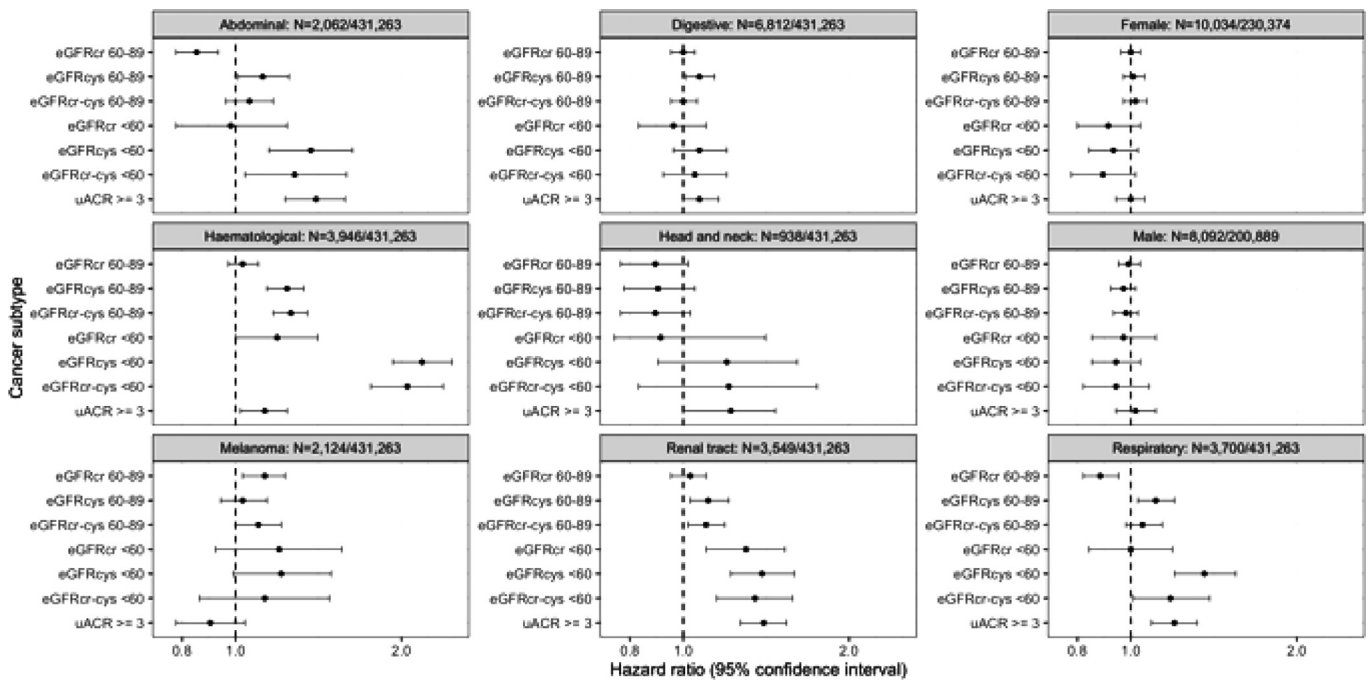
Fig. 2. *Forest plots for cancer incidence by cancer subtype according to eGFR and uACR categories.* Results are presented as the hazard ratio and 95% confidence intervals (adjusted for age, sex, smoking and alcohol history, BMI, ethnicity, deprivation index, C-reactive protein, uACR (for eGFR categories), eGFRcys (for uACR categories), systolic and diastolic blood pressure, total and LDL cholesterol, use of antihypertensive medication, use of cholesterol-lowering medication, baseline diabetes, hypertension and cardiovascular disease). Results are stratified by eGFRcr, eGFRcys and eGFRcr-cys categories and compared to reference group with eGFR >90 ml/min/1.73m². For uACR category, uACR >= 3 mg/mmol is presented compared to the reference group with uACR <3 mg/mmol, after adjustment for eGFRcys and other variables as above.
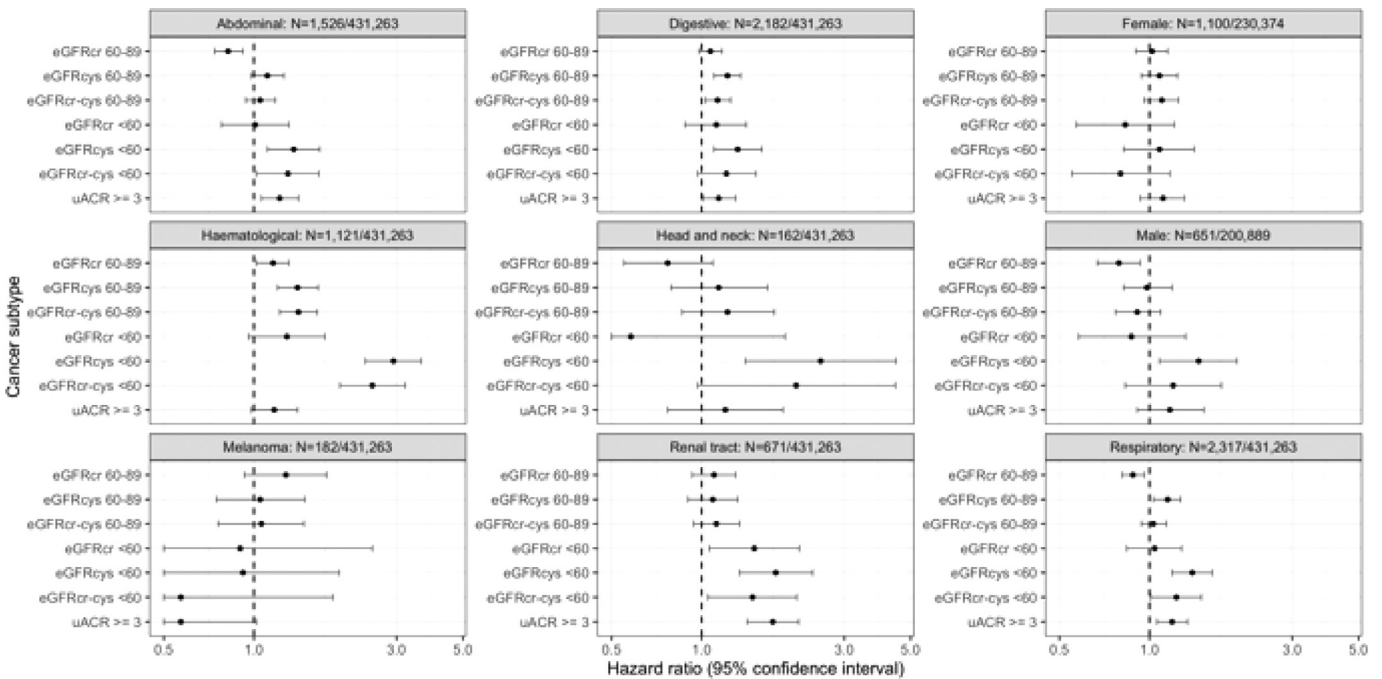

Fig. 3. *Forest plots for cancer death by cancer subtype according to eGFR and uACR categories.* Results are presented as the hazard ratio and 95% confidence intervals (adjusted for age, sex, smoking and alcohol history, BMI, ethnicity, deprivation index, C-reactive protein, uACR (for eGFR categories), eGFRcys (for uACR category), systolic and diastolic blood pressure, total and LDL cholesterol, use of antihypertensive medication, use of cholesterol-lowering medication, baseline diabetes, hypertension and cardiovascular disease). Results are stratified by eGFRcr, eGFRcys and eGFRcr-cys categories and compared to reference group with eGFR >90 ml/min/1.73m². For uACR category, uACR >= 3 mg/mmol is presented compared to the reference group with uACR <3 mg/mmol, after adjustment for eGFRcys and other variables as above.

4.3.6. One year landmark analysis

After exclusion of 6386 participants who were diagnosed with cancer or died within one year of enrolment, eGFRcys remained associated with increased risk of cancer incidence (eGFRcys 60−89: HR 1.04 (1.02−1.07), $p<0.001$; eGFRcys<60: HR 1.20 (1.15−1.25), $p<0.001$) and cancer death (eGFRcys60−89: HR 1.16 (1.11−1.21),

$p<0.001$); eGFRcys<60 HR 1.51 (1.40−1.63), $p<0.001$; Supplementary Table 10).

4.3.7. Rate advancement periods

After multivariable adjustment, eGFRcys<60 was associated with a RAP of 2.8 (−2.5 − 8.1) years, i.e., an advance in risk of cancer

Table 5
Rate advancement periods with 95% confidence intervals for overall cancer incidence and cancer death. The rate advancement period (RAP): the time by which the risk is advanced compared to 1 year of ageing) was estimated from the regression coefficients (β) in Cox proportional hazards models. All Cox proportional hazards models were adjusted for age, sex, smoking and alcohol history, BMI, ethnicity, deprivation index, C-reactive protein, uACR, eGFRcys, systolic and diastolic blood pressure, total and LDL cholesterol, use of antihypertensive medication, use of cholesterol-lowering medication, baseline diabetes, hypertension and cardiovascular disease. RAP = β_E/β_A, where β_E represents the (adjusted) coefficient of the exposure variable, and β_A represents the regression coefficient for age. Confidence intervals were estimated as follows: $\beta_E/\beta_A \pm 1.96 \sqrt{var(\beta_E/\beta_A)}$. *Townsend deprivation index: each participant was assigned a numerical score corresponding to their postcode (range $-6.26 - 11.00$) with higher number representing greater deprivation.

		Cancer incidence		Cancer death	
	Comparator	RAP	(95% CI)	RAP	(95% CI)
Male sex	Female	2.7	$(-1.7-6.0)$	2.5	$(-1.5-6.4)$
eGFRcys 60−89 ml/min/1.73m^2	eGFRcys ≥90 ml/min/1.73m^2	0.6	$(-2.8-4.1)$	1.7	$(-1.8-5.2)$
eGFRcys <60 ml/min/1.73m^2	eGFRcys ≥90 ml/min/1.73m^2	2.8	$(-2.5-8.1)$	4.5	$(-1.3-10.3)$
uACR ≥3 mg/mmol	uACR <3 mg/mmol	1.6	$(-2.6-5.8)$	2.0	$(-2.3-6.3)$
Previous smoking	Never smoker	2.3	$(-1.6-6.1)$	3.4	$(-1.2-7.9)$
Current smoking	Never smoker	6.8	$(-0.8-14.5)$	10.9	$(-0.5-22.2)$
Deprivation	+ 5 unit increase in Townsend deprivation index*	0.6	$(-2.2-3.4)$	1.8	$(-1.0-4.6)$
Body mass index	+ 5 kg/m^2 increase	0.5	$(-1.9-3.0)$	0.1	$(-2.1-2.3)$
Type 2 DM	No Type 2 DM	0.9	$(-3.7-5.6)$	2.9	$(-2.3-8.2)$
Cardiovascular disease	No CVD	0.2	$(-4.1-4.4)$	1.5	$(-2.6-5.5)$

incidence equivalent to an average of 2.8 years of additional age. This is similar to that observed for previous smoking (RAP 2.3 $(-1.6 - 6.1)$ years) and greater than observed for type 2 diabetes (RAP 0.9 $(-3.7 - 5.6)$ years; Table 5). Current smoking is associated with the greatest RAP (6.8 $(-0.9 - 14.5)$ years). eGFRcys<60 is associated with RAP of 4.5 $(-1.3-10.3)$ years for cancer death, suggesting that a person with more advanced CKD has a risk of cancer death equivalent to a person without CKD who is (on average) 4.5 years older. The effect is greater than that observed for greater deprivation: RAP 1.8 $(-1.0 - 4.6)$ years per 5-unit increase in deprivation score (equivalent to a transition up at least one deprivation quintile).

5. Discussion

We have demonstrated that increased risks of cancer incidence and cancer death may be detectable early in CKD, and are more readily detected using eGFRcys, which is more sensitive and intuitively linear than eGFRcr or eGFRcr-cys. eGFRcys and uACR are associated with increased risk of site-specific haematological, renal, respiratory and abdominal cancers. eGFRcys appears to advance the risk of cancer incidence and cancer death to a similar degree as other known risk factors, such as type 2 diabetes, higher BMI, greater deprivation and previous smoking.

To our knowledge, this is the first study to compare eGFRcr, eGFRcys and eGFRcr-cys for cancer risk. In contrast to studies that assessed the association between eGFRcr[3,5,7−11,27] or eGFRcr-cys [4] with cancer incidence and death, we have shown that eGFRcys 60−89 ml/min/1.73m^2 is associated with small but significant increases in cancer incidence, and a more pronounced association with cancer death.

The strong association between CKD and haematological cancers [10] may be due to shared risk factors including viral infections (hepatitis B, C, HIV, Epstein-Barr and cytomegalovirus) and the effects of immunosuppression [28]. Some haematological malignancies (e.g., multiple myeloma) may directly cause kidney failure: declining kidney dysfunction may represent an early manifestation of malignancy. We conducted sensitivity analyses (excluding participants who developed renal tract cancers and multiple myeloma, and one-year landmark analyses) in an attempt to assess and attenuate the impact of pre-symptomatic cancer on eGFR measures. Our conclusions were unchanged, but we accept that there remains potential for some of our findings being linked to reverse causality.

A more consistent association is observed between CKD and cancers of the urinary tract [1,3,7−9,29], which share common risk factors, such as the metabolic syndrome, smoking, prior nephrectomy, genetic conditions (such as tuberous sclerosis), occupational exposures and use of medications. Acute kidney injury (AKI) is known to contribute to CKD development [30] and is more likely to occur in those with CKD. Cell damage induced by AKI has been shown to promote clonal proliferation of renal progenitors as part of the healing response, leading to the development of renal cell carcinoma subtypes including metastatic disease [31]. Strategies to prevent both AKI and CKD (as a risk factor for AKI) may directly reduce the risk of renal tract cancers in this population.

Lung cancer has previously been associated with reduced eGFR [3] and more consistently with albuminuria [3−5,14]. This effect is slightly attenuated when taking account of history of smoking [4,14], suggesting that albuminuria may be a marker of susceptibility to cancer or tissue damage associated with smoking. Cancer and albuminuria have been associated with inflammatory states [32,33], and albuminuria may simply be a marker of increased inflammation and endothelial dysfunction. However, albuminuria remained association with risk of overall and site-specific haematological, abdominal, renal and respiratory and more weakly associated with digestive and head and neck cancers, even after adjustment for C-reactive protein as a marker of inflammation. Further exploration of the mechanisms underlying this association are warranted.

CKD is associated with cardiovascular disease: the heightened risk is detected earlier and more strongly by eGFRcys or eGFRcr-cys compared to eGFRcr [2,16,34]. Mendelian randomisation studies demonstrate that the association between elevated cystatin C and coronary artery disease is not causal, but is mediated by eGFR [35]. Cancer, cardiovascular disease and kidney disease share common risk factors such as increasing age, smoking, inflammation and the metabolic syndrome. eGFRcys appears to capture the aggregated metabolic and inflammatory profile associated with chronic disease in a way that is clinically relevant and straightforward for clinicians to test and interpret. Given the heightened risks of cardiovascular disease and cancer, improving knowledge about kidney function may help with risk stratification and healthcare planning, particularly in a condition that is largely asymptomatic until late in the disease course.

There are several possible explanations for the excess cancer death observed in CKD. People with CKD may be diagnosed with cancer at a more invasive stage, either through suboptimal symptom recognition or more aggressive disease. People with CKD are systematically under-represented in clinical cancer trials [36−38]: the evidence-base for cancer treatment in CKD is less well-established, and patients with CKD may receive cancer treatment regimens that are less effective or less aggressive. In CKD, side effects (especially renal side effects including AKI [39]) may be more common, and patients with CKD may be unable to tolerate the dose or duration of anti-cancer therapy for effective treatment. Medications used in

the treatment of CKD may interact with systemic anti-cancer therapies, limiting their effectiveness. Exploration of these issues is warranted in datasets with more granular information on cancer staging and treatments in participants with CKD.

We acknowledge some limitations to this work. First, kidney function is estimated based on a single baseline value of creatinine or cystatin C, with no information on kidney disease progression over time. Second, UK Biobank does not hold data on cancer symptoms, staging at diagnosis or treatment modalities, so we cannot assess the impact of CKD markers on treatments and outcomes. Third, cause of death was ascertained from linkage to death registry records, rather than as adjudicated endpoints: it is possible that misclassification of the cause of death could have occurred leading to over- or under-estimation of the risk associated with eGFR or albuminuria. Fourth, we have not adjusted for hormonal influences in women, however, CKD is associated with disruption in hormonal signalling and fertility [40] and eGFR measures may have captured some of these influences. Further, hormone profiles will not be routinely measured in primary care. Fifth, there are fewer participants with eGFR <30 ml/min/1.73m^2, so we are unable to comment on the impact of more advanced CKD. Sixth, the included participants were relatively young (all under 74 years old), therefore we cannot be confident the same associations would be observed in more elderly people, in whom cancer and lower eGFR are more common. Seventh, small representation of non-White ethnic groups may limit generalisability of the findings. Last, UK Biobank is not representative of UK population in terms of lifestyles. Cancer incidence in UK Biobank is around 30% lower than in the general population [41] and absolute risk may not be generalisable. However, hazard ratios should still be applicable to the general UK population [41].

There is an excess risk of cancer incidence and cancer death in CKD that is detected earlier and more readily by eGFRcys than by current measures. The heightened risk associated with eGFR<60 is at least as important as other recognised risk factors such as obesity, type 2 diabetes, deprivation and previous smoking. The impact of CKD markers on cancer death in particular is concerning and warrants further scrutiny.

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Data sharing

Data used in this study are available by open application through the UK Biobank. Full UK Biobank protocols and data dictionaries are available on www.ukbiobank.ac.uk.

Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.101030.

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