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Menstrual and Reproductive Factors and Risk of Renal Cell Cancer in the Multiethnic Cohort

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Abstract

A relationship between female reproductive and menstrual factors, including exogenous hormone use, and renal cell cancer (RCC) has been hypothesized, but supporting epidemiologic evidence is limited and inconsistent. Here, the association of reproductive and menstrual factors with RCC risk was examined among 106,036 Hawaii-Los Angeles Multiethnic Cohort female participants who entered the cohort between 1993 and 1996. During an average 10.6 years of follow-up, 229 RCC cases were identified among these women. Data on known and potential risk factors were obtained from the baseline questionnaire. Relative risks and 95% confidence intervals for RCC associated with each factor were estimated using Cox proportional hazard models stratified by race/ ethnicity, study center, and menopausal status and adjusted for age and several confounding factors. We found no evidence of association between RCC and parity, age at first birth, age at menarche, age and type of menopause (hysterectomy or bilateral oophorectomy), use and duration of oral contraceptive, and type and duration of postmenopausal hormone use. Our results do not support the hypothesis that hormone-related factors play an etiologic role in RCC among women.

Introduction

The incidence of renal cell cancer (RCC), the most common type of kidney cancer, has been steadily increasing in the United States and worldwide (1–3), although a recent report shows more favorable trends (the rates are slowing down, stabilizing, or declining) across most European countries (4). RCC is more common among men, but the annual increase in incidence is greater in women than in men (1). Among women in the United States, RCC ranks as the 9th leading cause of cancer with an estimated 21,260 new cases in 2008 (5).

The etiology of RCC remains enigmatic. Epidemiologic studies have consistently shown that cigarette smoking, obesity, and hypertension increase the risk of RCC. We found that, collectively, these three risk factors explained about half of the female RCC cases in the Multiethnic Cohort Study (6); therefore, a large proportion remains unexplained and the search for additional risk factors that might influence this increasing trend in women must continue.

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No potential conflicts of interest were disclosed.

Estrogens can induce RCC in laboratory animals and estrogen receptors are present in normal and cancerous renal cell tissue in humans (7); these findings prompted the hormonal hypothesis that female reproductive and menstrual factors, including exogenous hormone use, may be involved in the etiology of RCC. Only two cohort studies have tested this hypothesis with adjustment for known RCC risk factors [e.g., body mass index (BMI) or body weight] as potential confounders (8, 9). Here, we examined whether menstrual and reproductive factors may be potential risk factors for RCC in women from a large prospective multiethnic cohort study.

Materials and Methods

Study Population

The Multiethnic Cohort Study is a prospective cohort study that includes 215,251 men and women, primarily African Americans, Japanese Americans, Latinos, Native Hawaiians, and Whites living in Hawaii and California. The details of the study design, response rates, and baseline characteristics have been given elsewhere (10). Briefly, the cohort recruitment began in 1993 and was completed in 1996. Participants were between the ages of 45 and 75 at the time of recruitment. Each participant completed a self-administered mail questionnaire that included diet, demographic factors, anthropometric measures, personal behaviors (e.g., smoking, physical activity), history of medical conditions (e.g., hypertension, diabetes), and family history of common cancers and, for women, menstrual and reproductive history and exogenous hormone use. The response rates ranged from 20% in Latinos to 49% in Japanese Americans.

In the cohort, incident cancer cases were identified annually by record linkages to population-based cancer Surveillance, Epidemiology and End Results Program registries in Hawaii, Los Angeles County, and the California State Cancer Registry. At the time of this analysis, linkage with these registries was complete through December 31, 2004 in Hawaii and December 31, 2005 in California. Deaths within the cohort are determined from linkages to the death certificate files in Hawaii and California, supplemented with linkages to the National Death Index; the linkages in both locations were complete through December 31, 2005.

We limited our analysis to 110,706 women from the five major racial/ethnic groups without a prevalent report of kidney cancer based on self-report or from the Surveillance, Epidemiology and End Results registries. We excluded women with missing information for BMI, smoking status, and hypertension (n = 4,670) because these are known risk factors for RCC (6). After exclusion, 106,036 women comprised the final study cohort. The women who were excluded were slightly older than those who remained in the analyses, but they were generally similar with respect to the distribution of menstrual/reproductive factors. A total of 253 cases of kidney cancer were diagnosed among these women (229 renal cell, ICD-O-3 C64.9; and 24 renal pelvis, ICD-O-3 C65.9). Cases with renal pelvis cancer were not included in the case group, but follow-up was censored for these subjects at the date of diagnosis.

Data on known/potential kidney cancer risk factors (e.g., obesity, smoking status, and hypertension), menstrual and reproductive history, and exogenous hormone use were obtained from the baseline questionnaire. The following factors were examined in the current analysis: age at menarche, age and type of menopause, age at first full-term pregnancy, parity, number of children, oral contraceptive use and duration, and duration and type of postmenopausal hormone therapy. Duration of postmenopausal hormone therapy use was calculated using methods previously described (11). The Institutional Review Boards at

the University of Hawaii and at the University of Southern California approved the study protocol.

Statistical Analysis

Hazard ratios [reported as relative risks (RR) and 95% confidence intervals (CI)] for the effects of risk factors on RCC incidence were calculated using Cox regression (SAS version 9.1; SAS Institute). Age (in days) was used as the underlying time variable in the Cox regression starting with the participant's age at entry to one of the three end points (or whichever comes first): date of RCC diagnosis, date of death, or the end of follow-up. Cox models were stratified by race/ethnicity, study area (Hawaii, Los Angeles), and menopausal type (premenopausal, natural menopause, bilateral oophorectomy, hysterectomy), and adjusted for age, BMI (<25, 25 to <30, ≥30 kg/m^2), smoking status (never, past, current), hypertension (no, yes), alcohol intake (none, <24, ≥24 ethanol g/d), and diuretic use (never, ever). Stratified Cox models were used to allow the form of the underlying hazard function to vary across levels of stratification variables (i.e., race/ethnicity, study area, and menopausal status). The RRs associated with the exposure variables were assumed to be the same across strata. The likelihood ratio test was used to test for statistical interaction between exposures with respect to RCC. Trend tests were conducted by treating each category as a continuous term (0, 1, 2…) in the models and were based on the Wald statistics. We checked the proportional hazards assumption by adding interaction terms between log (age at end point) and exposures of interest in Cox models, and we found no evidence of violations against the proportionality assumption.

Results

A total of 229 incident cases of RCC were identified among 106,036 women during an average of 10.6 years of follow-up (1,129,254 person-years). The average age at diagnosis for RCC cases was 68.8 years.

The baseline characteristics by case status are presented in Table 1. The average age at cohort entry was 62.7 for cases and 60.1 for non-cases. Latinos constituted the largest subgroup in cases (26.6%), followed by African Americans (24.5%), Japanese Americans (22.7%), Whites (21.0%), and Native Hawaiians (5.2%). Compared with non-cases, RCC cases were heavier, were more likely to be ever-smokers, parous, postmenopausal, and hypertensive, were less likely to consume alcohol, but were more likely to use hormone therapy and diuretics.

Table 2 shows the association of menstrual/reproductive factors and exogenous hormone use with RCC risk. Later age at menarche seemed to be associated with increased risk. In the multivariate analysis, relative to women with an early age at menarche (≤12 years old), those who had menarche at ≥15 years had a statistically nonsignificant 42% elevation in risk (95% CI, 0.91–2.20). The trend did not reach statistical significance ($P = 0.13$). Later age at first birth was also associated with lowered risk, but there was no clear trend ($P = 0.15$) after adjustment for known RCC risk factors. Compared with women with one to two children, those with five or more children had a RR of 1.31 (95% CI, 0.87–1.98). The association was attenuated after adjustment for BMI and other factors (RR, 1.11; 95% CI, 0.72–1.71) with a statistically nonsignificant trend ($P = 0.71$). There was a tendency towards an increased risk for women who reported hormone therapy use compared with nonusers (RRs, ~1.3), but further analysis using type and duration of use (per 5 years), did not reveal significant association for any type of hormone therapy use (data not shown). There was no clear relationship between age at natural menopause, history of hysterectomy or oophorectomy, or oral contraceptive use with RCC.

We also examined whether BMI modified the associations between hormonal factors and RCC, and found no significant interaction for all risk factors tested.

Discussion

Gender differences in RCC incidence and findings from experimental and clinical studies support the possible role of female hormonal factors in RCC etiology, however, there is little epidemiologic evidence supporting an association in humans. In this multiethnic cohort, we did not find reproductive and menstrual factors such as parity, age at first birth, age at menarche, age at and type of menopause, and use of exogenous hormones to be significantly associated with RCC risk.

Several studies have examined the association of parity with RCC with mixed results (8, 9, 12–21). Body weight is a known risk factor for RCC and is associated with childbearing; therefore, the association between parity and RCC could be confounded by body weight if it is not sufficiently adjusted for in the analysis. Among studies with body weight/BMI adjustment, positive association with high parity has been reported in some (8, 9, 17, 20), but not all studies (12, 14, 15, 19, 21). Our results show no increase in RCC risk with increasing parity.

Findings regarding the association between oral contraceptive use and the risk of RCC have also been inconsistent (8, 9, 13, 17, 19, 21). Several studies have investigated the relationship between postmenopausal hormone therapy use and RCC risk, with the majority of studies finding no association (8, 14, 17, 19). Neither oral contraceptive nor hormone therapy use was significantly associated with RCC risk in our study.

Several studies, including ours, have shown an inverse association between age at first birth and risk of RCC (8, 9, 17, 19, 21), but most of these associations were nonstatistically significant. It is possible that the true association was missed due to small case numbers, and thus, much larger studies are needed to replicate this finding.

We found little evidence that age at menarche, age at natural menopause, and type of menopause (hysterectomy or oophorectomy) influence the risk of RCC. Our results are consistent with those reported in other cohort studies (8, 9).

The strengths of this study include its prospective design, the completeness of follow-up through Surveillance, Epidemiology and End Results registries, the ability to include a number of reproductive and hormonal factors and adjust for multiple potential confounders, and a relatively large number of cases compared with published reports from other cohort studies. One limitation of this study is that our analyses were based on exposures collected at baseline and did not consider changes during follow-up; however, given the participant's age at recruitment, the majority of hormonal factors tested (e.g., parity, age at menarche, age at first birth, oral contraceptive use) were unlikely to have changed during the follow-up period. Low response rates in certain ethnic groups may affect the generalizability of our results to the general population. As previously shown, however, the distribution of education level in our cohort generally resemble those reported by the U.S. census in Hawaii and Los Angeles County for the same ethnic and age groups; thus, we believe that findings from this cohort are broadly generalizable (10). In summary, our prospective data do not support the hypothesis that reproductive and menstrual characteristics the influence risk of RCC in women.

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Table 1

Baseline characteristics of RCC cases and non-cases

Characteristics	Cases (*n* = 229)	Non-cases (*n* = 105,807)
Age at cohort entry, mean (SD)	62.7 (7.7)	60.1 (8.8)
Race/ethnicity (%)		
African American	24.5	19.6
Japanese American	22.7	27.4
Latina	26.6	21.0
Native Hawaiian	5.2	7.4
White	21.0	24.6
BMI, kg/m^2 (%)		
<25	31.4	46.7
25 to <30	35.4	31.3
≥30	33.2	22.0
Smoking status (%)		
Never	48.5	55.6
Past	34.0	29.9
Current	14.5	14.5
Hypertension (%)	59.8	43.0
Alcohol drinkers (%)	29.2	38.3
Ever diuretic use (%)	45.1	26.1
Parous (%)	88.9	87.0
Postmenopausal (%)	94.3	84.6
Ever postmenopausal hormone use (%)*	56.3	53.4

*Among postmenopausal women only.

Table 2

Relative risks of RCC in relation to menstrual/reproductive factors

Factors	No. of cases	Person-years	Age-adjusted RR (95% CI)*	Multivariate RR (95% CI)*
Age at menarche (y)				
≤12	104	554,025	1.00 (reference)	1.00 (reference)
13–14	85	422,204	1.06 (0.77–1.44)	1.12 (0.81–1.55)
≥15	36	135,954	1.36 (0.90–2.06)	1.42 (0.91–2.20)
P trend			0.19	0.13
Age at natural menopause (y)				
<45	20	87,695	1.00 (reference)	1.00 (reference)
45–49	32	171,188	0.86 (0.49–1.51)	1.03 (0.57–1.88)
50–54	41	221,274	0.82 (0.48–1.42)	0.97 (0.54–1.73)
≥55	16	57,478	1.15 (0.59–2.23)	1.13 (0.54–2.36)
P trend			0.92	0.90
Type of menopause				
Natural	109	537,634	1.00 (reference)	1.00 (reference)
Bilateral oophorectomy	38	160,494	1.22 (0.84–1.77)	1.10 (0.74–1.63)
Hysterectomy	35	170,383	1.03 (0.70–1.51)	0.90 (0.59–1.35)
Age at first live birth (y)				
≤20	83	327,461	1.00 (reference)	1.00 (reference)
21–25	82	382,319	0.92 (0.57–1.10)	1.06 (0.73–1.54)
≥26	30	246,886	0.55 (0.34–0.88)	0.66 (0.40–1.09)
P trend			0.02	0.15
Parity				
Nulliparous	25	143,747	1.00 (reference)	1.00 (reference)
Parous	201	978,375	1.13 (0.72–1.77)	1.14 (0.71–1.85)
No. of children				
1–2 children	67	393,852	1.00 (reference)	1.00 (reference)
3–4 children	78	379,422	1.06 (0.74–1.51)	0.94 (0.64–1.36)
≥5 children	56	205,101	1.31 (0.87–1.98)	1.11 (0.72–1.71)
P trend			0.22	0.71
Oral contraceptive use				
Never	145	623,941	1.00 (reference)	1.00 (reference)
Ever	75	471,139	0.99 (0.70–1.39)	1.08 (0.75–1.55)
Duration of oral contraceptive use (y)				
Never	145	623,941	1.00 (reference)	1.00 (reference)
≤5	50	292,267	1.07 (0.73–1.57)	1.18 (0.79–1.75)
>5	25	172,521	0.93 (0.57–1.51)	1.01 (0.60–1.68)
P trend			0.86	0.82
Postmenopausal hormone use†				
Never	93	430,283	1.00 (reference)	1.00 (reference)
Former	54	189,344	1.31 (0.90–1.91)	1.28 (0.86–1.91)

Factors	No. of cases	Person-years	Age-adjusted RR (95% CI)*	Multivariate RR (95% CI)*
Current estrogen therapy	35	146,698	1.13 (0.69–1.83)	1.29 (0.78–2.14)
Current estrogen-progesterone therapy	31	167,795	1.11 (0.71–1.73)	1.27 (0.80–2.04)

*Stratified by study area, race/ethnicity, menopausal status, and adjusted for age. Multivariate RRs were further adjusted for BMI, smoking status, hypertension, alcohol intake, and diuretic use.

†Among postmenopausal women only.