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Association of cancer with moderately impaired renal function at baseline in a large, representative, population-based cohort followed for up to 30 years

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Abstract

Patients with chronic renal failure show a greater incidence of malignancies. We evaluated whether moderately impaired renal function at baseline influenced risk of all cancers during long-term follow in young persons. Our cohort included 33,346 subjects, aged 26–61 years at baseline, in a representative, population-based study enrolling subjects from 1974 to 1992. Median follow-up time was 28 years. Plasma creatinine was analysed as a single measure at baseline. Incident cases of cancer were identified from the Swedish Cancer Registry. We studied 24,552 subjects from the cohort. To account for the unique sampling design, participants were divided by sex and age at baseline into 1,132 older men (age 60), 14,254 younger men (age 40–52), 7,498 older women (age 47–57) and 1,688 younger women (age 35–43). Glomerular filtration rate (GFR) was estimated using the CKD-EPI formula. Patients were classified as having either normal to mildly impaired kidney function (eGFR≥60 mL/min/1.73m^2), or moderate kidney dysfunction (eGFR<60 mL/min/1.73m^2). We calculated the risk of all cancers using competing risks regression. Overall, 6,595 participants were diagnosed with cancer, and 854 subjects (3.5%) had moderately impaired renal dysfunction at baseline. There was a significant association between moderately decreased GFR and subsequent risk of kidney cancer in younger men (hazard ratio, 3.38; 95% CI, 1.48 to

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Brief description: To investigate the risk of all cancers and low GFR we studied a large representative population with a median follow-up time of 28 years. This study shows that not only terminal renal failure but also moderately reduced renal function is associated with increased risk of kidney cancer. However, there is no overall long-term risk of other cancers. The long follow-up time in a representative population strengthens our findings.

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Conflict of Interest Statement

We declare that the results presented in this paper have not been published previously in whole or part, except in abstract format.

7.71; *P*=0.004). However, we found no association with overall long-term cancer risk. Our confirmation of an association between moderately impaired renal function and risk of kidney cancer in younger men requires further exploration of high-risk groups and biological mechanisms.

Keywords

Cancer; chronic kidney disease; kidney cancer; renal function

Introduction

Epidemiologic studies have found that the prevalence of chronic kidney disease (CKD) in the United States is over 10% [1, 2]. The prevalence of CKD stages 1 to 4 increased from 10% in the 1988–1994 period to 13.1% in the 1999–2004 period [2]. For stage 3 alone, the prevalence was 5.4% and 7.7%, respectively.

Renal function impairment can manifest across multiple organs. It is well known that there is a strong association between decreased GFR and cardiac diseases and, importantly, increased risk of death [3, 4, 5]. It is also known that kidney function is a predictor of non-cardiovascular mortality [6], and higher incidence of malignancies in patients with chronic renal failure has been reported [7, 8, 9]. There are also reports implicating increased risk of cancer in patients with earlier stages of CKD [9, 10, 11]. One recent study showed an association between elevated albumin-to-creatinine ratio and cancer incidence in a longitudinal population-based study of older individuals, with highest incidence reported for bladder and lung cancer [12]. Wong et al found that in their prospective, population-based cohort of 3,654 individuals with a mean age of 66 years and a mean follow-up of 10 years, men, but not women, with stage 3 CKD or worse had significantly increased risk of cancer [13]. The increased risk in men was noted at an estimated GFR (eGFR) ≤ 55 mL/min/1.73 m^2 with hazard ratio (HR) of 1.39 (95% CI 1.00 to 1.92). Cancer risk increased linearly as GFR declined. The predominant cancer types were lung and urinary tract cancers but not prostate cancer. Weng et al recently published a report on a large cohort showing increased risk of death from liver, kidney, and urinary tract cancer in subjects with CKD compared to those without CKD [14]. The mean age among CKD patients was 66 years. To the best of our knowledge, no studies of the association between cancer risk and renal function impairment in younger individuals with a follow-up over several decades have been reported. The aim of our study was to assess the risk of developing cancer in just such a cohort. In order to investigate the representativeness of our cohort we also analysed the established association between impaired renal function and increased risk of cardiovascular disease.

Material and Methods

Patients

The Malmö Prevention Project (MPP), based in Malmö, Sweden, is a population-based cross-sectional screening and intervention program designed to study the risk of cardiovascular disease [15], but also the risk of cancer [16, 17]. Screening for breast cancer was offered to all women above 45 years of age. Every inhabitant in each selected age group living in Malmö was invited to participate in this broad health-screening program, which enrolled subjects from 1974 to 1992. Participation across each age group was high (average 71.2%) and included collection of anti-coagulated blood, a physical examination, and a panel of laboratory tests at baseline [18]. Every participant also completed a self-administered questionnaire on his or her medical and personal history, including lifestyle

factors. Men were mainly enrolled from 1974 to 1982, while women were enrolled from 1977 to 1979 and then again from 1983 to 1992. Additionally, men and women of different ages were targeted at different time points during recruitment (Table 1), resulting in different mean ages and follow-up periods within the cohort. A detailed description of the recruitment and screening protocol has been published previously [15, 18].

In total, there were 22,444 men and 10,902 women recruited between 1974 and 1992. In the original database mean age for men and women were 49.7 years and 43.7, respectively. We excluded participants with prevalent cancer diagnoses, a history of cancer diagnoses other than non-melanoma skin cancer (n=1,233), or missing (n= 131) or implausible (>600 μmol/L or <30 μmol/L; n=10) serum creatinine measurements at baseline. We divided males and females into younger and older cohorts, respectively. Due to the unique sampling scheme and age distribution of this study, male and female cohorts were not evenly age distributed. We performed separate analyses of older men (age 60), younger men (age 40–52), older women (age 47–57) and younger women (age 35–43), respectively. Consistent with the original study design, no men between 53 and 59 years or women between 44 and 46 were invited to participate in MPP. Among the 33,346 MPP-participants, men who were younger than 40 (n=6,797), women younger than 35 (n=572), or between age 43 and 47 (n=51) at baseline were not included in our current analysis, leaving 24,552 MPP-participants available for these analyses (Table 1). Incident cases of cancer were identified by linking this database to the Swedish Cancer Registry, updated to December 31, 2006. Data on cardiovascular disease morbidity and mortality (incident coronary event or stroke: ICD-10 diagnoses I20–25, I61–69, I70–72, I74, or ICD-9 diagnoses 410–414, 431–438, 440–442, 444) were retrieved from the National Inpatient Registry and from the National Mortality Registry. Smoking was defined as a positive response to one or more of the following questions: “Have you ever smoked regularly more than 6 months?”"Are you a current smoker?”, or “Do you smoke daily?”.

Laboratory methods

During the study period two different instruments were used to measure creatinine at Department of Clinical Chemistry at the University Hospital (MAS) in Malmö. From 1974 to 1980, creatinine was measured with the Jaffe method using a Technicon Auto Analyzer II. The reference range was 80–115 μmol/L for men and 60–100 μmol/L for women. From 1980 until the end of the study, creatinine was measured with the Jaffe method on a Prisma analyzer. The reference range was 80–115 μmol/L for men and 60–100 μmol/L for women.

eGFR

For our main analyses, GFR was estimated using the CKD-EPI formula. CKD-EPI GFR = $141 \times \min(\mathrm{Scr}/k, 1)^{a} \times \max(\mathrm{Scr}/k, 1)^{-1.209} \times 0.993^{\mathrm{Age}} \times 1.018$ [if female] × 1.159 [if black], where Scr is serum creatinine, k is 0.7 for females and 0.9 for males, a is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1 [19]. Adjustment for race was not necessary in this homogenous cohort of people of Caucasian race. If not stated otherwise CKD-EPI was the primary eGFR method used throughout the study. As a sensitivity analysis, we also estimated GFR using the Cockroft-Gault (CG) formula [20]. In order to compare the eGFR formulas we adjusted CG for body surface area (BSA) to CG/BSA in mL/min/1.73 m^2 by estimating BSA for all MPP-participants from the duBois formula [21]. For our analyses we classified GFR into the following two categories: normal kidney function or mild kidney disease (eGFR≥60 mL/min/1.73m^2) or moderate kidney dysfunction (eGFR<60 mL/min/1.73m^2) [22]. Less than one percent of the study population (n=120) presented with a GFR <50 mL/min/1.73m^2.

Statistics

Our primary aim was to determine whether there was an association between impaired renal function and subsequent development of cancer. As participants with impaired renal function were assumed to be at greater risk of death from other causes (most notably cardiovascular disease), we used competing risks regression to test the association of cancer diagnosis with eGFR with death from other causes as the competing risk.

Our primary analyses include all incident cancers as the outcome. Secondary analyses evaluated the association separately for specific cancers (breast, prostate, kidney, urinary tract, and lung). We performed all analyses univariately and adjusted for smoking history and age. We also evaluated the association between renal function and cardiovascular disease to confirm the representativeness of our study population. For the cardiovascular analyses, death from any cause was the competing risk.

Ethical considerations

The study was approved by the regional ethics committee at Lund University, Sweden, LU 85/2004 and all subjects provided written consent to participate in the study, allowing the investigators to retrieve information from medical records, the National Inpatient Registry, and the Swedish Cancer Registry.

Results

Patient characteristics are shown in Table 1. The median age at baseline for the four groups of participants was 60, 47, 54, and 40 years for older men, younger men, older women, and younger women, respectively. The median follow-up time for participants was 28 years (older men 28 years, younger men 29 years, older women 23 years and younger women 31 years). In general the men tended to have higher smoking rates (78% and 72% for older and younger cohorts, respectively) than the women (50% and 58%, respectively). Median GFR values were slightly lower in the older cohorts (75 and 77 for the men and women, respectively) than in the younger cohorts (85 and 87, respectively). Overall, few subjects (n=854; 3.5%) had moderately impaired renal dysfunction at baseline; this proportion was higher in older subjects (10% of men; 2% of women) than younger subjects (7% of men; 1% of women). Lastly, Table 1 also illustrates the unique sampling scheme.

In total there were 441, 4,015, 1,724, and 415 incident cases of cancer in the older men, younger men, older women, and younger women, respectively (Table 2). We analyzed the cumulative incidence of cancer in each of the cohorts, adjusted for the competing risk of death from other causes. For participants with GFR ≥60 mL/min/1.73m^2 versus GFR <60 mL/min/1.73m^2 at baseline the 15-year probability of cancer was 23% versus 19%, 7% versus 6%, 14% versus 13%, and 10% versus 10% in the older men, younger men, older women and younger women, respectively Hence, there was no evidence of an association between moderately impaired renal function at baseline and increased risk of developing cancer in older men (sub-hazard ratio (SHR): 0.80; 95% CI: 0.57, 1.12; p=0.2), younger men (SHR: 0.84; 95% CI: 0.64, 1.10; p=0.2), younger women (SHR: 0.91; 95% CI: 0.39, 2.14; p=0.8) or older women (SHR: 0.93; 95% CI: 0.77, 1.13; p=0.5) compared to normal or slightly decreased GFR (Table 3). Moreover, adjustment for age and smoking history did not importantly change these estimates (Table 3). These hazard ratios, both with and without adjustment for age and smoking history, clearly suggest that impaired renal function is unlikely to have an important impact on the long-term risk of cancer (Table 3).

The detailed information from the Swedish Cancer Registry made it possible to study separate cancer types. Overall, we did not find any association between impaired renal function and incidence of urinary bladder or lung cancer (Table 2). However, we did find a

statistically significant increased risk of later diagnosis of kidney cancer associated with moderately impaired renal function at baseline in younger men (14,254 participants and 118 cases of kidney cancer) (SHR, 3.38; 95% CI, 1.48 to 7.71; P=0.004). For older men the SHR for kidney cancer was 1.35 (95% CI, 0.31 to 5.94; p=0.7) and for older women SHR for kidney cancer was 1.92 (95% CI, 0.58 to 6.41; p=0.3). For younger women there were only six reported cases of kidney cancer, which meant that it was not possible to fit a competing risk model.

We performed several sensitivity analyses of our findings. First, we recalculated eGFR using the CG formula, instead of the CKD-EPI formula, and adjusted for body surface area (BSA) (Table 4). Overall, our findings were not importantly different from our main results using CKD-EPI.

We also conducted sensitivity analyses where we excluded cancers that are commonly detected by screening (ie, prostate and breast cancer). These cancers may be more frequently found in participants with impaired renal function as they may be more intensely monitored by medical practitioners. Conversely, participants with impaired renal function could be less likely to be subject to cancer screening due to their higher risk of death from other causes. Again, we found that our results were not significantly changed (Table 5).

Our last sensitivity analyses evaluated the previously established association between impaired renal function and increased risk of cardiovascular disease, which served as a positive control and a further check of our methods. In total, there were 308, 2558, 473 and 50 incident cases of cardiovascular disease in the older men, younger men, older women, and younger women, respectively. We found a significant association between impaired renal function and increased risk of a cardiovascular event in the older men, younger men and older women when controlling for age and smoking history (Table 6). The risk could not be estimated in the younger women as few women had impaired GFR (20/1668) and none of them had a coronary event during the follow-up period.

Discussion

The aim of this study was to evaluate whether moderately decreased GFR is associated with cancer. To detect changes in cancer incidence within a narrow GFR range, it is necessary to have a large cohort linked to data on vital status, comorbidity and highly accurate cancer registry data from long-term follow-up. In this large and highly representative population-based cohort from a cross-sectional screening program with a median follow-up of 28 years, we found no association between overall risk of cancer and moderately impaired renal function compared to normal or close-to-normal renal function at baseline. However, we did find that the long-term risk of kidney cancer among younger men with moderately impaired renal function at baseline was significantly higher than those with normal or mild kidney function impairment at baseline. Furthermore, these findings were not importantly different when we used an alternative formula to estimate eGFR or when we adjusted for smoking history. Consistent with previously established findings, we also found a significantly increased risk of cardiovascular events among men and women with moderately impaired renal function at baseline. This is important as it demonstrates that this large, representative cohort is highly informative in reference to long-term health risks associated with moderately impaired kidney function.

Previous studies have shown that patients on dialysis have a higher prevalence of renal cell carcinoma than the general population [8], but the first reported data [9] on the increased incidence of malignancy in uremic patients have been criticized as inconclusive due to lack of control groups. A few studies have suggested an increased risk of cancer in patients with

early stages of CKD [12, 13]. However, Wong et al were unable to find any increased risk among those with stage 2 CKD (GFR 60–90 mL/min/1.73 m2) (n=2,153) [13]. At a mean follow-up time of 9.1 years, Jorgensen et al [12] found higher incidence of bladder and lung cancer in both men and women with CKD but only a non-significant trend to associate with renal cancer and no association with colo-rectal, breast or prostate cancer. Adjustment for GFR did not change their results, and an increased cancer risk associated with albuminuria was not clarified [12]. A study from Norfolk [23] did not find any association between albuminuria and cancer. Weng et al analyzed a large cohort (n=123,000) and found an increased risk of death from liver, kidney, and urinary tract cancer in subjects with CKD vs. those without CKD. The mean age among subjects with CKD was 66 years [14]. Our current study showed an increased risk of kidney cancer in subjects with moderate CKD, but only in younger men.

There are several differences in patient characteristics that may help explain the various findings. Compared to our current study, the mean age at inclusion was about 20 years higher in the studies by Wong and Weng. There were 6,595 cases of cancer diagnosed in our study compared to 711 cases of cancers included in the report by Wong [13], and there were 1,117 deaths due to cancer in the study by Weng et al [14]. Also, MPP-participants had higher average GFR compared to Wong (78 vs 65 mL/min/1.73m^2). Individuals with eGFR < 30 mL/min/1.73 m^2 were rare in both studies.

The MPP cohort was designed for studies of the risk of cardiovascular diseases and metabolic intervention studies but also for the study of risk of cancer, eg breast cancer and prostate cancer [16, 17]. The invitation of relatively young persons in Malmö, a city with a low migration of the population and only one hospital, facilitates long term follow-up. Female persons were not included at start and they were only half as many as the male persons. The original MPP cohort demonstrates an uneven distribution of men and women with respect to numbers and ages. No men between 53 and 59 years or women between 44 and 46 were invited to participate in MPP. Thus, in this study the four groups also differ in ages due to this unique sampling at inclusion. Men were younger in the whole cohort and this explains why the group of young men is the greatest.

The strengths of our study are a large population-based cohort with a high participation rate (71 %), a follow-up period close to 30 years, similar methodology to estimate creatinine throughout the study, and a middle-aged population with long life expectancy. The relatively young age at inclusion and long follow-up in a population-based cohort makes it possible to study biological processes over many years.

The limitations of our study include the small number of individuals with eGFR below 50 mL/min/1.73m^2. The analysis is based on a measure of creatinine at a single point which may diminish the ability to find changes of renal function over time. The lack of statistical significance for increased risk of kidney cancer among women and older men may be due to too few observations. Therefore, it remains possible that increased risk of kidney cancer is present in other groups, although gender-specific differences may still exist. One causative factor for our findings might be that patients with renal impairment undergoes ultrasound examination which may increase detection of renal tumours. We can not rule out this possibility. However, these mild impairments of renal function are seldomly found by the primary care physicians using serum creatinine as screening for renal function. Thus, the use of ultrasound is not frequent in moderately impaired renal function.

We used the CKD-EPI formula as it is recognized as the most reliable formula for eGFR based on creatinine. However, we also made calculations from CG and MDRD (not shown)

without showing any important differences in our results on association between renal cancer and decreased GFR in younger men.

There are several reasons why chronic kidney disease may be associated with higher risk of cancer. The prevalence of other risk factors, such as age, smoking, metabolic disorders and obesity, are greater among those with CKD, which is why we adjusted for age and smoking status in our analyses. We did not have data on metabolic diseases.

In patients on dialysis the uremic environment may be a significant factor promoting the development of malignancy. Retention of uremic toxins, low molecular mass substances, can impair the immune system. This complex interaction has been demonstrated in patients with end-stage renal disease [24, 25]. Faure et al [25] found that p-cresol, by impairing transendothelial migration of leukocytes, may play a role in the immune dysfunction of uremic patients. Altered immune status and accumulated carcinogenic factors in a uremic environment might promote the development of neoplasia. This explanation is not likely in these individuals with only mildly impaired renal function. With the confirmation of an association between CKD and kidney cancer in younger men, other potential mechanisms should be further explored.

Another variable that may have impacted our study population is use of the drug phenacetin during the 1950s and 1960s. Phenacetin is an analgesic associated with kidney damage and cancer of the renal pelvis but not kidney cancer. The participants in the MPP-cohort may have been exposed to phenacetin, but as we did not detect an increased risk of renal pelvis cancer, it is unlikely that phenacetin contributes an important cancer risk in this cohort.

In conclusion, few studies, including ours, show an increased risk of kidney cancer among younger men with eGFR less than 60 mL/min/1.73m^2. However, we can not rule out an increased risk for women since our female cohort was smaller. These findings should be explored further to discover possible pathological mechanisms of carcinogenesis and identify more specific high-risk groups. Surveillance for kidney cancer with ultrasonography may be appropriate for high-risk groups.

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Abbreviations

CKD	chronic kidney disease
GFR	glomerular filtration rate
eGFR	estimated GFR
CG	Cockroft-Gault
CKD-EPI	chronic kidney disease epidemiology collaboration

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Table 1

Participant characteristics and distribution of years of MPP-enrollment and assessment at baseline (e.g. creatinine, smoking history), separately for older men, younger men, older women and younger women

All values are median (IQR) or frequency (proportion).

	Older men N=1,132	**Younger men N=14,254**	**Older women N=7,498**	**Younger women N=1,668**
Age at baseline, years	60 (60, 60)	47 (45, 48)	54 (51, 56)	40 (39, 42)
Smoking history	880 (78%)	10301 (72%)	3727 (50%)	966 (58%)
Creatinine, μmol/L	95 (86, 104)	93 (85, 101)	76 (69, 83)	74 (67, 82)
eGFR (CKD-EPI) mL/min/1.73m^2	75 (67, 84)	85 (76, 95)	77 (69, 87)	87 (77, 97)
eGFR (CG/BSA) mLmin/1.73m^2	73 (61, 86)	87 (74, 103)	62 (52, 74)	67 (56, 81)
eGFR<60 (CKD-EPI) *mL/min/1.73m^2*	115 (10%)	215 (2%)	504 (7%)	20 (1%)
eGFR<60 (CG/BSA) mL/min/1.73m^2	238 (21%)	852 (6%)	3308 (44%)	569 (34%)
Year of screening				
1974–1976	0 (0%)	3891 (27%)	0 (0%)	0 (0%)
1977–1979	0 (0%)	4721 (33%)	1070 (14%)	898 (54%)
1980–1982	1132 (100%)	4733 (33%)	0 (0%)	0 (0%)
1983–1984	0 (0%)	909 (6%)	1471 (20%)	770 (46%)
1985–1992	0 (0%)	0 (0%)	4957 (66%)	0 (0%)

Table 2

Distribution of specific cancer types

Any cancer are all cancers after exclusion of participants with prevalent cancer diagnoses and a history of cancer diagnoses other than non-melanoma skin cancer. Numbers and (percent) are shown in the four groups.

	Older men N=1,132	Younger men N=14,254	Older women N=7,498	Younger women N=1,668
Any cancer	441 (100%)	4015 (100%)	1724 (100%)	415 (100%)
Prostate	115 (26%)	1213 (30%)	-	-
Breast	-	-	541 (31%)	146 (35%)
Lung	70 (16%)	495 (12%)	132 (8%)	28 (7%)
Urinary	38 (9%)	352 (9%)	48 (3%)	5 (1%)
Kidney	15 (3%)	118 (3%) *	25 (1%)	6 (1%)
Other	202 (46%)	1829 (46%)	978 (57%)	230 (55%)

* Denotes statistically significantly increased risk in subjects with eGFR less than 60 vs. those with more than 60 mL/min/1.73 m^2.

Table 3

Competing risk regression models for the association between renal function at baseline and long-term risk of cancer diagnosis

Sub-hazard ratio(SHR) for eGFR<60 mL/min/1.73m^2 compared to normal or slightly decreased GFR. eGFR estimated from CKD-EPI. Competing risk is death without cancer diagnosis.

	Unadjusted		Adjusted for smoking history and age	
	SHR (95% CI)	**P-value**	**SHR (95% CI)**	**P-value**
Older men	0.80 (0.57, 1.12)	0.2	0.81 (0.58, 1.13)	0.2
Younger men	0.84 (0.64, 1.10)	0.2	0.80 (0.61, 1.06)	0.12
Older women	0.93 (0.77, 1.13)	0.5	0.92 (0.75, 1.12)	0.4
Younger women	0.91 (0.39, 2.14)	0.8	0.90 (0.39, 2.07)	0.8

Table 4

Sensitivity analyses 1

Competing risk regression models for the association between renal function at baseline and long-term risk of cancer diagnosis. Sub-hazard ratio for eGFR<60 mL/min/1.73m^2 compared to normal or slightly decreased GFR. In this sensitivity analysis eGFR was estimated using CG/1.73*BSA formula instead of CKD-EPI. Competing risk is death without cancer diagnosis.

	Unadjusted		Adjusted for smoking history and age	
	SHR (95% CI)	**P value**	**SHR (95% CI)**	**P value**
Older men	0.85 (0.70, 1.05)	0.13	0.86 (0.70, 1.05)	0.14
Younger men	0.97 (0.87, 1.09)	0.6	0.93 (0.83, 1.04)	0.2
Older women	0.94 (0.85, 1.03)	0.18	0.92 (0.83, 1.01)	0.078
Younger women	0.96 (0.76, 1.21)	0.7	0.94 (0.75, 1.19)	0.6

Table 5

Sensitivity analyses 2

Competing risk regression models for the association between renal function at baseline and long-term risk of cancer diagnosis excluding prostate or breast cancers. Sub-hazard ratio for eGFR<60 mL/min/1.73m^2 compared to normal or slightly decreased GFR. eGFR estimated from CKD-EPI. Competing risk is death without cancer diagnosis.

	Unadjusted		Adjusted for smoking history and age	
	SHR (95% CI)	**P value**	**SHR (95% CI)**	**P value**
Older men	0.84 (0.57, 1.23)	0.4	0.84(0.58, 1.24)	0.4
Younger men	0.88 (0.64, 1.20)	0.4	0.85 (0.62, 1.17)	0.3
Older women	1.02 (0.82, 1.28)	0.8	0.99 (0.79, 1.25)	1
Younger women	1.13 (0.43, 2.97)	0.8	1.11 (0.43, 2.84)	0.8

Table 6

Competing risk regression models for the association between renal function at baseline and subsequent risk of cardiovascular event (defined as an incident coronary event or stroke)

Sub-hazard ratio for eGFR<60 mL/min/1.73m^2 compared to normal or slightly decreased GFR. Competing risk is death without cardiovascular disease. There were no coronary events among younger women.

	Unadjusted		Adjusted for smoking history and age	
	SHR (95% CI)	**P value**	**SHR (95% CI)**	**P value**
Older men	1.38 (1.00, 1.90)	0.051	1.40 (1.01, 1.93)	0.043
Younger men	1.54 (1.18, 2.01)	0.002	1.43 (1.09, 1.87)	0.009
Older women	1.48 (1.09, 2.03)	0.013	1.41 (1.03, 1.93)	0.03