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Renal cell carcinoma incidence rates and trends in young adults aged 20-39 years

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ABSTRACT

Background: The burden of renal cell carcinoma (RCC) in young adults received marginal attention. We assessed contemporary gender, race and stage-specific incidence and trends of RCC among young adults (20–39 years-old) in the United States.

Methods: Within Surveillance, Epidemiology, and End Results database (2000–2016), patients aged 20–39 years with histologically confirmed RCC were included. Age-standardized incidence rates (ASR per 100,000 person-years) were estimated. Temporal trends were calculated through joinpoint regression analyses to describe the average annual percent change (AAPC).

Results: From 2000–2016, 7767 new RCC cases were recorded (ASR 0.6, AAPC + 5.0 %, $p < 0.001$). ASRs were higher in males than in females (0.7 and 0.5, respectively) and increased significantly in both genders (AAPC + 5.0 % and +4.7 % both $p < 0.001$, respectively). Non-Hispanic American Indian/Alaska Native had the highest incidence (ASR 1.0) vs. non-Hispanic Asian or Pacific Islander the lowest (ASR 0.3). ASRs significantly increased in all ethnic groups. T1aN0M0 and T1bN0M0 stages showed the highest incidence and increase (ASR 0.3, AAPC + 5.9 %, $p < 0.001$ and ASR 0.1, AAPC + 5.7 %, $p < 0.001$, respectively). Also regional and distant stages increased (AAPC + 3.7 %, $p = 0.001$ and AAPC + 1.5 %, $p = 0.06$). The most frequent tumor characteristics were G2 (44.4 %, ASR 0.3, AAPC + 6.3 %, $p < 0.001$) and G1 (13.1 %, ASR 0.1, AAPC + 1.1 %, $p = 0.2$), as well as clear cell histology (54.8 %, ASR 0.3, AAPC + 7.6 %, $p < 0.001$).

Conclusions: RCC in young adults is rare, but increasing. This is mainly due to T1aN0M0 tumors. Nonetheless, also regional diseases are significantly increasing. Differences between ethnic groups exist and may warrant further research.

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1. Introduction

Renal cell carcinoma (RCC) represents the eighth (4.2 %) most frequently diagnosed cancer, with 65,340 new cases estimated for year 2018 in the United States alone [1]. Recent data showed that North America has the highest RCC incidence worldwide, with a cumulative risk of respectively 1.8 % in males and 0.9 % in females [2]. Generally, RCC is most frequently diagnosed between ages 65–74 years with less than 9% of new cases diagnosed in patients younger than 45 years [1]. Nonetheless, cancer in young adults may be a cause of premature morbidity with long-lasting health and socioeconomic effects. To date, few studies large scale [3–6] addressed the topic of cancer burden incidence among young adults. Despite the strengths of these studies, more granular information on incidence according to race, stage and tumor characteristics in young adults is needed. Indeed, more detailed information only derived from institutional series [7–9] that however did not report on incidence rates.

We hypothesized that most RCCs in young adults are diagnosed as low risk cancers, which would confirm timely diagnosis. Nonetheless, this may also imply over-diagnosis with risk of potential unnecessary treatments and potential impairment of long-term kidney health. To test these hypotheses, we assessed incidence rates of RCC in young adults (20–39 years-old) in the United States, using the most recent version of the SEER database (2000–2016). We reported on age-standardized incidence rates and trends over time in the overall population, as well as after stratification according to gender, race, stage and tumor characteristics.

2. Materials and methods

2.1. Data source and study population

The SEER Program covers approximately 34.6 % of the U.S. population [10]. Within the SEER 18 registry database (2000–2016), we focused on patients diagnosed with primary histologically confirmed tumors of renal parenchyma (International Classification of Disease for Oncology [ICD-O] site code C64.9). Young adults were defined as those aged from 20–39 years, according to the definition of the Adolescent and Young Adult Oncology Progress Review Group [11]. Autopsy and death certificates only cases were excluded. This study followed SEER reporting guidelines. In accordance to the anonymous nature of SEER, no formal ethical approval was required.

Race was coded according to SEER race and origin code, as Hispanic within all races, non-Hispanic White (NHW), non-Hispanic African-American (NHAA), non-Hispanic American Indian/Alaska Native (NHAIAN), non-Hispanic Asian or Pacific Islander (NHAPI) and individuals of non-Hispanic unknown race. Stage was coded according to SEER summary stage (localized [T1 − 2N0M0] vs. regional [T3N0M0 or TanyN1M0] vs. distant [T4NanyM0 or TanyNanyM1] vs. unknown [TxNxMx]). Localized stage was further divided as T1aN0M0 vs. T1bN0M0 vs. T2N0M0. Grade was coded according to the SEER four-grade system from grade I, well- differentiated, which corresponds to Fuhrman G1 to grade IV, undifferentiated or anaplastic, which corresponds to Fuhrman G4 (G1 vs. G2 vs. G3 vs. G4 vs. GX). Histology was coded as clear cell vs. non-clear cell (papillary, chromophobe, cyst-associated RCC, collecting duct and sarcomatoid) vs. non-specified (NOS). Socioeconomic status was derived from an established combination of median household income, percentage of population with at least a high school education and percentage of population living 200 % below poverty level and it was divided according to quartiles (1 quartile vs 2 − 3-4 quartiles).

2.2. Statistical analysis

Total counts and incidence rates were presented. Incidence rates per 100,000 person-years were age-adjusted and standardized to 2000 United States standard population (19 age groups, United States Bureau of the Census, Current Population Reports, Publication 25–1130 [Census P25–1130]). Age-standardized rates (ASRs) represented weighted averages of age-specific rates, where weights corresponded to proportions of persons in each age group of a standard population. Zero- knot Joinpoint regression model identified changes in trends. Additionally, the average annual percent change (AAPC), which uses the underlying Joinpoint model, computed a summary measure of the trend over a pre-specified fixed interval (from 2000 to 2016) [12]. According to SEER reporting guidelines, ASRs were not reported for NH unknown race, due to the low number of observations. Survival estimates were based on the Kaplan Meier estimator. Specifically, Kaplan Meier-derived five-year cancer-specific survival rates calculated for cases diagnosed between 2000 and 2011 and reported for the overall population, as well as for all planned stratifications.

All statistical tests were two-sided with a level of significance set at $p < 0.05$. Analyses were performed using the R software environment for statistical computing and graphics (version 3.4.1; http://www.r-project.org/) and SEER*Stat (version 8.3.5; https://seer.cancer.gov/seer stat/).

3. Results

3.1. Incidence and incidence trends

From 2000–2016, 7767 new RCC cases in young adults aged 20–39 years were recorded (Table 1). The average ASR was 0.6/100,000 person-years and significantly increased from 0.4/100,000 person-years in 2000 to 0.8/100,000 person-years in 2016 (AAPC + 5.0 %, $p < 0.001$) (Fig. 1A).

Males (58.5 % of the cases) showed higher ASRs than females (average ASRs 0.7/100,000 person-years vs. 0.5/100,000 person-years, respectively). Incidence rates significantly increased over time in both males (AAPC + 5.0 %, $p < 0.001$) and females (AAPC + 4.7 % $p < 0.001$) (Fig. 1B).

After stratification according to ethnicity, NHW represented the majority (56.7 %), followed by Hispanics (22.5 %), NHAA (13.0 %), NHAPI (5.7 %) and NHAIAN (1.4 %). The ASRs were the highest in NHAIAN (average ASR 1.0/100,000 person-years), followed by NHW (ASR 0.6), NHAA (ASR 0.6), Hispanic (ASR 0.5) and NHAPI (ASR 0.3). The ASRs significantly increased over time in all ethnic groups (Fig. 1C).

After stratification according to stage, T1aN0M0 was the most frequent stage (51.4 %), followed by T1bN0M0 (19.8 %), T2N0M0 (12.1 %), regional (8.6 %), distant (6.5 %) and unknown (1.5 %). The ASRs were the highest for T1aN0M0 stage (average ASR 0.3/100,000 person-years). A significant increase over time was recorded for T1aN0M0 (AAPC + 5.2 %), T1bN0M0 (AAPC + 5.7 %), T2N0M0 (AAPC + 1.5 %) and regional stages (AAPC + 3.7 %). Conversely, the ASR of distant and unknown stages did not significantly change over time (Fig. 1D).

After stratification according to grade, G2 was most frequent grade (44.4 %) and along with G1 (13.1 %) accounted for most RCCs. The ASR of G2 was the highest (average ASR 0.3/100,000 person-years) and significantly increased over time (AAPC + 6.3 %, $p = 0.001$). Conversely, the ASR of G1 was the second lowest (average ASR 0.1/100,000 person-years) and did not change over time. The ASRs of G3 and G4 grade increased over time (AAPC + 6.0 and +8.3 %, respectively), while the ASRs of GX grade remained stable (Fig. 1E).

After stratification according to histology, clear cell was most frequent histology (54.8 %). The ASR of clear cell histology was the highest (average ASR 0.3/100,000 person-years) and significantly increased over time (AAPC + 7.6 %, $p < 0.001$). Similarly, the ASR of non-clear cell histology significantly increased over time (AAPC + 6.9 %, $p < 0.001$). Conversely, the ASRs of NOS RCC remained stable over time (Fig. 1F).

After stratification according to SES, the ASRs were the highest for

Table 1
Age-standardized incidence rates of renal cell carcinoma and corresponding average annual percentage changes in young adult patients (20-39 years-old), identified within the Surveillance, Epidemiology, and End Results database from 2000 to 2016.

		Age- standardized incidence[a]			Time trends	
	No. patients (%)	Average	From (2000)	To (2016)	AAPC	p
Overall	7767 (100)	0.6	0.4	0.8	+5.0	< 0.001
Gender						
Male	4547 (58.5)	0.7	0.4	0.9	+5.0	< 0.001
Female	3220 (41.5)	0.5	0.3	0.6	+4.7	< 0.001
Race[b]						
NHW	4386 (56.5)	0.6	0.4	0.9	+5.0	< 0.001
NHAA	1007 (13.0)	0.6	0.6	0.7	+3.4	< 0.001
NHAPI	441 (5.7)	0.3	0.2	0.4	+4.7	< 0.001
NHAIAN	110 (1.4)	1.0	0.7	1.9	+5.5	0.02
Hispanic	1744 (22.5)	0.5	0.3	0.8	+6.4	< 0.001
Stage						
T1aN0M0	3995 (51.4)	0.3	0.1	0.4	+5.9	< 0.001
T1bN0M0	1540 (19.8)	0.1	0.06	0.2	+5.7	< 0.001
T2N0M0	938 (12.1)	0.07	0.07	0.08	+1.5	0.004
Regional	671 (8.6)	0.05	0.04	0.05	+3.7	0.001
Distant	505 (6.5)	0.04	0.03	0.05	+1.5	0.06
Unknown	118 (1.5)	0.01	0.01	0.01	+2.7	0.1
Grade						
G1	1016 (13.1)	0.1	0.07	0.1	+1.1	0.2
G2	3451 (44.4)	0.3	0.1	0.4	+6.3	< 0.001
G3	1325 (17.1)	0.1	0.04	0.1	+6.0	< 0.001
G4	284 (3.7)	0.02	0.01	0.03	+8.3	< 0.001
GX	1691 (21.8)	0.1	0.1	0.2	+2.4	0.06
Histology						
Clear cell	4255 (54.8)	0.3	0.1	0.5	+7.6	< 0.001
Non-clear cell	1548 (19.9)	0.1	0.01	0.2	+6.9	< 0.001
NOS RCC	1875 (24.1)	0.1	0.2	0.1	−3.8	< 0.001

Abbreviations. AAPC = average annual percentage changes; NHW = non-Hispanic White; NHAA = non-Hispanic African-American; NHAPI = non-Hispanic Asian or Pacific Islander; NHAIAN = non-Hispanic American Indian/Alaska Native; NOS RCC = non-otherwise specified renal cell carcinoma.

[a] Age-standardized incidence rates are reported per 100,000 person/years and age-adjusted and standardized to 2000 United States Standard population (Census P25–1130).

[b] Due to low numbers, the results of non-Hispanic unknown race were not reported, according to SEER reporting guidelines.

the highest quartiles and increased to a similar extent for both the lowest and highest quartiles (average ASR 0.1, AAPC + 5.2 %, $p < 0.001$ for 1-quartile vs. average ASR 0.4, AAPC + 4.8 %, $p < 0.001$ for 2 − 3-4 quartiles).

3.2. Renal cell carcinoma survival and survival trends

The average five-year cancer-specific survival rates were 89.9 % in the overall cohort, 88.6 % in males and 91.6 % in females and significantly increased over time (Table 2, Fig. 2A-B).

Stratification according to ethnicity (Fig. 2C) showed that NHW and NHAA had respectively the highest (91.8 %) and lowest (81.7 %) average five-year cancer-specific survival rates that significantly increased in both ethnic groups over time. Conversely, five-year cancer-specific survival rates did not change over time in NHAPI, NHAIAN and Hispanics.

Stratification according to stage (Fig. 2D) showed that T1aN0M0 and T1bN0Mo stages were associated with highest five-year cancer-specific survival rates (99.3 and 97.3 %, respectively). Nonetheless, no significant changes over time in five-year cancer-specific survival rates were recorded across all stages.

Stratification according to grade (Fig. 2E) showed that lower grade was associated with better survival rates: 98.3 % in G1, 97.7 % in G2, 79.0 % in G3 and 45.1 % in G4. However, over time five-year cancer-specific survival rates only significantly improved for G3 tumors.

Stratification according to histology (Fig. 2F) showed that clear cell histology had the highest average five-year cancer-specific survival rate (93.9 %). It was followed by non-clear cell histology with five-year cancer-specific survival of 86.9 %. In both histological subtypes, the five-year cancer-specific survival rates significantly increased over time.

Stratification according to SES showed similar five-year cancer-specific survival rates for both the lowest and highest quartiles that marginally improved over time (91.4 %, AAPC + 0.4, $p = 0.1$ for 1-quartile vs. 89.3 %, AAPC + 0.8, $p < 0.001$ for 2 − 3-4 quartiles).

4. Discussion

Few previous reports investigated cancer incidence trends in young adults [3–5]. Moreover, these previous reports also focused on the whole cancer spectrum, without providing the ability to focus on RCC. In those reports [3–5], different age definition were used (15–39 years [3] vs. 20–39 years [4] vs. 25–39 years[5]). However, regardless of age definition, consistently low ASRs that were nonetheless increasing over time [5] were reported. These omissions may mask important differences in RCC distribution in young adults. In consequence, we focused on gender and race, as well as stage, grade and histology, in the most contemporary version of the SEER database (2000–2016). We hypothesized that young adults will be diagnosed at lowest stage and grade. Moreover, we also hypothesized that potential differences may exist according to ethnic groups. Our results showed several noteworthy findings.

First, average RCC incidence rates in young adults were 0.6/100,000 person-years and significantly increased from 2000 to 2016 (AAPC + 5.0 %). Our results validate previous studies, where a significant increase in RCC incidence in adolescent and young adults was reported [3–5]. Additionally, the incidence rates in young adults are much lower than those recorded for the general population [2,13–15], where incidence rates ranged from 9.4 to 12.0/100,000 person-years. These findings corroborate that RCC represents a rare entity in young

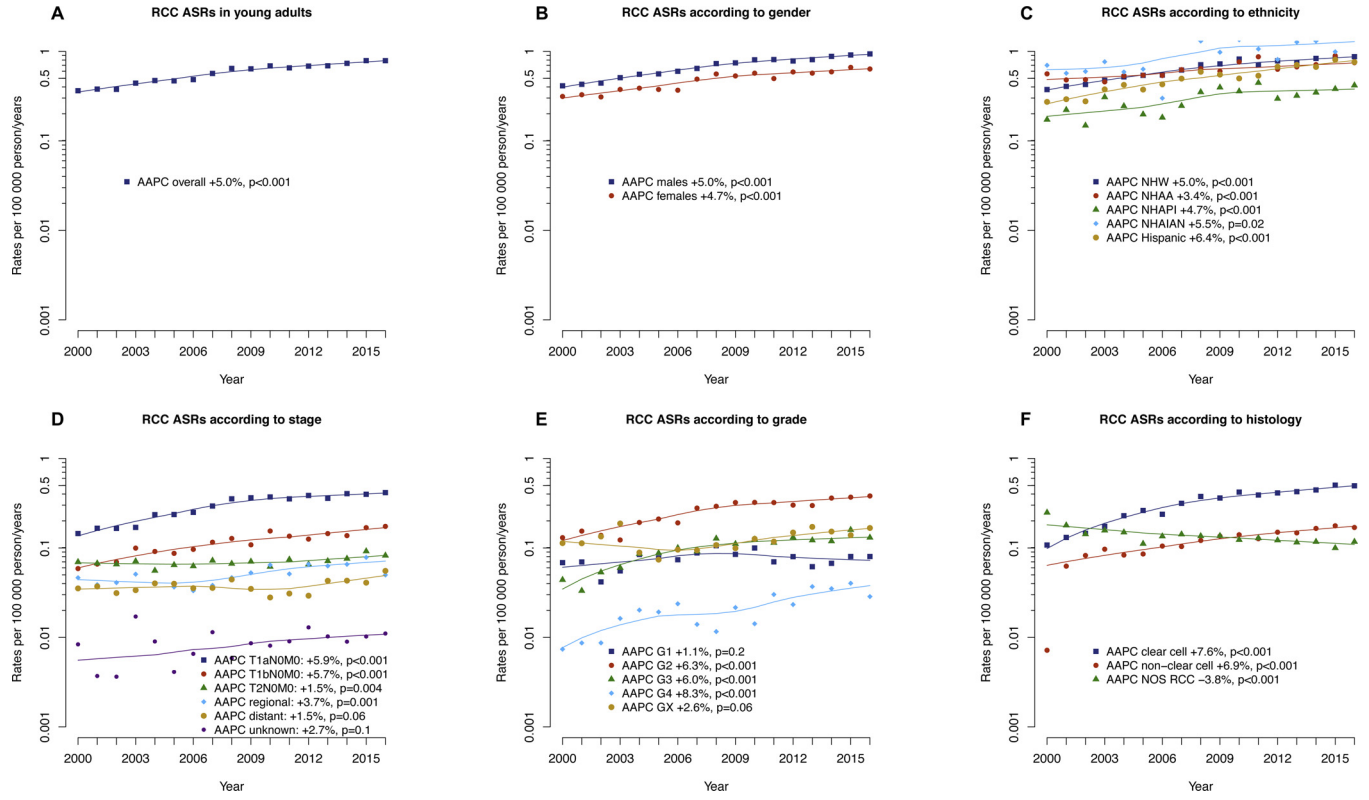

Fig. 1. Incidence and trends over time of renal cell carcinoma in young adults (20-39 years-old) in the United States from 2001 to 2016, displayed in the entire cohort (A) and by gender (B), race (C), stage (D), grade (E) and histology (F).
Abbreviations. RCC renal cell carcinoma; ASRs age-standardized incidence rates; AAPC average annual percentage changes; NHW non- Hispanic White; NHAA non-Hispanic African- American; NHAPI non-Hispanic Asian or Pacific Islander; NHAIAN non-Hispanic American Indian/Alaska Native; NOS non-otherwise specified. Incidence rates were reported per 100,000 person/years and were age-adjusted and standardized to 2000 United States standard population (Census P25–1130). Temporal trends were calculated through joinpoint regression analyses to describe the average annual percent change.

adults, since its incidence is 50-fold lower than that of the general population. However, although an increase in ASRs has been consistently reported for the general population [13,16,17], the magnitude of this increase seems to be inferior to the one reported in the current study, as well as in previous analyses of young adults [5].

Second, to date only one large scale study addressed potential incidence gender differences in incidence rates [4]. Specifically, worldwide incidence rates were 0.7 vs. 0.5/100,000 person-years and accounted for 2.2 % and 0.9 % of all new cancer diagnosis in young adults, in respectively males and females. The current analyses confirm a male predilection (0.7 vs 0.5/100,000 person-years). The higher absolute value in males validates the effect of maleness, as a risk factor for RCC in young adults. Nonetheless, virtually the same time trends were recorded for both genders, with a similar increase in incidence rates over time. Conversely, survival rates increased more in males (AAPC + 1.0 %) than in females (AAPC + 0.4 %). Nonetheless, higher absolute five-year cancer-specific survival rates were reported in females (91.6 vs. 88.6 %). These differences are in agreement with those reported by Moke et al. [18], where female gender was associated with lower mortality. These differences may be attributable to a more favorable stage and grade distribution in females, as previously described [19].

Third, racial disparities in RCC incidence have not been examined in young adults in the United States. Our analyses showed that NHAIAN and NHAPI had respectively the highest and the lowest ASRs, while Hispanics exhibited the highest increase over the study period. These findings are similar to those recently reported for the general population [16,17]. Additionally, average cancer-specific survival rates were highest for NHW and lowest for NHAA. Nonetheless, NHW and NHAA were the only two groups that exhibited a significant increase in survival rates over time. It should be noted that for some groups, differences in survival may be due to low number rather than real difference. These observations are in agreement with a previous study that investigated overall mortality among adolescent and young adults [18]. Although, in this report race and ethnicity were not mutually exclusive and the endpoint was overall rather than cancer-specific mortality, these observations suggest that some ethnic groups may harbor more renal cancers of more aggressive nature. Indeed, differences in well-established risk factors prevalence, such as smoke and hypertension, have been demonstrated across ethnic groups. For example, current cigarette smoking has the highest prevalence among NHAIAN and the lowest among NH Asian [20]. Higher rates of hypertension are recorded within NHAA, compared to NHW, while Hispanics and NH Asian have lower rates than both groups [21]. Finally, specific genetic and environmental factors may also play a prominent role in developing RCC in different ethnic groups. These groups may represent prime targets for further studies.

Fourth, T1aN0M0 RCC showed the highest ASR (0.3/100,000 person-years), as well as the highest increase over time (AAPC + 5.9 %), followed by T1bN0M0 (AAPC + 5.7 %). Nonetheless, also regional and distant stages showed an increase over time (AAPC + 3.7 %, p = 0.001 and AAPC + 1.5 %, p = 0.06, respectively). These findings are in agreement with Kehm et al. [5] that showed a significant increase in both localized and, to a lesser extent, regional stages in patients aged 25–39 years from 1975 to 2015. Moreover, they are also in agreement with data from the general population that showed highest ASRs for localized stage [13,16]. These findings may be at least partially attributable to the increasing use of cross-sectional imaging that leads to early diagnosis, as we postulated. However, this may also imply overdiagnosis with risk of potentially unnecessary treatments eventually

Table 2
Five-year cancer-specific survival rates of renal cell carcinoma and corresponding average annual percentage changes in young adult patients (20-39 years-old), identified within the Surveillance, Epidemiology, and End Results database from 2000 to 2011.

	Five-year cancer-specific survival[a]			Time trends	
	Average	From 2000 (95 % CI)	To 2011 (95 % CI)	AAPC	p
Overall	89.9	86.2 (82.4 – 90.3)	91.5 (89.1 – 94.0)	+0.7	< 0.001
Gender					
Males	88.6	84.9 (79.6 – 90.5)	90.3 (87.0 – 93.7)	+1.0	< 0.001
Females	91.6	88.0 (82.5 – 93.9)	93.5 (90.1 – 97.1)	+0.4	0.04
Race[b]					
NHW	91.8	89.3 (84.8 – 93.9)	93.4 (90.4 – 96.4)	+0.7	0.01
NHAA	81.7	73.8 (63.1 – 86.7)	89.7 (83.2 – 96.7)	+2.2	< 0.001
NHAPI	86.2	75.0 (54.1 – 100)	84.1 (73.7 – 96.7)	+0.7	0.3
NHAIAN	90.4	100.0 (100 – 100)	80.0 (51.6 – 100)	−0.7	0.6
Hispanic	90.8	90.5 (82.1 – 99.8)	91.3 (86.0 – 96.9)	+0.08	0.7
Stage					
T1aN0M0	99.3	98.3 (95.9 – 100)	99.2 (98.1 – 100)	+0.1	0.2
T1bN0M0	97.3	95.6 (89.8 – 100)	96.8 (93.3 – 100)	+0.2	0.4
T2N0M0	94.8	92.8 (86.3 – 99.8)	96.3 (99.8 – 100)	+0.4	0.2
Regional	73.9	73.6 (60.8 – 89.1)	61.5 (48.0 – 78.8)	−0.1	0.9
Distant	16.4	25.5 (13.3 – 48.6)	11.4 (3.1 – 41.2)	−1.0	0.8
Unknown	83.2	83.3 (58.2 – 100)	85.7 (63.3 – 100)	+0.3	0.9
Grade					
G1	98.3	100.0 (100 – 100)	98.0 (94.2 – 100)	+0.1	0.4
G2	97.7	95.3 (91.3 – 99.4)	99.1 (99.4 – 100)	+0.2	0.05
G3	79.0	61.1 (47.1 – 79.3)	84.7 (77.3 – 92.7)	+3.2	0.01
G4	45.0	50.0 (22.5 – 100)	43.5 (27.3 – 69.3)	+3.4	0.2
GX	81.6	80.0 (72.1 – 79.7)	86.5 (79.7 – 93.9)	+0.5	0.3
Histology					
Clear cell	93.9	90.8 (84.9 – 97.1)	95.5 (93.1 – 97.9)	+0.5	0.01
Non-clear cell	86.9	83.3 (58.3 – 100)	89.6 (83.7 – 95.9)	+0.9	0.01
NOS RCC	84.7	84.3 (79.3 – 89.5)	82.1 (74.8 – 89.9)	+0.1	0.6

Abbreviations. CI = confidence intervals; AAPC = average annual percentage changes; NHW = non-Hispanic White; NHAA = non- Hispanic African-American; NHAPI = non-Hispanic Asian or Pacific Islander; NHAIAN = non-Hispanic American Indian/Alaska Native; NOS RCC = non- otherwise specified renal cell carcinoma.

[a] Kaplan Meir-derived five-year cancer-specific survival rates. Temporal trends were calculated through joinpoint regression analyses to describe the average annual percent change.

[b] Due to low numbers, the results of non-Hispanic unknown race were not reported, according to SEER reporting guidelines.

leading to renal function impairment. Nonetheless, the significant increase in T1bN0M0, T2N0M0 and regional stages incidence may also suggest a real incidence RCC increase in young adults. Finally, survival rates remained stable over time, showing very low rates of five-year cancer specific mortality for T1aN0M0 and T1bN0M0.

Fifth, we are the first to report on incidence rates according grade and histology. Here, we validate our hypothesis that most RCC are diagnosed at lower grade (G1-G2) and with clear cell histology. These findings are encouraging, since grade is a well-known unfavorable prognostic risk factor in RCC [22] and clear cell histology can be treated with the largest spectrum of therapeutic measures that vastly exceed those available for non-clear cell. However, we also recorded an increase both higher grade (G3 or G4). The increase in non-clear cell histology is difficult to interpret due to low counts and lack of ability to further stratify non-clear cell histology patients according to specific histological subgroups and stage. Nonetheless, we recorded an increase in survival of G3 and non-clear cell tumors. These findings are highly encouraging and may suggest that an increasing proportion of favorable non-clear cell histology subtypes is diagnosed [23,24]. Nonetheless, this increase may be attributable to a decrease overtime in assignment of NOS RCC.

Sixth, the lowest SES quartile showed the lowest ASR, suggesting that poorer people who eventually have limited access to medical care may be underdiagnosed. Nonetheless, the similar incidence increased over time in both the lowest and highest quartiles may also suggest that socioeconomic factors and different access to medical care may not explain at all the rising incidence of RCC.

Taken together, RCC incidence rates in young adults were low but increased over time. This increase seems to be higher in young adults relative to that reported in the entire population. Similar to the older RCC patients, a male predilection was recorded. Differences in both incidence and survival emerged across different ethnic groups that may warrant further researches. Similar to older RCC patients, young adults were predominantly diagnosed with localized stage, low grade tumors or clear cell histology. Overall, five-year cancer-specific survival rates were high and showed an increase over time. Our findings suggest that despite the rarity of this disease, young adults seem to be promptly investigated and diagnosis is not delayed. The increasing incidence in young adults can be explained on the basis of ascertainment bias, due to over-diagnosis of small renal masses. Nonetheless, increasing incidence of higher stages, as well as similar increase in both the lowest and highest SES quartiles, may also suggest that a real increase in RCC incidence in young adults is occurring. Finally, further studies are needed to assess health-care needs in survivors, that may face lifelong risks to their physical, psychosocial, and financial health [25].

Our study is not devoid of limitations. First, our findings that relied on the United States population may not be generalizable to other Western countries. Second, although SEER relied on data-collecting protocols, missing information on stage and grade, as well as non-standardized histopathological review, may represent biases of the current study. Third, misclassification in race and ethnicity may have occurred. Furthermore, cancer rates for broad racial/ethnic groups such as Hispanic and API may mask important variation by county of origin. Additionally, low counts prevented us to further analyze stage distribution and trend over time within each ethnic group. Fourth, no standardized specimen handling, as well as no central histological review, was applied within the SEER database. Finally, it was not possible to account for some well-recognized risk factors, such as smoking, obesity and occupational exposure [26–29], since these data are not available in the SEER database.

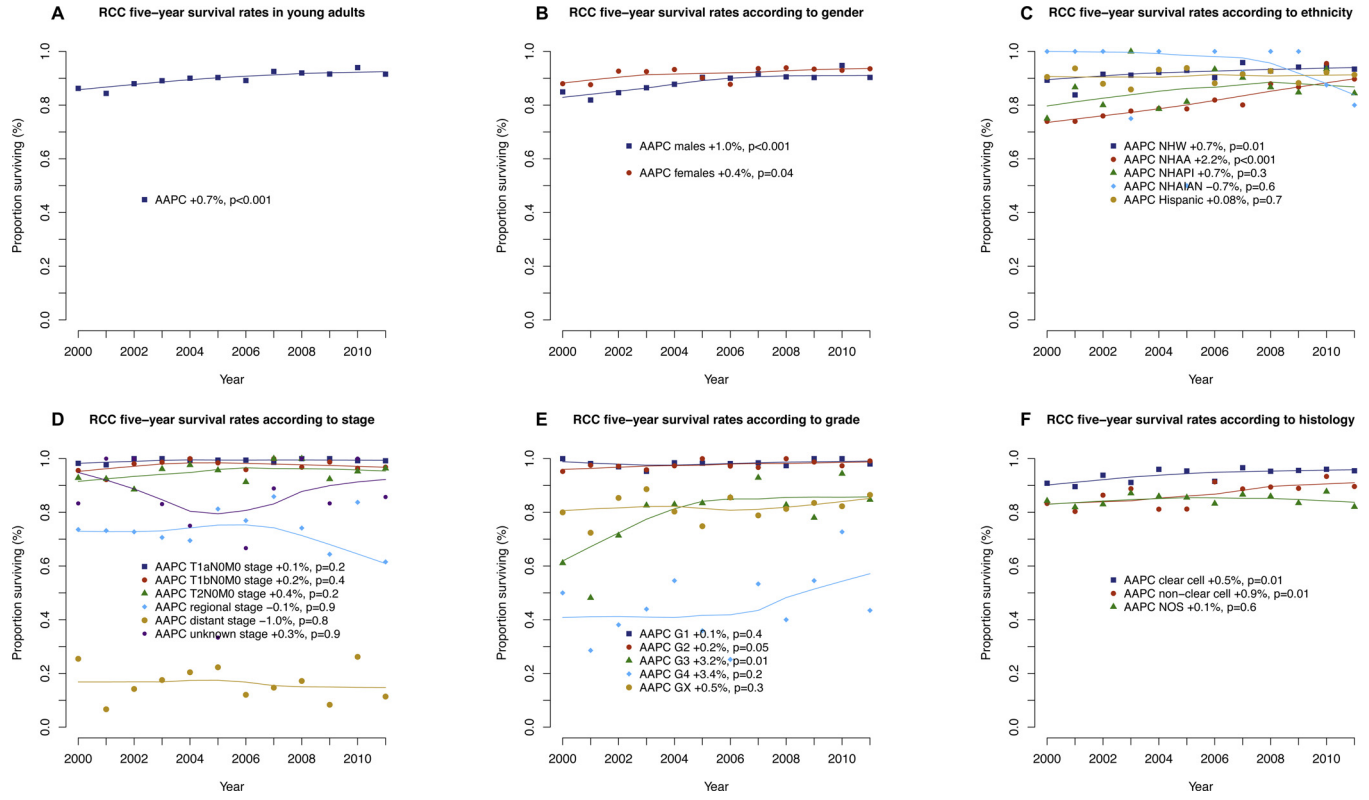

Fig. 2. Five-year cancer-specific survival and trends over time of renal cell carcinoma in young adults (20-39 years-old) in the United States from 2001 to 2011, displayed in the entire cohort (A) and by gender (B), race (C), stage (D), grade (E) and histology (F).
Abbreviations. RCC = renal cell carcinoma; ASRs = age-standardized incidence rates; AAPC = average annual percentage changes; NHW = non-Hispanic White; NHAA = non-Hispanic African-American; NHAPI = non-Hispanic Asian or Pacific Islander; NHAIAN = non-Hispanic American Indian/Alaska Native; NOS = non-otherwise specified.
Fivecancer- specific survival rates were Kaplan Meir-derived and calculated for patients diagnosed from 2001 to 2011. Temporal trends were calculated through joinpoint regression analyses to describe the average annual percent change.

5. Conclusions

RCC in young adults is rare, but increasing. This is mainly due to T1aN0M0 tumors. Nonetheless, also regional diseases are significantly increasing. Differences between ethnic groups exist and may warrant further research.

Authorship contribution statement

All the authors have made significant contribution to the manuscript.

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CRediT authorship contribution statement

Carlotta Palumbo: Conceptualization, Formal analysis, Investigation, Methodology, Writing - original draft. **Angela Pecoraro:** Data curation, Methodology, Visualization, Writing - review & editing. **Giuseppe Rosiello:** Data curation, Methodology, Visualization, Writing - review & editing. **Stefano Luzzago:** Data curation, Methodology, Visualization, Writing - review & editing. **Marina Deuker:** Data curation, Methodology, Visualization, Writing - review & editing. **Franziska Stolzenbach:** Data curation, Methodology, Visualization, Writing - review & editing. **Zhe Tian:** Data curation, Formal analysis, Validation. **Shahrokh F. Shariat:** Investigation, Writing - review & editing. **Claudio Simeone:** Investigation, Writing - review & editing. **Alberto Briganti:** Investigation, Writing - review & editing. **Fred Saad:** Investigation, Writing - review & editing. **Alfredo Berruti:** Investigation, Writing - review & editing. **Alessandro Antonelli:** Investigation, Writing - review & editing. **Pierre I. Karakiewicz:** Conceptualization, Methodology, Investigation, Supervision, Writing - original draft.

Declaration of Competing Interest

All the authors declare no potential conflict of interest to disclose

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