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Original Contribution

Reproductive Factors and Risk of Renal Cell Cancer

The Nurses' Health Study

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Few prospective studies have examined associations between reproductive factors and risk of renal cell cancer (RCC). The authors prospectively examined whether postmenopausal hormone (PMH) use, oral contraceptive use, parity, and other reproductive factors were associated with RCC risk among 118,219 US women in the Nurses' Health Study. A total of 247 RCC cases were confirmed between 1976 and 2004. Multivariate relative risks, adjusted for known risk factors, were calculated using Cox proportional hazards models. Compared with 1 or 2 childbirths, the multivariate relative risks were 1.75 (95% confidence interval (CI): 1.21, 2.53) for 4 childbirths and 1.50 (95% CI: 1.00, 2.23) for $\geq$5 childbirths ($P_{trend} = 0.02$). Comparing an age at first birth of $\geq$28 years with an age at first birth of $\leq$22 years, the multivariate relative risk was 0.66 (95% CI: 0.43, 1.01; $P_{trend} = 0.01$). Compared with 1–3 childbirths and an age at first birth of $\geq$26 years, the multivariate relative risk was 2.17 (95% CI: 1.49, 3.14) for $\geq$4 childbirths and an age at first birth of $<$26 years. No clear associations were observed for PMH use or duration, time since last PMH use, oral contraceptive use or duration, age at menarche, age at menopause, or history of hysterectomy or oophorectomy.

carcinoma, renal cell; kidney neoplasms; parity; prospective studies

Abbreviations: PMH, postmenopausal hormone(s); RCC, renal cell cancer.

Renal cell cancer (RCC) is more than twice as common in men as in women, but it is unknown whether this sex difference is due to differences in sex-hormone-related factors. Although it is known that obesity (1), hypertension (2), and smoking (3) are independently associated with a greater risk of RCC, the relations of postmenopausal hormone (PMH) use, oral contraceptive use, parity, and other reproductive factors to RCC risk remain unclear.

Previous epidemiologic studies on exogenous hormone use and incidence of RCC have been few, and findings have been inconsistent. Some studies examining the relation between female hormone use (described as hormone replacement therapy, postmenopausal estrogen use, or estrogen replacement) among postmenopausal women and RCC have found no associations (4–8). However, 1 prospective follow-up study found incidence of RCC to be elevated in former users of estrogen (9). For oral contraceptive use, an inverse association among nonsmokers was found in the studies that examined oral contraceptive use by smoking status (4–6). In the studies that did not stratify results by smoking status, no overall association was observed (7–9). Most of these studies utilized retrospective data (5–8), and previous prospective studies (4, 9) examined duration of PMH or oral contraceptive use before recruitment into the cohort because of 1-time assessment of these variables.

We examined the associations between menopausal and reproductive factors (including parity; PMH use, duration, and type; and oral contraceptive use and duration) and the risk of RCC in the Nurses' Health Study. Details on PMH use were collected every 2 years over 28 years of follow-up, allowing us to examine updated measures of duration of use and time since discontinuation in relation to incident RCC.

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MATERIALS AND METHODS

Study population

The Nurses' Health Study was established in 1976, when 121,700 female registered nurses aged 30–55 years from 11 US states returned a mailed questionnaire. Women in the Nurses' Health Study provided detailed information about medical history, lifestyle, and various risk factors for chronic diseases. Follow-up questionnaires have been sent at 2-year intervals.

This investigation was approved by the institutional review board of Brigham and Women's Hospital in Boston, Massachusetts.

Case ascertainment and definition

We obtained self-reported information on the occurrence of kidney cancer on each questionnaire, and asked participants who reported a diagnosis of kidney cancer (or next of kin, for those who had died) for permission to access medical records related to the diagnosis. Deaths occurring in the cohort were ascertained through reports made by family members in response to the follow-up questionnaires. In addition, the National Death Index (10) was used to identify fatalities. Physicians blinded to participants' risk factor status reviewed medical records. We included only those participants with RCC diagnosis codes (*International Classification of Diseases for Oncology*, Second Edition (11), code C64.9 or *International Classification of Diseases, Ninth Revision, Clinical Modification* (12), code 189.0) as cases, because transitional cell cancer, which arises from the renal pelvis, may have a different etiology. After a review of medical records, we included cases of clear cell carcinoma ($n = 155$), papillary carcinoma ($n = 18$), chromophobe carcinoma ($n = 8$), collecting duct carcinoma ($n = 2$), and renal cell carcinoma not otherwise specified ($n = 64$), based on the classification developed at a World Health Organization workshop (13). A total of 247 cases among all women and 216 cases among postmenopausal women were confirmed and included here.

Assessment of reproductive factors

In 1976, women were asked about their number of childbirths, and they were asked this subsequently on the biennial mailed questionnaires until 1984, when few additional births were reported. In addition, participants responded to questions about their age at the time of their first pregnancy of $\geq$6 months' duration. Age at menarche was reported on the initial 1976 questionnaire. Women were asked to record the ''intervals of oral contraceptive use starting from first use and continuing until the present time'' in 1976; information on months of use during the intervening 2 years was collected on all subsequent biennial questionnaires through 1982, when few women reported use of oral contraceptives.

For PMH use, women were asked, ''Have you used female hormones (other than oral contraceptives)?''. Total duration of PMH use in 1976 and data on months of use during the intervening 2 years were collected on all subsequent biennial questionnaires. Women who report using female hormones have also been asked about the brand name or type of hormone preparation used (i.e., estrogen alone or estrogen with progesterone) every 2 years since 1978.

Questions about menopausal status, the reason for cessation of menses (natural menopause, radiation, surgery with 1 ovary removed, removal of both ovaries, or simple hysterectomy), and age at onset of menopause have been asked every 2 years since 1976. We considered women who reported that their menstrual periods had ceased or who had undergone bilateral oophorectomy as having been postmenopausal since the time this had occurred. Women who reported cessation of menses after a simple hysterectomy or removal of only 1 ovary or who did not report the reason for cessation were considered postmenopausal when they reached the age at which natural menopause had occurred in 90% of the cohort (54 years for a current smoker and 56 years for a nonsmoker). Hence, we evaluated PMH use (estrogen alone or estrogen with progesterone) in women who were postmenopausal. We calculated the reproductive period as the number of years between the ages of menarche and menopause.

Assessment of dietary factors and other risk factors

Dietary information was collected from the Nurses' Health Study participants using validated semiquantitative food frequency questionnaires (14) in 1980, 1984, and 1986, and every 4 years thereafter. Participants were asked how frequently during the past year (on average) they had consumed 1 standard serving of a specific food item, with responses in 9 categories (less than once/month, 1–3 times/month, once/week, 2–4 times/week, 5–6 times/week, once/day, 2–3 times/day, 4–5 times/day, or $\geq$6 times/day). Responses for each food item were converted to average daily intake. We determined alcohol intake by multiplying the reported frequencies of 1 serving size of each specific alcoholic beverage by its ethanol content: 12.8 g of ethanol for a 12-ounce (355-mL) can or bottle of beer, 11.0 g for a 4-ounce (118-mL) glass of wine, and 14.0 g for a standard serving of liquor (15).

Cumulative average dietary intakes using equal weights were calculated from all available questionnaires up to the end of each 2-year follow-up interval. For example, fruit intake in 1980 was used for analyses of RCC diagnosed from 1980 through 1984, and the average of fruit intakes in 1980 and 1984 was used for analyses of RCC diagnosed from 1984 through 1986.

Information on body mass index (weight (kg)/height (m^2)), smoking, and history of hypertension has been updated using the self-administered questionnaires every 2 years since 1976. Body mass index was calculated using height in 1976 and updated weight. Pack-years of smoking were calculated by multiplying the duration and dose of smoking; 1 pack-year is equivalent to having smoked 1 pack per day for 1 year.

Table 1. Characteristics[a] of the Study Population According to Postmenopausal Hormone Use and Number of Childbirths, Nurses' Health Study, 1990

	PMH Use[b]						No. of Childbirths					
	Never Use (n = 24,452)		Past Use (n = 14,394)		Current Use (n = 22,916)		0 (Nulliparous) (n = 6,715)		1–3 (n = 62,034)		≥4 (n = 30,770)	
	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%
Age, years	60 (5)[c]		62 (5)		59 (6)		58 (7)		56 (7)		59 (6)	
Past PMH use[b]				100				24		22		22
Current PMH use[b]						100		42		41		34
Duration of PMH use[b,d], years			3		8		7		6		5	
Past use of oral contraceptives		34		41		45		37		49		48
Duration of oral contraceptive use[e], years	4		4		4		4		4		4	
Age at menopause[b], years	50		47		48		47		48		49	
Age at menarche, years	13		12		13		12		12		12	
Nulliparity		6		8		8		100				
Parity[f], no. of childbirths	3		3		3							
Body mass index[g]	26		26		25		26		26		26	
Pack-years of smoking	16		17		13		14		13		14	
Hypertension		35		39		35		31		31		31
Alcohol intake, g/day	5		5		5		6		5		5	
Fruit intake, servings/day	2		2		2		2		2		2	
Vegetable intake, servings/day	3		3		3		3		3		3	

Abbreviation: PMH, postmenopausal hormone(s).

[a] All values were standardized to the age distribution of the study, except those for age.

[b] Among postmenopausal women only. We considered women who reported that their menstrual periods had ceased or who had undergone bilateral oophorectomy as having been postmenopausal since the time this had occurred. Women who reported cessation of menses after a simple hysterectomy or removal of only 1 ovary or who did not report the reason for cessation were considered postmenopausal when they reached the age at which natural menopause had occurred in 90% of the cohort (54 years for a current smoker and 56 years for a nonsmoker).

[c] Numbers in parentheses, standard deviation.

[d] Calculated among ever users of PMH only.

[e] Calculated among ever users of oral contraceptives only.

[f] Calculated among parous women only.

[g] Weight (kg)/height $(m)^2$.

Statistical analyses

We excluded participants who did not return the baseline (1976) questionnaire or had been diagnosed with cancer (except nonmelanoma skin cancer) prior to baseline. As a result, 118,219 women in the Nurses' Health Study were included in these analyses, for which follow-up started in 1976. Person-years of follow-up were estimated from the date on which the baseline questionnaire was returned to the date of RCC diagnosis, the date of death, or the end of follow-up (May 31, 2004), whichever came first. Relative risks were calculated using the Cox proportional hazards model (16) with SAS PROC PHREG (SAS Institute Inc., Cary, North Carolina). We evaluated whether the proportional hazards assumption was satisfied by adding terms for interaction between age and each of the main exposures and found that the terms were not statistically significant; thus, the assumption was satisfied (data not shown). By stratifying by age in months at the start of each questionnaire cycle and calendar year of the current questionnaire cycle, we controlled as finely as possible for confounding by age, calendar time, and any possible 2-way interactions between these 2 time scales.

In the multivariate models, we also adjusted for possible risk factors for RCC, including body mass index (<25, 25–26.9, 27–29.9, or ≥30), smoking (never smoker or 1–19, 20–39, or ≥40 pack-years of smoking), history of hypertension (yes, no), total fruit intake (servings/day; continuous), total vegetable intake (servings/day; continuous), and alcohol intake (g/day; continuous). Two-sided 95% confidence intervals were obtained for the relative risks. To calculate the P value for the trend test, we assigned participants the median value of each category and treated this variable as a continuous term in the model.

We examined whether the associations for PMH duration and parity varied by body mass index (<25, ≥25), history of hypertension (yes, no), or smoking habits (ever, never). For tests for interaction for parity, the model fit, including the cross-product term of the continuous parity variable with a binary modifier variable, was compared with the model

Table 2. Relative Risk of Renal Cell Cancer Associated With Reproductive Factors, Nurses' Health Study, 1976–2004

	No. of Cases[a]	Age-Adjusted RR	95% CI	Multivariate RR_1[b]	95% CI	Multivariate RR_2	95% CI
Parity, no. of childbirths							
0 (nulliparous)	12	0.93	0.50, 1.72	1.15[c]	0.59, 2.24		
1 or 2	61	1.00	Referent	1.00[c]	Referent	1.00[c,d]	Referent
3	65	1.32	0.93, 1.87	1.24[c]	0.87, 1.76	1.24[c,d]	0.87, 1.77
4	59	1.92	1.33, 2.76	1.75[c]	1.21, 2.53	1.70[c,d]	1.17, 2.47
≥5	46	1.65	1.11, 2.44	1.50[c]	1.00, 2.23	1.50[c,d]	1.00, 2.25
P_{trend}		<0.001		0.02		0.01	
Age at first birth, years							
≤22	47	1.00	Referent	1.00[e]	Referent		
23	49	1.08	0.72, 1.61	1.08[e]	0.72, 1.61		
24 or 25	72	0.92	0.63, 1.33	0.95[e]	0.65, 1.38		
26 or 27	33	0.68	0.43, 1.07	0.73[e]	0.46, 1.15		
≥28	46	0.56	0.37, 0.85	0.66[e]	0.43, 1.01		
P_{trend}		<0.001		0.01			
Oral contraceptive use							
Never use	139	1.00	Referent	1.00	Referent		
Ever use	97	1.04	0.79, 1.38	0.99	0.75, 1.32		
Duration of oral contraceptive use, years							
0 (never use)	139	1.00	Referent	1.00	Referent		
<3	53	1.20	0.86, 1.68	1.14	0.81, 1.60		
≥3	39	0.89	0.61, 1.30	0.85	0.58, 1.24		
P_{trend}		0.43		0.31			
Age at menarche, years							
≤11	135	1.00	0.72, 1.38	0.92	0.67, 1.27		
12 or 13	52	1.00	Referent	1.00	Referent		
14	38	1.28	0.89, 1.84	1.35	0.94, 1.93		
≥15	21	1.02	0.64, 1.62	1.06	0.67, 1.69		
P_{trend}		0.57		0.23			
Hysterectomy							
No	143	1.00	Referent	1.00	Referent		
Yes	104	1.26	0.97, 1.62	1.18	0.91, 1.52		
Oophorectomy							
No	172	1.00	Referent	1.00	Referent		
Yes	76	1.25	0.95, 1.65	1.17	0.89, 1.55		

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Total numbers of cases and controls varied because there were missing data for the main exposures.

[b] Adjusted for history of hypertension (yes, no), body mass index (weight (kg)/height $(m)^2$; <25, 25–26.9, 27–29.9, or ≥30), smoking status (never smoker or 1–19, 20–39, or ≥40 pack-years), fruit intake (servings/day; continuous), vegetable intake (servings/day; continuous), and alcohol intake (g/day; continuous).

[c] Additionally adjusted for age at first birth (≤25, 26–27, or ≥28 years; nulliparous women were included in the highest category).

[d] Nulliparous women were excluded.

[e] Additionally adjusted for parity (≤3 births, ≥4 births).

fit without the cross-product term using the likelihood ratio test. For PMH duration, we conducted a test for interaction using a 2-sample Wald test to compare the multivariate relative risks for the exposure level of interest (e.g., the relative risk for the top-to-bottom category contrast) across the 2 levels of the potential modifier.

Table 3. Relative Risk of Renal Cell Cancer Associated With Reproductive Factors among Postmenopausal Women[a], Nurses' Health Study, 1976–2004

	No. of Cases	Age-Adjusted RR	95% CI	Multivariate RR[b]	95% CI
Age at menopause, years					
≤46	35	1.00	Referent	1.00[c]	Referent
47 or 48	21	0.97	0.56, 1.67	1.00[c]	0.58, 1.71
49 or 50	45	0.93	0.60, 1.45	0.94[c]	0.60, 1.47
51 or 52	70	1.42	0.94, 2.13	1.44[c]	0.95, 2.19
≥53	45	1.30	0.83, 2.04	1.33[c]	0.84, 2.09
P_{trend}		0.16		0.14	
Reproductive period, years[d]					
≤34	44	1.00	Referent	1.00	Referent
35 or 36	32	1.11	0.70, 1.75	1.15	0.73, 1.82
37–39	82	1.14	0.79, 1.65	1.17	0.81, 1.69
≥40	58	1.14	0.77, 1.70	1.16	0.78, 1.73
P_{trend}		0.53		0.48	
PMH use					
Never use	59	1.00	Referent	1.00[c]	Referent
Past use	54	0.99	0.68, 1.44	0.91[c]	0.63, 1.30
Current use	65	1.02	0.70, 1.49	1.01[c]	0.70, 1.45
Type of PMH use					
Never use	59	1.00	Referent	1.00[c]	Referent
Past use	54	1.00	0.69, 1.46	1.04[c]	0.71, 1.51
Current use of estrogen	45	1.09	0.73, 1.62	1.19[c]	0.80, 1.77
Current use of estrogen with progesterone	16	0.64	0.36, 1.13	0.73[c]	0.41, 1.29
Duration of PMH use, years					
0 (never use)	59	1.00	Referent	1.00[c]	Referent
<5	50	1.01	0.69, 1.47	1.05[c]	0.72, 1.54
5–<10	30	0.97	0.62, 1.52	1.06[c]	0.68, 1.67
≥10	35	0.83	0.54, 1.28	0.90[c]	0.58, 1.40
P_{trend}		0.40		0.64	
Time since last PMH use, years					
Never use	59	1.00	Referent	1.00[c]	Referent
<5	21	0.89	0.54, 1.48	0.94[c]	0.56, 1.56
5–<10	16	1.31	0.75, 2.29	1.38[c]	0.79, 2.41
≥10	16	0.94	0.53, 1.66	0.93[c]	0.52, 1.64
Current use	65	0.91	0.63, 1.31	1.01[c]	0.70, 1.45

Abbreviations: CI, confidence interval; PMH, postmenopausal hormone; RR, relative risk.

[a] We considered women who reported that their menstrual periods had ceased or who had undergone bilateral oophorectomy as having been postmenopausal since the time this had occurred. Women who reported cessation of menses after a simple hysterectomy or removal of only 1 ovary or who did not report the reason for cessation were considered postmenopausal when they reached the age at which natural menopause had occurred in 90% of the cohort (54 years for a current smoker and 56 years for a nonsmoker).

[b] Adjusted for history of hypertension (yes, no), body mass index (weight (kg)/height $(m)^2$; <25, 25–26.9, 27–29.9, or ≥30), smoking status (never smoker or 1–19, 20–39, or ≥40 pack-years), fruit intake (servings/day; continuous), vegetable intake (servings/day; continuous), and alcohol intake (g/day; continuous).

[c] Additionally adjusted for parity (≤3 births, ≥4 births).

[d] Number of years from age at menarche to age at menopause.

Table 4. Relative Risk of Renal Cell Cancer Associated with Parity, by Age at First Birth and Postmenopausal Hormone Use, Nurses' Health Study, 1976–2004

	1–3 Childbirths			≥4 Childbirths		
	No. of Cases	Multivariate RR[a]	95% CI	No. of Cases	Multivariate RR[a]	95% CI
Age at first birth[b], years						
≥26	25	1.00	Referent	24	1.47	0.89, 2.43
<26	83	1.46	1.00, 2.12	85	2.17	1.49, 3.14
$P_{interaction}$			0.96			
Postmenopausal hormone use[c]						
Never use	31	1.00	Referent	24	1.14	0.67, 1.96
Ever use	61	0.89	0.57, 1.38	54	1.48	0.95, 2.32
$P_{interaction}$			0.25			

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Adjusted for history of hypertension (yes, no), body mass index (weight (kg)/height (m)^2; <25, 25–26.9, 27–29.9, or ≥30), smoking status (never smoker or 1–19, 20–39, or ≥40 pack-years), fruit intake (servings/day; continuous), vegetable intake (servings/day; continuous), and alcohol intake (g/day; continuous).

[b] Among parous women only.

[c] Among postmenopausal women only.

RESULTS

During 28 years of follow-up of 118,219 women, a total of 247 RCC cases were identified. Table 1 presents characteristics of the study population in 1990, the midpoint of the follow-up period, according to PMH use and number of childbirths. Current PMH users were more likely to have used oral contraceptives in the past and to have fewer pack-years of smoking compared with never and past users. Women with children were less likely to have used PMH and were more likely to have used oral contraceptives in the past compared with nulliparous women.

We found an increased risk of RCC for women with greater numbers of childbirths (Table 2). When we simultaneously included parity and age at first birth, the associations for age at first birth and parity were attenuated, but P values from the trend tests were still statistically significant. The Spearman correlation coefficient for the correlation between age at first birth and parity was −0.34 ($P < 0.01$), suggesting that an increasing number of childbirths was correlated with early age at first birth. There was a 10% higher risk of RCC for each childbirth (relative risk = 1.10, 95% confidence interval: 1.02, 1.19). Because nulliparous women could have different characteristics than parous women, which could be related to potentially confounding factors such as alcohol intake or unknown risk factors for RCC, we also examined the association among parous women only and found an increased risk of RCC with an increasing number of childbirths. Delayed first childbirth was associated with a lower risk of RCC.

We did not observe any statistically significant associations between PMH use and duration and RCC risk (Table 3). The results from the age-adjusted models were similar to those from the multivariate models for PMH use and duration. When we examined the association between PMH use and RCC risk using premenopausal women as the referent group, we did not observe any statistically significant association (data not shown).

Time since last PMH use, age at menopause, age at menarche, oral contraceptive use, and duration of oral contraceptive use were not associated with risk of RCC (Tables 2 and 3). Reproductive period, which we calculated as the number of years from age at menarche to age at menopause, was not associated with risk of RCC. We did not find any significant associations for history of hysterectomy or oophorectomy (either 1 ovary or both ovaries removed). The results from the age-adjusted models were similar to those from the multivariate models for these reproductive factors.

When we also examined the associations for parity and age at first birth by cross-classifying these 2 variables, the highest risk was observed among women who had high parity and early age at first birth (Table 4). However, the interaction was not statistically significant ($P_{interaction} = 0.96$).

We examined whether the associations of parity, age at first birth, duration of PMH use, and duration of oral contraceptive use with RCC risk varied by smoking habits (ever, never), body mass index (<25, ≥25), or history of hypertension (yes, no). Body mass index and history of hypertension did not modify the associations for duration of PMH use, age at first birth, parity, or duration of oral contraceptive use ($P_{interaction} \geq 0.18$; data not shown). Smoking habits did not modify the effect of duration of PMH use, age at first birth, or parity ($P_{interaction} \geq 0.44$), but a nonsignificant inverse association was observed for ≥3 years of oral contraceptive use among never smokers (relative risk = 0.57, 95% confidence interval: 0.28, 1.14). No association was observed among ever

smokers (relative risk = 1.05, 95% confidence interval: 0.66, 1.67; $P_{interaction} = 0.15$).

DISCUSSION

We found an increased risk of RCC with increasing number of childbirths and decreasing age at first birth. There was a 10% increased risk per child for number of childbirths. Women who had their first child at age ≥28 years had a 34% lower risk of RCC than women who had their first child at age ≤22 years. No associations were observed for the other reproductive hormonal factors examined.

Our results for increased risk of RCC among women who had a high number of childbirths concur with those of most epidemiologic studies that have examined this association (4, 6, 9, 17). In these studies, women who had 3, 4, or ≥5 childbirths had an approximately doubled RCC risk compared with nulliparous women or women with 1 or 2 births. Age at first birth has been examined in a few studies. In a multicenter study that included parity and age at first birth in the same model (6), late age at first birth was not significantly associated with a lower risk of RCC, whereas higher parity remained associated with a higher risk of RCC. However, another study found a decreasing risk of RCC for a 5-year increment of age at first birth in the models including both parity and age at first birth (17). In studies that did not control for parity, late age at first birth was associated with a lower risk of RCC (4, 5, 8, 9).

Results for female hormone use among postmenopausal women have been inconsistent, and we did not find any association. In a large multicenter case-control study from 5 countries that included 504 postmenopausal RCC cases, ever use of estrogen replacement therapy and duration of estrogen replacement therapy were not associated with risk of RCC (6). Other case-control studies with fewer numbers of cases than the multicenter case-control study found no associations for use of estrogen (5, 7, 18) or hormone replacement therapy (8) or duration of estrogen use (7). In 2 prospective studies (4, 9) in which postmenopausal women were asked about the use of hormone replacement therapy at baseline, 1 study found that neither ever use nor duration of use was associated with risk of RCC (4) and the other found an increased risk of RCC among past users but not among current users (9).

For oral contraceptive use and duration, significant inverse associations were observed among nonsmokers in 3 studies (4–6), and no overall association was observed in other studies (7–9) in which the associations were not examined by smoking status. Similarly, we observed a more pronounced inverse association between duration of oral contraceptive use and risk of RCC among women who had never smoked, although the interaction was not statistically significant.

Age at menarche (4, 6, 9) and age at menopause (6, 8, 9) were not associated with RCC risk in most previous studies. This is consistent with our findings.

Women who had ever undergone hysterectomy, oophorectomy, or combined hysterectomy and oophorectomy had a higher risk of RCC than women who did not undergo gynecologic surgery in several case-control studies (6–8) but not in a prospective study (9).

Potential mechanisms by which frequent and early childbearing increases the risk of RCC include changes in renal vascular environment, estrogen level, and renal anatomy during pregnancy. First, it is possible that the renal vascular bed becomes more vulnerable to inflammation or oxidative stress during pregnancy because, during pregnancy, there are an excess risk of urinary tract infection (19, 20), increases in maternal blood volume (21), cardiac output (21), glomerular filtration rate (22), and renal plasma flow (22), and a decrease in systemic vascular resistance (21). Oxidative stress has been hypothesized to be responsible for renal carcinogenesis (23). Second, anatomic change in the kidney during pregnancy may damage the organ. Anatomically, there is a slight increase in kidney size and marked dilation of the renal pelvis, calyces, and ureter during pregnancy (22). These changes may make the nephrons vulnerable to oxidative stress (24) and inflammation (25), resulting in renal cell carcinogenesis. Third, estrogen and progesterone could be involved in the pathogenesis of RCC; some studies have found reduced levels of estrogen and progesterone among parous women (26–28). In addition, men have a more than 2-fold higher risk of RCC than women (29, 30). Although we did not observe a lower risk of RCC among long-term PMH users, the association between prolonged change in the estrogen and progesterone profile and RCC risk needs to be studied further.

The prospective and repeated collection of exposure data was the primary strength of this study. With multiple assessments over 28 years of follow-up, we were able to examine duration of PMH use and time since last PMH use. We were able to adjust for most of the established risk factors for RCC, including body mass index, history of hypertension, smoking habits, and alcohol intake. Limitations of this study include the possible existence of unknown or residual confounding factors.

In conclusion, we found that high parity and early age at first birth were associated with an increased risk of RCC.

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