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A case-control study of reproductive factors and renal cell carcinoma among black and white women in the United States

Mark P. Purdue[1], **Joanne S. Colt**[1], **Barry Graubard**[1], **Faith Davis**[2], **Julie J. Ruterbusch**[3], **Ralph DiGaetano**[4], **Sara Karami**[1], **Sholom Wacholder**[1], **Kendra Schwartz**[3,5], and **Wong-Ho Chow**[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD

[2]University of Illinois at Chicago, Chicago, IL

[3]Karmanos Cancer Institute and Department of Family Medicine, Wayne State University, Detroit, MI

[4]Westat, Inc., Rockville, MD

[5]Department of Family Medicine and Public Health Sciences, Wayne State University, Detroit, MI

Abstract

Objective—Renal cell carcinoma (RCC) incidence is higher among blacks than whites in the United States, and has been associated with the frequency and timing of childbirth among women in some epidemiologic studies. We investigated whether reproductive factors are associated with RCC, overall and by race, within a population-based case-control study.

Methods—Between 2002 and 2007, 497 female cases of incident RCC (136 black, 361 white) and 546 female controls (273 black, 273 white) within the Detroit and Chicago metropolitan areas were enrolled. Information on reproductive history and other factors was collected through in-person interviews. Multivariate adjusted odds ratios (OR) and 95% confidence intervals (CI) were computed using unconditional logistic regression.

Results—Reduced RCC risk was observed among women aged ≥30 years at first live birth, relative to an age of <20 years (OR 0.5, 95% CI 0.3–0.9). This association was present among both white (OR 0.4, 95% CI 0.2–0.9) and, though not statistically significant, black women (OR 0.6, 95% CI 0.2–1.8). In analyses restricted to clear cell adenocarcinoma, the most common RCC histologic subtype, the association was particularly strong (OR 0.3, 95% CI 0.2–0.8). We did not observe clear evidence of association with RCC for other reproductive factors.

Conclusions—Our findings further support an association between late maternal age at first birth and reduced RCC risk, and suggest that the association may be particularly strong for clear cell adenocarcinoma.

Keywords

Renal cell carcinoma; reproductive factors; case-control studies; hysterectomy; parity

Address correspondence to: Mark Purdue, Occupational and Environmental Epidemiology Branch, National Cancer Institute, 6120 Executive Boulevard, Room 8114, Bethesda, MD 20892-7240; Phone number: (301) 451-5036; FAX number (301) 402-1819; purduem@mail.nih.gov.

INTRODUCTION

Renal cell carcinoma (RCC) is the deadliest form of urologic cancer, with an estimated five-year survival rate of 60%. In the United States (U.S.), RCC is diagnosed more frequently among men than women, and among blacks than whites; incidence rates within the U.S. Surveillance, Epidemiology, and End Results (SEER) program for the period 1992–2000 were 15.9, 13.4, 7.7, and 6.4 cases per 100,000 black men, white men, black women and white women, respectively [1]. The established modifiable risk factors for RCC identified to date include smoking, obesity, and hypertension [1]. Several additional possible risk factors have been reported, including diabetes, alcohol consumption, and reproductive factors [1].

Epidemiologic investigations of reproductive factors and RCC have been motivated by the observed difference in incidence by sex, the presence of estrogen and progesterone receptors in normal and malignant renal cells [2;3], and experimental evidence of estrogen effects on RCC development [4–6]. Findings from several epidemiologic studies suggest that the timing and frequency of childbirth may be associated with RCC risk in women. An increase in RCC risk with increasing number of live births has been observed in some studies [7–11], but not others [12–19], and younger maternal age at first birth has been frequently associated with increased RCC risk [8;10;11;13;15;17–19]. Other reproductive factors have generally not been associated with RCC, although some case-control studies have reported evidence of an increased risk among women who had undergone a hysterectomy or oophorectomy [7;8;12;15;16;18].

Despite the recognized racial disparity in RCC incidence, to our knowledge no studies have investigated whether associations with reproductive factors differ between blacks and whites. To address this question, we investigated the associations between RCC risk and parity, maternal age at first birth and other reproductive factors separately for white and black women in a large population-based case-control study.

MATERIAL AND METHODS

Study Population

The U.S. Renal Cancer Study was conducted in Detroit, Michigan (Wayne, Oakland, and Macomb Counties) and Chicago, Illinois (Cook County). All men and women newly diagnosed with histologically confirmed adenocarcinoma of the renal parenchyma [renal cell carcinoma (ICD-O3-C64.9)] between the ages of 20 and 79 years were eligible for study. Case ascertainment periods and procedures differed by study center. In Detroit, cases diagnosed between February 2002 through July 2006 (for whites) or through January 2007 (for blacks) were identified through the Metropolitan Detroit Cancer Surveillance System, a member of the National Cancer Institute's Surveillance, Epidemiology and End Results program. In Chicago, cases diagnosed in 2003 were identified through review of pathology reports at hospitals in Cook County. In both study centers, eligible controls were selected from the general population and frequency matched to cases on age group (5-year intervals), sex, and race. Controls aged 20 to 64 were identified from department of motor vehicle (DMV) records, while controls aged 65 to 79 were identified from Medicare eligibility files.

We designed a sampling strategy to increase the number of black participants in the study. All black cases were recruited, while some strata (age-race-sex combinations) of white cases were sampled. We frequency matched controls to cases at a 2 to 1 ratio for blacks and a 1 to 1 ratio for whites. As information on race was unavailable in the DMV records, we used the racial density of the census block group (according to the 2000 Census) in which each control resided as a surrogate for race for the purpose of sampling controls under age 65. We

oversampled people living in high density black areas to help achieve the targeted matching ratio for blacks.

Of the 762 eligible female cases identified, 54 died prior to contact or interview, 33 could not be located with the available contact information, 7 moved out of the area, and physicians of 30 refused permission to contact their patients. Among the remaining 638 cases we sought to enroll, 94 declined participation and 47 were not interviewed due to serious illness, impairment, or not responding to multiple contact attempts. Thus, 497 cases (78% of those we attempted to recruit; 136 black, 361 white) participated. Copies of medical records were obtained from all 497 cases to confirm diagnosis and collect information on histologic and clinical factors. In addition, the original diagnostic slides were obtained for 294 of these cases for review by an experienced pathologist.

Of the 1,122 presumed eligible female controls, 11 died before contact or interview, 127 could not be located, and 26 had moved away. Among the 958 controls we attempted to recruit, 289 declined participation and 123 were not interviewed due to serious illness, impairment, or not responding to multiple contact attempts. Thus, 546 eligible controls (57% of those we attempted to recruit; 273 black, 273 white) participated. The study was approved by human subjects review boards at all institutions, and written informed consent was obtained from each participant before interview. Respondents received a monetary token of appreciation for their participation.

Assessment of Reproductive Factors and Other Exposure Variables

Trained interviewers conducted computer-assisted personal interviews to collect information on demographic characteristics, height and weight, medical history, smoking history, family history of cancer, and other potential risk factors, including reproductive factors for women. Female participants provided information regarding a variety of reproductive factors, including number of live births, age at first live birth, history of hypertension or diabetes diagnosed during pregnancy, history of hysterectomy or oophorectomy, use of oral contraceptives, and post-menopausal hormone therapy use. Participants were also asked to provide blood and mouth rinse samples, and cases were asked for consent to access medical records and tumor tissue samples.

Statistical Analysis

We developed sample weights to reduce the potential for bias arising from differential sampling rates for controls and cases, from survey nonresponse, and from deficiencies in coverage of the population at risk in the DMV and Medicare files. Sample weights for controls also include a post-stratification adjustment, so that the weighted distribution of controls across the matching variables matches exactly the weighted distribution of cases. In addition to being consistent with the objectives of the frequency matching, the post-stratification adjustment reduces the variability of the weights [20].

We estimated the risk of developing RCC for different categories of each reproductive factor by computing odds ratios (ORs) and corresponding 95% confidence intervals (CIs) from multiple logistic regression models using post-stratified weights. The jackknife replicate weight method was used to estimate standard errors [21]. Regression models were adjusted for study site, age at reference date (20–44, 45–54, 55–64, 65–74, 75+ years), self-reported race (white, black), sex, education (<12 years, high school graduate, some college, 4+ years of college), smoking history as of two years before the reference date (never, occasional [smoked more than 100 cigarettes but never smoked one cigarette daily for six months or couldn’t provide a definitive answer], regular former, regular current), body mass index (BMI, based on height at interview and weight five years prior to interview, <25, 25-<30,

30-<35, 35+ kg/m^2, unknown [n=14 women]), self-reported history of hypertension as of two years before the reference date, and history of cancer among first-degree relatives (none, cancer other than kidney cancer, kidney cancer, unknown [n=10 women]). Analyses of menopausal hormone therapy use were restricted to women 55 years of age or older. Tests for trend of selected reproductive factors (number of live births, age at first live birth, oral contraceptive use, menopausal hormone therapy use) were performed by modeling the intra-category median among controls as a continuous variable. We also conducted analyses restricted to cases of clear cell adenocarcinoma (N=303), the most common RCC histologic subtype, and to more aggressive cases, defined by a Fuhrman grade of 3 or 4 (N=75). Interactions between two variables were tested by including multiplicative terms for the variables in the logistic regression, testing for the joint significance of the additional terms using the Wald chi-square test that is appropriate for weighted data [22]. Analyses were conducted with SAS software version 9.2 using procedures appropriate for sample-weighted data. All statistical tests were determined to be significant at a two-sided $p<0.05$.

RESULTS

A summary of selected characteristics of female cases and controls, stratified by race, is provided in Table 1. Black and white controls had on average a higher level of education than their respective cases. Cases of both races were more likely than their respective controls to be current smokers and to have a BMI greater than 25 kg/m^2, a history of hypertension, and a family history of kidney cancer.

Findings from analyses of number of live births and maternal age at first live birth, both among all subjects and stratified by race, are summarized in Table 2. Number of live births was not associated with RCC overall, although among black subjects weak evidence of an association was observed (3–4 [vs. 0] births: OR 1.5, 95% CI 0.7–3.4; 5+ births: OR 1.7, 95% CI 0.7–4.0; P_{trend}=0.09). A statistically significant 50% reduced risk of RCC was observed among women aged 30 years or older at first live birth, relative to an age at first live birth less than 20 years (OR 0.5, 95% CI 0.3–0.9); a test for trend in ORs across maternal age categories approached statistical significance (P=0.07). This association remained statistically significant upon additional adjustment for number of live births (OR 0.5, 95% CI 0.2–0.9) and upon restriction to white women (OR 0.4, 95% CI 0.2–0.9). A suggestive association was observed among black women, though not at a level of statistical significance (OR 0.6, 95% CI 0.2–1.8). When associations with RCC for joint effects of number of live births and maternal age at first live birth were examined, the highest risk among white women was observed for subjects with 3 or more live births who were aged <20 at their first live birth (OR 3.1, 95% CI 1.3–7.4 vs. women with 1–2 live births and aged 30+ at first birth). Among black women, the highest risk was observed for subjects who had 3 or more live births and were aged 20–29 at their first live birth, although this association was not statistically significant (OR 1.9, 95% CI 0.5–7.1). A test of interaction between these joint effects and race was statistically significant ($P < 0.0001$).

The results from analyses of other reproductive factors are reported in Table 3. There was no clear evidence of an association with RCC among women who developed hypertension or diabetes during pregnancy, although non-significant associations with increased risk were observed for having these conditions during two or more pregnancies. Among black women, associations with RCC were observed for having a history of hysterectomy (OR 1.8, 95% CI 1.1–3.1) or oophorectomy (OR 2.4, 95% CI 1.4–4.2). Among white women, no associations with hysterectomy or oophorectomy were found. However, when we conducted analyses stratified on study center (Supplemental Table 1), we observed that these associations among black women were present only among Chicago participants; findings among black women from Detroit, who make up 82% of all black subjects, were null (hysterectomy: OR

1.2, 95% CI 0.6–2.3; oophorectomy: OR 1.5, 95% CI 0.8–2.9). Use of oral contraceptives or postmenopausal hormones was not associated with RCC.

When we restricted our analyses to cases of clear cell adenocarcinoma histology (N=303 overall, 273 among parous women), we observed a stronger association with maternal age at first birth of 30 years or older (OR 0.3, 95% CI 0.2–0.8, P_{trend} = 0.007; Table 4). We also observed suggestive evidence of an association with this risk factor for RCC cases with a Fuhrman grade of 3 or 4 (N=75 overall, 65 among parous women), although the confidence limits are wide and include the null (OR 0.3, 95% CI 0.03–2.3). The findings for other reproductive factors restricted to these case subgroups did not materially change. Tests of interaction between reproductive factors and other variables (BMI, hypertension, smoking status, age, education level) were not statistically significant (data not shown).

DISCUSSION

In this population-based case-control study we found a reduced risk of RCC among women aged 30 years or older at their first live birth, relative to women aged less than 20 years at that event. This association was present among both white and, though not statistically significant, black women, and was particularly strong in analyses restricted to RCC cases of clear cell adenocarcinoma histology.

The timing and frequency of childbirth has been associated with RCC risk in several other epidemiologic studies, mainly involving white women. An inverse association with RCC for older maternal age was previously observed in four case-control studies [8;13;15;18] and four cohorts [10;11;17;19], although these findings generally achieved only borderline statistical significance. Four other studies (three case-control, one cohort) reported null findings [7;9;14;23]. Increasing number of live births has been associated with increased RCC risk in some studies [7–11], but not others [12–19]. While we did not find clear evidence of an association with number of live births in our study, we did observe a non-significant association with increased risk among black women. Moreover, in our analysis of joint effects from maternal age and number of live births among white women, the strongest association with RCC risk was observed for subjects with both a maternal age at first birth less than 20 years and three or more live births.

A variety of mechanisms potentially underlying an increased RCC risk for early and frequent childbirth have been proposed. Renal tubular cells may be rendered more susceptible to inflammation or oxidative stress through pregnancy-induced physiologic changes such as increases in maternal blood volume, cardiac output, renal plasma flow, glomerular filtration, kidney size and dilation of the renal pelvis [24;25]. It has been speculated that changes in sex hormone levels following pregnancy may influence RCC pathogenesis; evidence suggesting pro-neoplastic effects in the kidney from hormones include the induction of renal tumors in the Syrian hamster and renal cell proliferation *in vitro* following estrogen administration [4–6], as well as the presence of estrogen and progesterone receptors in normal and malignant renal cells [2;3]. We note, however, that our null findings for menopausal hormone therapy and oral contraception use do not support such hormonal effects. Lastly, pregnancy-associated weight gain may contribute towards an increased risk of RCC [9]. It is plausible that the relative risk from any such childbirth-related effects would be stronger in magnitude the earlier they begin in life, through a younger maternal age at first birth.

Our study is, to our knowledge, the first to report associations with reproductive factors for clear cell adenocarcinoma, the most common histologic subtype of RCC. We found the observed association with reduced risk for maternal age at first birth of 30 years or older to

be particularly strong for clear cell RCC, suggesting that the biologic effects underlying the timing of childbirth may be particularly relevant to the pathogenesis of this disease subtype. Subtype-specific investigations in other studies are needed to confirm this novel finding.

Our study of RCC is also the first to investigate the effects of pregnancy-related hypertension (preeclampsia) and diabetes (gestational diabetes), conditions known to be associated with an increased risk of developing hypertension and diabetes, respectively, later in life [26;27]. Overall, we did not observe associations with RCC risk for either condition, although non-significantly increased risks were observed for subjects reporting two or more affected pregnancies. Given the established role of hypertension, and possible role of diabetes, in the development of RCC [1], further investigation of these pregnancy conditions is warranted.

In our analysis we observed associations with RCC for histories of hysterectomy and oophorectomy among black, but not white, participants. Upon further analysis stratified by study center, however, the associations among black women were found to be present only among Chicago participants; the findings for the considerably larger Detroit study center (including 82% of all female black participants) were null. Given this inconsistency across study centers, we believe it is likely that our observed findings for hysterectomy and oophorectomy among black women do not reflect a real association.

Our study has several strengths. It is, to our knowledge, the first RCC case-control study with enough blacks to evaluate the effects of reproductive factors by race. Detailed information on reproductive factors was collected, enabling the evaluation of previously unstudied conditions such as pregnancy-related hypertension and diabetes. Information on smoking, hypertension, BMI, and family history of cancer allowed adjustment for potential confounders. Histologic confirmation of cases is an additional strength, as is our investigation of associations with cases of clear cell adenocarcinoma histology.

Our study also has limitations. The number of RCC cases among black women in our study (N=136) is small, which limited statistical power to detect associations of moderate magnitude. Our analyses involving oophorectomy are limited by our inability to distinguish between bilateral and unilateral procedures, and our reliance upon self-report, the accuracy of which is questionable [28]. The deaths of 54 cases prior to interview could have led to study bias if the association with a given reproductive factor is different for aggressive cases, although in the case of maternal age at first birth our finding for cases of Fuhrman grade 3 or 4 does not suggest this possibility. Another limitation of this study was the low response rate among controls, which is typical of recent population-based case-control studies. The use of sample weights can help to reduce the potential for bias arising from nonresponse, as the weights account for differential nonresponse across subgroups defined by factors such as age, sex, and county of residence, for which data were available for both respondents and nonrespondents. However, we cannot entirely rule out the possibility that selection bias influenced our results.

In conclusion, our study findings offer further evidence that late maternal age at first birth is associated with a reduced risk of RCC. The association between late maternal age at first birth and reduced RCC risk appears to be particularly strong for clear cell adenocarcinoma. Additionally, the association may also be present among black women, although we note that our finding for this racial group was not statistically significant. These new findings warrant further investigation in other studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Selected characteristics of cases and controls in the U.S. Renal Cancer Study, stratified by race.

	White Women				Black Women			
	Cases (N=361)		Controls (N=273)		Cases (N=136)		Controls (N=273)	
	N	(%)[a]	N	(%)	N	(%)	N	(%)
Age								
20–44	49	(10.7)	44	(10.6)	13	(11.7)	46	(11.5)
45–54	68	(17.1)	47	(17.6)	38	(24.9)	60	(25.8)
55–64	113	(28.1)	75	(28.2)	40	(26.5)	83	(26.8)
65–74	87	(27.3)	76	(27.0)	37	(28.0)	70	(27.7)
75+	44	(16.8)	31	(16.7)	8	(8.9)	14	(8.2)
Study center								
Chicago	41	(13.2)	41	(17.1)	26	(18.2)	48	(21.3)
Detroit	320	(86.8)	232	(82.9)	110	(81.8)	225	(78.7)
Education								
≤11 years	38	(11.1)	20	(7.6)	37	(28.2)	39	(15.2)
12 years / HS graduate / GED / Voc / Tech	166	(46.8)	100	(37.9)	41	(31.6)	86	(30.2)
1–3 years College	92	(25.5)	84	(30.7)	42	(29.8)	108	(39.6)
4+ years College / College graduate	65	(16.6)	69	(23.9)	16	(10.4)	40	(15.0)
Smoking status								
Never	161	(45.3)	128	(45.9)	62	(44.2)	112	(41.0)
Occasional / Don't know	12	(3.7)	9	(3.2)	3	(2.4)	18	(6.4)
Regular, Former	97	(27.2)	91	(35.3)	38	(28.3)	81	(31.1)
Regular, Current	91	(23.7)	45	(15.6)	33	(25.0)	62	(21.4)
Body mass index (kg/m^2)								
<25	96	(26.9)	120	(41.5)	27	(20.0)	76	(28.5)
25-<30	102	(28.3)	83	(33.2)	33	(25.9)	94	(33.2)
30-<35	74	(21.1)	39	(14.4)	28	(20.7)	54	(20.9)
35+	83	(21.9)	29	(10.5)	46	(31.5)	45	(16.3)

	White Women				Black Women			
	Cases (N=361)		Controls (N=273)		Cases (N=136)		Controls (N=273)	
	N	(%)[a]	N	(%)	N	(%)	N	(%)
Unknown	6	(1.8)	2	(0.5)	2	(1.9)	4	(1.1)
History of hypertension								
No	177	(46.1)	184	(64.9)	32	(24.0)	145	(51.8)
Yes	182	(50.4)	88	(34.5)	104	(76.0)	128	(48.2)
Unknown	2	(0.6)	1	(0.6)	0		0	
History of diabetes								
No	304	(83.9)	253	(91.6)	104	(76.8)	234	(86.2)
Yes	57	(16.1)	19	(8.0)	32	(23.2)	39	(13.8)
Unknown	0		1	(0.4)	0		0	
Family history of cancer								
No relative with cancer	140	(38.9)	100	(33.8)	65	(47.9)	151	(51.3)
Relative with kidney cancer	14	(4.2)	7	(2.7)	8	(4.9)	6	(2.2)
Relative with other cancer	205	(56.4)	163	(62.3)	61	(45.5)	113	(45.5)
Unknown	2	(0.5)	3	(1.3)	2	(1.7)	3	(1.1)

Abbreviations: HS, high school; GED, General Education Development test; Voc, vocational school; Tech, technical college.

[a]Percentages incorporate poststratified weights.

Table 2

Number of live births, age at first live birth and risk of renal cell carcinoma in the U.S. Renal Cancer Study: overall and race-specific results

	All Women		White		Black		
	N_{Case} / $N_{Control}$	OR[a] (95% CI)	N_{Case} / $N_{Control}$	OR[a] (95% CI)	N_{Case} / $N_{Control}$	OR[a] (95% CI)	P_{int}[b]
Number of live births							
0	58 / 68	1.0	45 / 36	1.0	13 / 32	1.0	
1–2	189 / 241	1.0 (0.6–1.7)	145 / 122	0.9 (0.5–1.8)	44 / 119	1.0 (0.4–2.1)	
3–4	185 / 171	1.2 (0.8–2.0)	140 / 90	1.1 (0.6–2.0)	45 / 81	1.5 (0.7–3.4)	
5+	65 / 66	1.2 (0.7–2.2)	31 / 25	1.0 (0.4–2.3)	34 / 41	1.7 (0.7–4.0)	0.82
		P_{trend} = 0.30		P_{trend} = 0.72		P_{trend} = 0.09	
Age at first live birth (parous women only)							
<20	160 / 172	1.0	84 / 49	1.0	76 / 123	1.0	
20–24	170 / 178	0.9 (0.6–1.3)	138 / 105	0.8 (0.5–1.3)	32 / 73	0.9 (0.5–1.8)	
25–29	85 / 80	1.0 (0.6–1.6)	76 / 54	1.0 (0.6–1.8)	9 / 26	0.8 (0.3–2.1)	
30+	24 / 47	**0.5 (0.3–0.9)**	18 / 29	**0.4 (0.2–0.9)**	6 / 18	0.6 (0.2–1.8)	0.75
		P_{trend} = 0.07		P_{trend} = 0.11		P_{trend} = 0.36	
Age at first live birth and number of live births (parous women only)							
30+ years, 1–2 births	21 / 40	1.0	15 / 25	1.0	6 / 15	1.0	
20–29 years, 1–2 births	126 / 137	1.8 (0.9–3.6)	108 / 76	2.3 (1.0–5.2)	18 / 61	0.8 (0.2–2.8)	
<20 years, 1–2 births	42 / 64	1.5 (0.7–3.2)	22 / 21	1.7 (0.6–4.8)	20 / 43	0.9 (0.3–2.9)	
30+ years, 3+ births	3 / 7	0.8 (0.1–5.0)	3 / 4	1.3 (0.2–9.9)	0 / 3	-	
20–29 years, 3+ births	129 / 121	1.9 (1.0–3.6)	106 / 83	2.2 (1.0–4.7)	23 / 38	1.9 (0.5–7.1)	
<20 years, 3+ births	118 / 109	**2.4 (1.2–4.7)**	62 / 28	**3.1 (1.3–7.4)**	56 / 81	1.5 (0.5–5.0)	<0.0001

Statistically significant ($P < 0.05$) findings are shown in bold-face type.

Abbreviations: OR, odds ratio; CI, confidence interval.

[a]Adjusted for sex, age, study center, education, smoking status, body mass index, hypertension and family history of kidney cancer

[b]Test of multiplicative interaction between reproductive factor and race.

Table 3

Other reproductive factors and risk of renal cell carcinoma in the U.S. Renal Cancer Study: overall and race-specific results

	All Women		White		Black		
	N_{Case} / $N_{Control}$	OR[a] (95% CI)	N_{Case} / $N_{Control}$	OR[a] (95% CI)	N_{Case} / $N_{Control}$	OR[a] (95% CI)	P_{int}[b]
Diagnosed with hypertension during pregnancy							
No	382 / 435	1.0	285 / 224	1.0	97 / 211	1.0	
Yes	64 / 64	1.2 (0.7–1.9)	34 / 21	1.1 (0.6–2.2)	30 / 43	1.3 (0.7–2.5)	
1 pregnancy	42 / 47	1.0 (0.6–1.7)	23 / 17	0.9 (0.5–1.8)	19 / 30	1.4 (0.6–3.1)	
2+ pregnancies	21 / 17	1.5 (0.6–3.5)	11 / 4	2.4 (0.5–11.5)	10 / 13	1.0 (0.3–3.4)	0.65
Diagnosed with diabetes during pregnancy							
No	420 / 472	1.0	300 / 231	1.0	120 / 241	1.0	
Yes	28 / 26	1.0 (0.5–1.9)	21 / 13	1.2 (0.5–6.6)	7 / 13	0.8 (0.3–2.3)	
1 pregnancy	15 / 21	0.7 (0.3–1.6)	12 / 10	0.8 (0.3–2.4)	3 / 11	0.4 (0.1–1.9)	
2+ pregnancies	13 / 5	2.2 (0.6–8.2)	9 / 3	2.2 (0.4–10.9)	4 / 2	3.5 (0.6–20.8)	0.70
Hysterectomy							
No	301 / 376	1.0	228 / 187	1.0	73 / 189	1.0	
Yes	195 / 168	1.3 (0.9–1.8)	132 / 85	1.2 (0.8–1.8)[c]	63 / 83	**1.8 (1.1–3.1)** [c]	0.18
Oophorectomy							
No	350 / 425	1.0	265 / 212	1.0	85 / 213	1.0	
Yes	143 / 116	1.3 (0.9–1.8)	94 / 59	1.1 (0.7–1.6) [d]	49 / 57	**2.4 (1.4–4.2)** [d]	0.03
Use of oral contraceptives							
No	180 / 199	1.0	128 / 97	1.0	52 / 102	1.0	
Yes	317 / 346	1.1 (0.8–1.5)	233 / 175	1.1 (0.8–1.6)	84 / 171	1.2 (0.7–2.0)	
≤5 years	188 / 188	1.2 (0.9–1.7)	139 / 94	1.2 (0.8–1.8)	27 / 94	1.4 (0.8–2.4)	
6–10 years	65 / 72	1.1 (0.7–1.7)	51 / 40	1.2 (0.7–2.0)	14 / 32	0.9 (0.4–2.0)	
11–15 years	24 / 40	0.8 (0.4–1.5)	17 / 22	0.8 (0.4–1.6)	19 / 18	1.1 (0.4–3.5)	
>15 years	31 / 37	1.1 (0.6–2.1)	22 / 15	1.2 (0.6–2.4)	12 / 22	1.0 (0.3–2.9)	0.86
		P_{trend} = 0.64		P_{trend} =0.79		P_{trend} = 0.67	
Menopausal hormone therapy use (among women aged 55+)							
No	190 / 184	1.0	130 / 80	1.0	60 / 104	1.0	
Yes	139 / 164	0.8 (0.5–1.1)	114 / 101	0.7 (0.5–1.1)	25 / 63	0.8 (0.4–1.5)	

	All Women		White		Black		
	N_{Case} / $N_{Control}$	OR[a] (95% CI)	N_{Case} / $N_{Control}$	OR[a] (95% CI)	N_{Case} / $N_{Control}$	OR[a] (95% CI)	P_{int}[b]
≤5 years	56 / 61	0.8 (0.5–1.3)	45 / 31	0.8 (0.4–1.5)	11 / 30	0.8 (0.4–1.7)	
6–10 years	25 / 32	0.5 (0.3–1.1)	21 / 23	0.5 (0.2–1.1)	4 / 9	0.6 (0.2–2.2)	
11–15 years	23 / 26	1.0 (0.5–2.0)	22 / 14	1.2 (0.5–2.7)	1 / 12	-	
>15 years	27 / 41	0.6 (0.4–1.1)	21 / 30	0.6 (0.3–1.1)	6 / 11	1.3 (0.3–5.1)	0.83
		P_{trend} = 0.33		P_{trend} = 0.43		P_{trend} = 0.64	

Statistically significant ($P < 0.05$) findings are shown in bold-face type.

Abbreviations: OR, odds ratio; CI, confidence interval.

[a] Adjusted for sex, age, study center, education, smoking status, body mass index, hypertension and family history of kidney cancer

[b] Test of multiplicative interaction between reproductive factor and race.

[c] In analyses restricted to subjects from the Detroit study center (85% of all subjects), the OR (95% CI) for a history of hysterectomy was 1.1 (0.8–1.7) among white subjects and 1.2 (0.6–2.3) among black subjects; see Supplemental Table 1.

[d] In analyses restricted to subjects from the Detroit study center (85% of all subjects), the OR (95% CI) for a history of oophorectomy was 1.1 (0.7–1.6) among white subjects and 1.5 (0.8–2.9) among black subjects; see Supplemental Table 1.

Table 4

Age at first live birth and risk of clear cell adenocarcinoma in the U.S. Renal Cancer Study: overall and race-specific results

	All Women		**White**		**Black**		
	N_{Case} / $N_{Control}$	**OR[a] (95% CI)**	**N_{Case} / $N_{Control}$**	**OR[a] (95% CI)**	**N_{Case} / $N_{Control}$**	**OR[a] (95% CI)**	**P_{int}[b]**
Age at first live birth (parous women only)							
<20	101 / 172	1.0	58 / 49	1.0	43 / 123	1.0	
20–24	112 / 178	0.8 (0.5–1.2)	95 / 105	0.8 (0.5–1.3)	17 / 73	1.0 (0.4–2.1)	
25–29	48 / 80	0.7 (0.4–1.2)	43 / 54	0.7 (0.4–1.4)	5 / 26	0.8 (0.2–2.8)	
30+	12 / 47	**0.3 (0.2–0.8)**	10 / 29	**0.3 (0.1–0.8)**	2 / 18	0.4 (0.1–4.1)	0.99
		P_{trend} = 0.007		**P_{trend} = 0.02**		P_{trend} = 0.35	

Statistically significant ($P < 0.05$) findings are shown in bold-face type.

Abbreviations: OR, odds ratio; CI, confidence interval.

[a]Adjusted for sex, age, study center, education, smoking status, body mass index, hypertension and family history of kidney cancer

[b]Test of multiplicative interaction between reproductive factor and race.