



Cancer

The long-term rapid increase in incidence of adenocarcinoma of the kidney in the USA, especially among younger ages

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Editorial decision 4 June 2019; Accepted 17 June 2019

Abstract

Background: We previously observed a rapid increase in the incidence of renal cell carcinoma (RCC) in men and women between 1935 and 1989 in the USA, using data from the Connecticut Tumor Registry. This increase appeared to be largely explained by a positive cohort effect, but no population-based study has been conducted to comprehensively examine age-period-cohort effects by histologic types for the past decade.

Methods: We calculated age-adjusted and age-specific incidence rates of the two major kidney-cancer subtypes RCC and renal urothelial carcinoma, and conducted an age-period-cohort analysis of 114 138 incident cases of kidney cancer reported between 1992 and 2014 to the Surveillance, Epidemiology, and End Results programme.

Results: The age-adjusted incidence rates of RCC have been increasing consistently in the USA among both men and women (from 12.18/100 000 in 1992–1994 to 18.35/100 000 in 2010–2014 among men; from 5.77/100 000 in 1992–1994 to 8.63/100 000 in 2010–2014 among women). Incidence rates generally increased in successive birth cohorts, with a continuing increase in rates among the younger age groups (ages 0–54 years) in both men and women and among both Whites and Blacks. These observations were confirmed by age-period-cohort modelling, which suggested an increasing birth-cohort trend for RCC beginning with 1955 birth cohorts, regardless of the assumed value for the period effect for both men and women and for Whites and Blacks.

Conclusions: Known risk factors for kidney cancer may not fully account for the observed increasing rates or the birth-cohort pattern for RCC, prompting the need for additional etiologic hypotheses (such as environmental exposures) to investigate these descriptive patterns.

Key words: Renal cell carcinoma, descriptive epidemiology, SEER

Key Messages

- We previously observed a rapid increase in the incidence of renal cell carcinoma (RCC) in both men and women from 1935 to 1989 using data from the Connecticut (USA) Tumor Registry.
- We conducted age-period-cohort analyses of kidney cancer rates in the USA using data from the population-based Surveillance, Epidemiology, and End Results programme from 1992 to 2014.
- Our findings suggest a rapid increase in RCC rates among younger age groups between 0 and 54 years of age in both men and women in the USA, and an increasing birth-cohort trend for RCC beginning with 1955 birth cohorts.
- Known risk factors for RCC may not fully account for these patterns, prompting the need for additional etiologic hypotheses.

Introduction

The American Cancer Society estimates that at least 65 340 new cases of kidney cancer will be diagnosed in 2018 in the USA.¹ Kidney cancer is one of the most common malignancies in adults¹ and includes two major histologic types: renal cell carcinoma (RCC, also known as renal cell adenocarcinoma) and renal urothelial carcinoma (RUC). RCC originates in the renal parenchyma and is the most common type of kidney cancer in adults, responsible for about 90–95% of cases. It is also the most lethal of the malignant urological tumours.² RUC originates in the lining of the renal pelvis (also known as urothelial carcinomas) and contributes to about 5–10% of kidney cancers. Kidney cancer also includes several other rare histologic types, such as renal sarcoma (<1%) and Wilms tumour (occurring in children).²

Using data from the Connecticut Tumor Registry, the oldest population-based cancer registry in the USA, we previously observed a rapid increase in the incidence of RCC in both men and women from 1935 to 1989, and this observed increase appeared to be largely explained by a positive cohort effect (i.e. from the changes in the risk factors of the disease of interest).³ Based on this cohort analysis, we predicted that rates of RCC would rise continuously in the immediate future. An increase in the incidence of kidney cancer was also reported by others,^{4,5} but no population-based study has been conducted to comprehensively examine age-period-cohort effects by histologic types for the past decade.

To better understand contemporary time trends and the potential birth-cohort pattern of histologic types of kidney

cancer in the USA, we conducted a birth-cohort analysis utilizing data from the US Surveillance, Epidemiology, and End Results (SEER) programme for the time period 1992–2014, the most recent matured data available to us. Birth-cohort analyses and age-period-cohort (APC) modelling allow us to determine the relative importance of age, period and cohort effects on the observed time trends, and thus may aid in understanding the risk factors that might be responsible for the observed time trends.

Methods

The current study was based on 114 138 incident cases of kidney cancer reported between 1992 and 2014 to the SEER programme from 13 SEER registries: Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound and Utah, Los Angeles, San Jose-Monterey, Rural Georgia and the Alaska Native Tumor Registry.⁶ Based on the coding for the site (topography) of cancer as found in the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3), cases with site code C64.9 (kidney parenchyma or kidney) and site code C65.9 (renal pelvis) were included in this study. We did not attempt to analyse the data by anatomic sub-site, due to the high percentage of cases without specification of anatomic site (ICD-O-3 C69).

Analysis by histology (as defined by ICD-O-3) was limited to the two major subtypes: adenocarcinomas (ICD-O-3 codes 8140–8389, RCC) and RUC (ICD-O-3 codes 8120, 8123 and 8130). The proportion of cases with

histological confirmation was 90% in 1992 and had increased to 94% by 2014.

Age-specific and age-adjusted incidence rates were calculated for RCC and RUC by sex (men vs women) for all the cases reported to the SEER registries during the study period. Analysis by race was limited to Whites and Blacks only because of the small numbers for other racial groups. To calculate age-specific incidence rates, cases were grouped into 5-year age intervals. Data were also presented for those aged 0–54 and 54 years and older, and for all age groups. Age-adjusted incidence rates were calculated using the direct method, standardized to the 2000 Standard US population.

The data are presented by calendar year and by cohort year of birth to explore the secular trends and potential birth-cohort patterns. An APC model was used to analyse age-specific incidence rates for both RCC and RUC. Methodological details regarding this analysis have been described elsewhere.^{7–9} Briefly, this analytical method allows a simultaneous evaluation of the effects of age, years of diagnosis (period) and generation or year of birth (cohort). APC models were based on 12 5-year age intervals beginning at age 30 years (there are very few cases reported for persons under age 30) and five period intervals (1992–1994, 1995–1999, 2000–2004, 2005–2009 and 2010–2014).

Because of the non-identifiability problem (cohort = year – age), the independent effects of age, period and cohort cannot be evaluated.^{10,11} The cohort effect can be evaluated by constraining the period effect to different assumptions (here, the

parameter values $\beta_p = 0, -0.01$ or 0.01), where $\beta_p = 0$ represents a slope of zero, $\beta_p = -0.01$ indicates that the period slope was decreasing and $\beta_p = 0.01$ denotes that the period slope was increasing during the study period. All models were fit using SAS (version 9.3).¹² The significance level was set at 0.05 for a two-sided test.

Results

A total of 114 138 incident cases of kidney cancer were reported to the SEER programme between 1992 and 2014. Of these, 99 062 (86.79%) were RCC, 8717 (7.64%) were RUC and 6359 (5.57%) were of another histologic type. In men, the overall age-adjusted incidence rates for RCC increased from 12.18/100 000 in 1992–1994 to 18.35/100 000 in 2010–2014 (Table 1). The overall age-adjusted incidence rates for RUC, on the other hand, were low and showed a slight decrease from 1.54/100 000 in 1992–1994 to 1.32/100 000 in 2010–2014. In women, the incidence rates showed similar trends during the study period: a continuing increase in RCC from 5.77/100 000 in 1992–1994 to 8.63/100 000 in 2010–2014 (Table 2), and a slight decrease in RUC from 0.80/100 000 in 1992–1994 to 0.74/100 000 in 2010–2014.

The age-specific incidence rates of RCC by median year of birth are shown in Figure 1. Examination of rates by birth cohort showed that the incidence rates for RCC generally increased in successive birth cohorts, with a more rapid increase in rates among the younger age groups under age 55 years in men (Figure 1A) and women

Table 1. Kidney cancer by two main histological types for men only

Period	Renal cell carcinoma			Renal urothelial carcinoma		
	Age-adjusted rate	Crude rate	Number of cases	Age-adjusted rate	Crude rate	Number of cases
1992–1994	12.18	9.51	5092	1.54	1.13	606
1995–1999	12.95	10.43	9703	1.45	1.08	1005
2000–2004	15.02	12.83	12 492	1.42	1.09	1065
2005–2009	17.87	16.52	16 565	1.32	1.09	1093
2010–2014	18.35	18.37	19 198	1.32	1.19	1241

Table 2. Kidney cancer by two main histological types for women only

Period	Renal cell carcinoma			Renal urothelial carcinoma		
	Age-adjusted rate	Crude rate	Number of cases	Age-adjusted rate	Crude rate	Number of cases
1992–1994	5.77	5.51	3030	0.80	0.79	435
1995–1999	6.15	5.99	5715	0.81	0.82	778
2000–2004	7.35	7.39	7377	0.75	0.78	775
2005–2009	8.73	9.23	9508	0.74	0.80	826
2010–2014	8.63	9.68	10 382	0.74	0.83	893

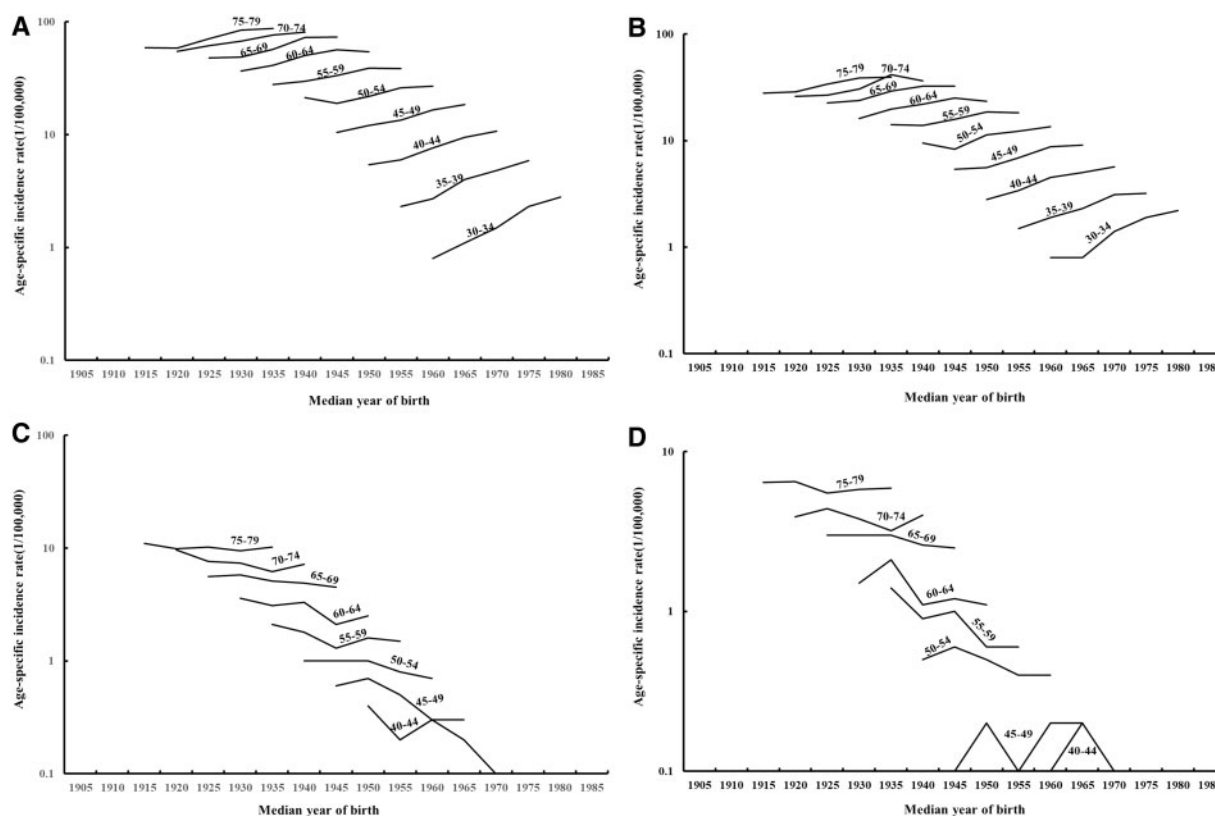


Figure 1. Incidence rates of kidney cancer presented by age and median year of birth for renal cell carcinomas for men (A) and women (B) and for renal urothelial carcinomas for men (C) and women (D).

(Figure 1B). On the other hand, incidence rates for RUC showed a decrease in successive birth cohorts in both men (Figure 1C) and women (Figure 1D), whereas the very low rates of RUC made the cohort trend unstable. Further examination of the rates for Whites and Blacks (Figure 2A–D) showed similar patterns, whereas the rates are less stable among Blacks due to the smaller numbers of cases.

Because the birth-cohort analyses showed a continuing rapid increase in RCC among the younger age group (<55 years), we analysed the time trends of RCC by age (0–54 and 55+ years) for Whites and Blacks and presented for men in Table 3 and women in Table 4. Black men and women had higher incidence rates in both younger and older age groups during the study period. The incidence rates of RCC increased continuously for the younger age group during the study period, whereas the rates for those aged 55 years and over levelled off in the last time period for both men and women and in both Whites and Blacks.

Figure 3 presents the results of APC modelling for RCC for men (Figure 3A) and women (Figure 3B). Each figure shows plots of the estimated effects for age, period and cohort, using three plausible assumptions for the period effect ($\beta p = 0, -0.01$ or 0.01). As described previously, several sets of parameters are used, as a unique set of parameters is impossible to ascertain. The resulting plots

suggested an increasing birth-cohort trend for RCC, beginning with 1955 birth cohorts, regardless of the assumed value for the period effect, for both men and women. In contrast, a decreasing birth-cohort trend was observed for RUC in both men (Figure 3C) and women (Figure 3D). Stratified analyses for Whites and Blacks showed similar birth-cohort trends as observed for the all racial groups (data not shown).

Discussion

The results of our time-series analysis of SEER incidence data from 1992 to 2014 indicate that RCC rates have indeed been increasing consistently in the USA, in contrast to RUC, for which the incidence rates have stabilized. Our cohort analysis and APC modelling confirmed that the observed increase in RCC is a birth-cohort phenomenon, which was previously observed in our study of Connecticut Tumor Registry data alone over the period 1935–1989.

What factors may be responsible for this observed long-term increase and the birth-cohort pattern for RCC in the USA? Since image acquisition and interpretation of RCC may benefit from more advanced techniques,¹³ increasing access to improved imaging technology may have led to increased earlier detection of localized kidney cancer. Several

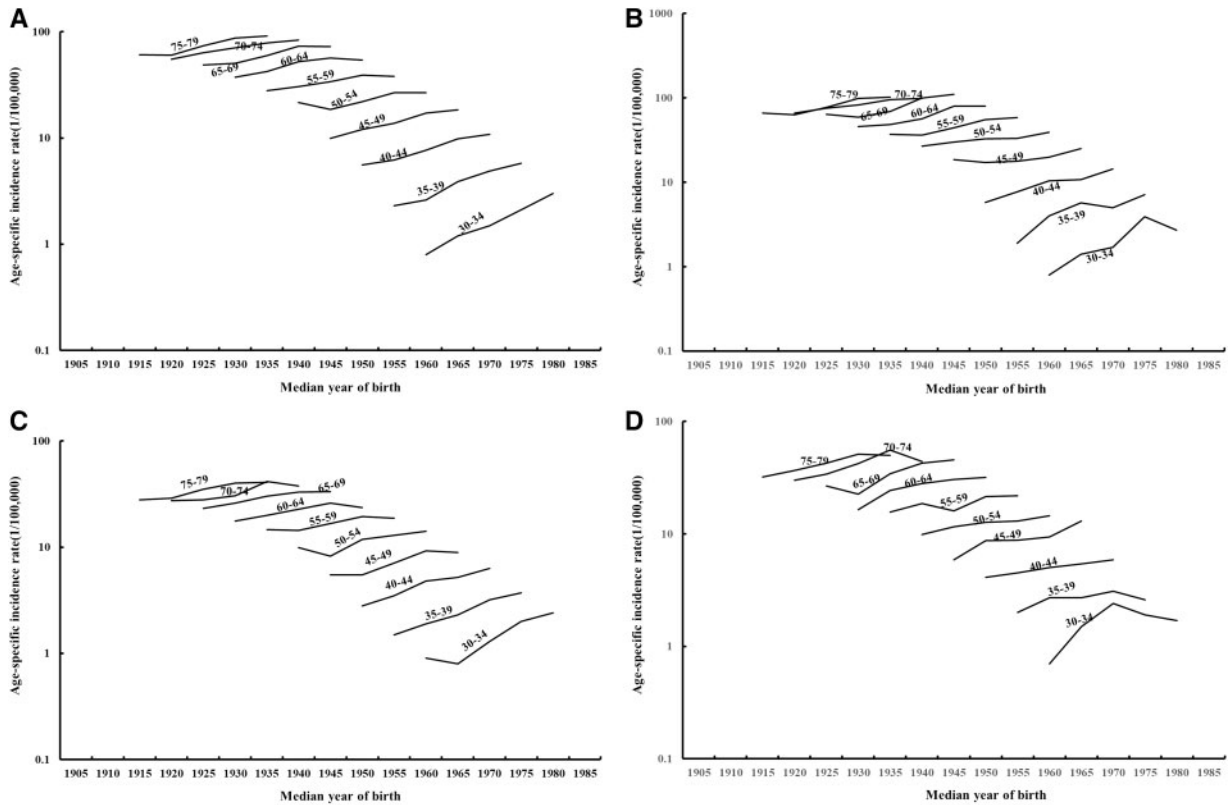


Figure 2. Incidence rates for renal cell carcinoma presented by age and median year of birth for (A) White men; (B) Black men; (C) White women; and (D) Black women.

Table 3. Crude and age-adjusted incidence rates for renal cell carcinoma (1/100 000) by age (0–54 and 55+ years) for Whites and Blacks among men only

Year of diagnosis	Whites						Blacks					
	0–54			55+			0–54			55+		
	Crude rate	Age-adjusted rate ^a	Count	Crude rate	Age-adjusted rate ^a	Count	Crude rate	Age-adjusted rate ^a	Count	Crude rate	Age-adjusted rate ^a	Count
1992–1994	3.0	3.6	1036	44.2	44.6	3224	3.1	4.8	157	51.6	51.7	349
1995–1999	3.4	3.7	1996	47.8	48.4	6049	4.0	5.4	348	52.9	54.4	638
2000–2004	4.4	4.4	2664	54.5	56.1	7573	5.2	6.2	478	61.7	64.7	847
2005–2009	5.8	5.5	3400	61.8	64.9	9789	5.9	6.6	560	80.3	85.7	1326
2010–2014	6.2	6.0	3612	61.6	65.3	11 297	7.3	8.1	715	80.5	83.3	1629

^aRates are age-adjusted to the 2000 US Standard Population.

observations, however, do not support that a period effect is likely the sole reason for the observed long-term increase in RCC rates. Whereas RCC rates have been increasing, the RUC has been decreasing during the same study period; the RCC rates increase continuously in the young age groups that clearly show a birth-cohort pattern whereas the RCC rates in the older age groups started to level off in the recent period. Taking together our previous study of Connecticut Tumor Registry data,³ the rate of RCC has been increasing in Connecticut for decades, dating back to

the period 1935–1939. In fact, if the current increasing trend in the young cohorts does not stabilize, we would anticipate a much more rapid increase in RCC in the coming years in the USA. Others have also argued against the idea that the observed increase in RCC among Blacks could be a result of long-term greater access to and utilization of imaging technologies by Blacks.^{14,15} Whereas some have suggested that kidney-cancer incidence has shown signs of stabilizing,¹⁶ this phenomenon can mostly be attributed to the flat rate among older age groups during the most recent

Table 4. Crude and age-adjusted incidence rates for renal cell carcinoma (1/100 000) by age (0–54 and 55+ years) for Whites and Blacks among women only

Year of diagnosis	Whites						Blacks					
	0–54			55+			0–54			55+		
	Crude rate	Age-adjusted rate ^a	Count	Crude rate	Age-adjusted rate ^a	Count	Crude rate	Age-adjusted rate ^a	Count	Crude rate	Age-adjusted rate ^a	Count
1992–1994	1.7	1.9	555	21.3	20.9	2005	1.7	2.2	88	22.9	23.1	217
1995–1999	1.8	1.8	1010	23.0	22.6	3688	2.2	2.7	210	25.9	26.3	436
2000–2004	2.6	2.5	1511	26.2	26.2	4477	2.7	3.0	270	29.8	30.8	564
2005–2009	3.2	3.1	1832	30.0	30.9	5659	3.0	3.1	301	36.3	38.8	815
2010–2014	3.5	3.3	1958	28.6	29.8	6070	3.5	3.5	354	34.2	35.9	922

^aRates are age-adjusted to the 2000 US Standard Population.

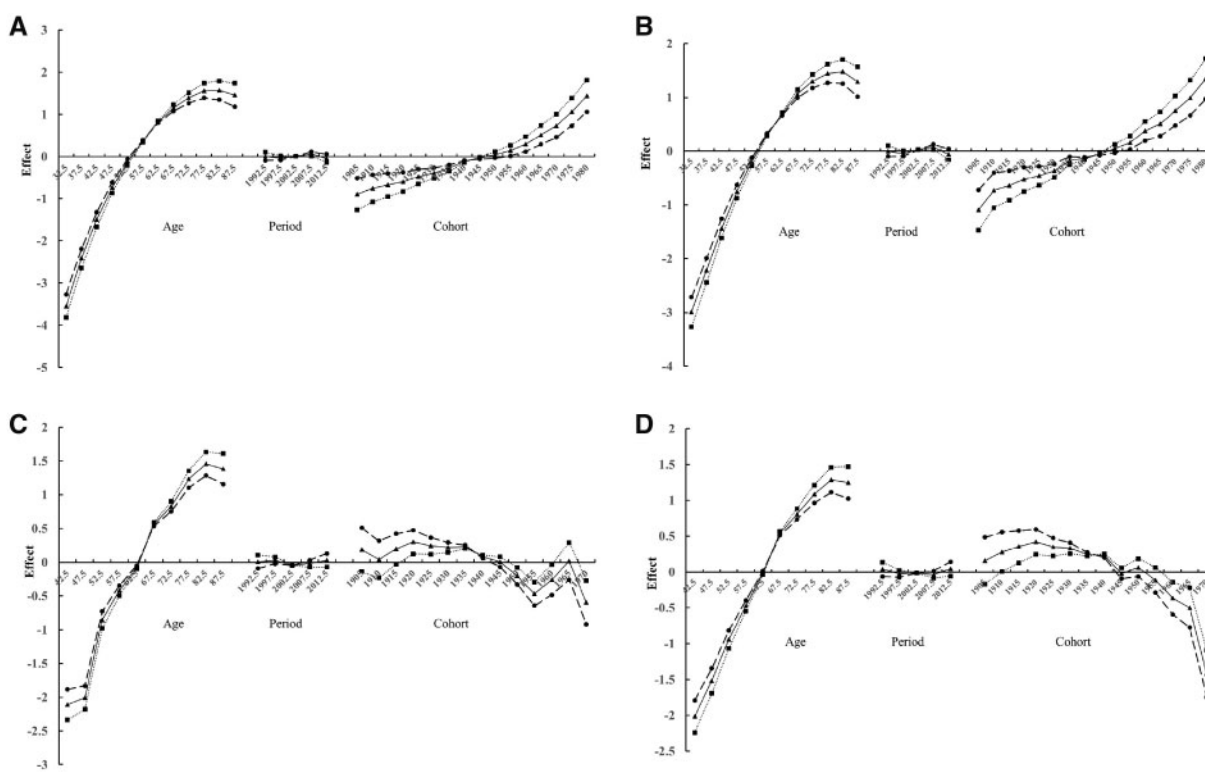


Figure 3. Age-period-cohort effects on the incidence of renal cell carcinomas for men (A) and for women (B) and on renal urothelial carcinomas for men (C) and for women (D).

period of observation. Our results clearly show a continuing increase in birth-cohort effects, without any apparent deceleration, among younger age groups.

Several factors have been linked to kidney-cancer risk, including tobacco smoking, chronic kidney diseases and dialysis treatment, obesity, hypertension, diabetes, family history of kidney cancer and rare genetic conditions.^{14–18} But, as pointed out by Lipworth *et al.*,¹⁴ ‘the factors most consistently associated with increased renal cell cancer risk in epidemiologic studies—obesity, hypertension, cigarette smoking—likely account for less than half of these cancers

among Whites, and there is scant published evidence pertaining to their association among Blacks with renal cell cancer’. These factors together also do not appear to be able to completely explain the observed time trends and the birth-cohort pattern for RCC in the USA during the past decades, as we further consider below.

Tobacco smoking

Tobacco smoking has been linked to kidney cancer and has been identified as the most significant risk factor for

RUC.^{14,19,20} Based on the report from CDC,²¹ the smoking rates have steadily declined over the past decade, from 20.9% in 2005 to 15.5% in 2016. Those who continue using cigarettes are smoking less, with the average number of cigarettes per day decreasing from 17 to 14 during the same time period. The number of people who have quit smoking has increased from 50.8% in 2005 to 59.0% in 2016, with the age range of 25–44 years making the most progress. Thus, smoking could explain the observed decrease in RUC. Smoking may even explain part of the flat rates of RCC in older age groups, especially in the last time period. However, smoking cannot explain the long-term continuing increase in rates of RCC, especially the increase in RCC incidence for those under age 54 years that have the most people quitting smoking. Indeed, almost all smoking-related cancer-incidence rates have either stabilized or started decreasing in recent birth cohorts, including adenocarcinoma of the lung in women,²² reflecting the effects of anti-smoking campaigns during the past several decades.

Chronic kidney diseases and dialysis treatment

RCC of the kidney has long been associated with chronic kidney conditions and long-term dialysis.^{14,23–27} Thus, increases in the prevalence of well-managed end-stage renal disease and of long-term dialysis may explain, in part, the high rate and increasing rate of RCC, especially among older adults.

Obesity and hypertension

The global epidemic of overweight and obesity has become a major public-health problem in the world, with recent WHO statistics revealing that 39% of adults aged 18 years and over (39% of men and 40% of women) were overweight in 2016.²⁸ In the USA, the data from the National Health and Nutrition Examination Survey (NHANES) showed that the prevalence of obesity was 39.8% in adults and 18.5% in the youth in 2015–2016.²⁹

Epidemiologic studies have linked overweight and obesity to increased risk of kidney cancer,^{14,30,31} particularly the risk of clear-cell RCC.³² Based on the literature, this relationship between obesity and risk of RCC is established. However, additional studies are needed to evaluate the risk of RCC in relation to obesity across the lifecourse.³³ In our study, the cohort analysis showed a continuing and more rapid increase in rates among younger age groups under age 55 years of both sexes in cohorts born in late 1950s and later. It is also unknown to what extent observed associations between excessive body weight and kidney-cancer risk may actually be related to initiation or the promotion and progression of existing kidney cancers. For example,

obesity-related agents such as adipokines have been shown to be both initiators of new cancerous tumours and stimulators of existing cancerous tumours.³⁴

Hypertension is an established risk factor for RCC with a dose-dependent relationship per increase in blood pressure measurement.^{14,35} Several studies have estimated the proportion of RCC cases attributable to this risk factor. In a population-based case–control study conducted in Minnesota, an estimated 21% of the RCC cases were attributable to hypertension.³⁶ Subsequently, a population-based case–control study of kidney cancer in Detroit and Chicago estimated that incidence rates of RCC would be 44% lower for Black men and 35% lower for White men in the absence of hypertension. The corresponding percentages for Black and White women were 51 and 30%, respectively.³⁷ An estimated 1 in 17 young adults under the age of 40 meets diagnostic thresholds for hypertension,³⁸ but the prevalence of this condition generally increases with age. The rising prevalence of hypertension likely contributes to the overall increasing rates of RCC in the USA, although it is currently unclear the extent to which this risk factor is driving the rate increase among younger individuals specifically.

Diabetes

Diabetes mellitus has also been associated with the risk of kidney cancer, as demonstrated, e.g., in the findings of the Nurses' Health Study (for women). Insulin, blood glucose and inflammation phenomena may have contributed to the observed association.^{39–42} A meta-analysis of cohort studies reported an overall relative risk of 1.42 (95% confidence interval = 1.06–1.91) for diabetes and kidney-cancer risk, with a stronger association in women than men. However, these results were attenuated after restricting to studies that adjusted for body mass index and cigarette smoking.⁴³

Genetics and family history

About 2–3% of kidney cancers are related to familial syndromes and several autosomal-dominant syndromes,^{44,45} but these factors cannot explain the observed birth-cohort patterns.

Occupational and environmental factors

Occupational and environmental exposure to solvents, particularly trichloroethylene (TCE), and cadmium have been associated with RCC risk.^{14,16,46,47} IARC has concluded that TCE is a human carcinogen (Group 1) that causes kidney cancer.⁴⁸ Occupational exposure to

perchloroethylene (PERC) has also been inconsistently associated with kidney cancer risk, including in a larger population-based case-control study in the USA that observed an increased risk of kidney cancer in relation to higher occupational exposure to PERC, independently of TCE.⁴⁹ Cadmium is mainly stored in the kidney⁵⁰ and positive associations with kidney cancer have been reported for cadmium and cadmium compounds.⁵¹

Concern is growing about the potential relationship between exposure to perfluorinated compounds (PFCs) and risk of kidney cancer. Humans are exposed to PFCs on a daily basis through intake of contaminated food, water, air and dermal exposure as a result of the widespread use of PFCs in consumer and industrial products since the 1950s.^{52–57} The kidney is the main organ for PFCs bioaccumulation^{58–62} and also the ‘target organ’ of PFCs. PFCs accumulated in the kidneys were shown to cause serious kidney damage and increased uric-acid levels even at the levels commonly experienced by US children/adolescents and adults.^{63–68} Higher uric-acid levels are associated with increased risk of hypertension, metabolic syndrome and chronic kidney disease in adults and children.^{69–73} PFCs at concentrations similar to exposures observed in the US population increase the production of reactive oxidative species⁷⁴ that cause renal microvascular disease⁷⁵ and result in alterations in renal microvascular endothelial cell permeability,^{74,76–78} which plays a critical role in ischemic renal injury.^{79–81} Higher body PFC levels have been linked to higher cholesterol levels in humans,^{82–86} which, in turn, is associated with an increased risk of chronic kidney disease.^{87,88} PFCs also cause a reduction in renal tubular secretion of uric acid, and thus cause an increase in body levels of uric acid,⁸⁹ which in turn is associated with increased systemic inflammation, insulin resistance, metabolic syndrome, diabetes mellitus, hypertension and chronic kidney disease.^{69,90–95} Hypertension, chronic kidney diseases and diabetes are risk factors for kidney cancer. PFCs can cross the placental barrier, reaching fetal circulation, and can also pass to infants through breast-feeding.^{96–100} PFC levels in children are generally higher than PFC levels in adults^{58,101} and, thus, children are at greater risk of developing disrupted renal physiologic functions,⁶⁴ which might make children more susceptible to the PFC exposure. Increased production of PFC products since the late 1950s and the subsequent increased population exposure also align with our APC modelling results.^{52,102} To support the hypothesis, PFC-exposed workers and residents living in PFC-contaminated communities have an increased risk of kidney cancer,^{103–107} whereas not others.^{108,109} It is interesting to note that the liver is also an organ (other than the kidney) for PFC bioaccumulation¹¹⁰ and liver cancer has been reported to be increasing during the past decades.¹¹¹ Epidemiological studies have also implicated obesity,

diabetes and cigarette smoking as risk factors for liver cancer in addition to hepatitis B and C infection.¹¹¹

Conclusion

Our analysis of the incidence of kidney cancer using SEER data suggests that RCC has increased during the past several decades and that the observed increase is a birth-cohort phenomenon. The known risk factors for kidney cancer may not fully account either for the observed increase or for the birth-cohort pattern. Population-based epidemiologic studies are urgently needed to identify the risk factors for kidney cancer that can be used to explain the observed increase and the birth-cohort pattern of kidney cancer.

Conflict of interest: None declared.

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