Increased Risk of Renal Cell Carcinoma Subsequent to Hysterectomy[1]

Manuela Gago-Dominguez,[2] J. Esteban Castelao, Jian-Min Yuan, Ronald K. Ross, and Mimi C. Yu

Department of Preventive Medicine, University of Southern California/Norris Comprehensive Cancer Center, University of Southern California School of Medicine, Los Angeles, California 90033-0800

Abstract

In etiological studies of renal cell carcinoma, the associations between exogenous hormones, reproductive factors, or gynecological operations have not been well examined. Our aim was to evaluate gender-specific risk factors for renal cell carcinoma using data from a population-based case-control study conducted in Los Angeles, California and to elucidate possible underlying mechanisms. A population-based case-control study involving 422 female renal cell carcinoma patients, ages 25–74 years, and an equal number of sex-, age-, and race-matched neighborhood controls was conducted in Los Angeles, California. Detailed information regarding reproductive history, hysterectomy, use of exogenous estrogens, and other medical and lifestyle factors was collected through in-person interviews. Compared to women with an intact uterus, those who had undergone hysterectomy were at an increased risk for renal cell carcinoma (odds ratio, 1.8; 95% confidence interval, 1.3–2.5). Parity and use of estrogen replacement therapy were no longer risk factors for renal cell carcinoma when hysterectomy was adjusted for in the analysis. No association between renal cell carcinoma and use of oral contraceptives was found. Limited epidemiological data do not support an endocrine explanation for the observed hysterectomy-renal cell cancer association. We conjecture that unintentional injury to the ureter during the surgical procedure, which results in renal cell damage and consequent renal cell proliferation, may be a cause of the increased cancer risk in hysterectomized women.

Introduction

Kidney cancer is a relatively rare malignancy. In the United States, there are roughly 30,000 new cases each year, which account for ~2% of all incident cancer cases diagnosed annually (1). Nonetheless, the incidence of kidney cancer has been increasing during the last three decades, such that the rates for both men and women in the mid-1990s are 50% higher than the comparable rates in the early 1970s (2, 3). Renal cell carcinoma accounts for 80–85% of all kidney cancers in the United States. The remaining 15–20% of kidney cancers are mostly cancers of the renal pelvis, which are anatomically and histologically distinct from renal cell carcinoma (4).

Very little is known about possible gender-specific risk factors for renal cell carcinoma in women. Several case-control studies have investigated parity in relation to risk. Whereas some have noted a 1.8- to 2.4-fold risk among women with a very high parity (≥5 births; Ref. 5–7), others have observed no association with parity (8–11). A few case-control studies have reported a lower risk of renal cell cancer among users of oral contraceptives (5–7), but cohort investigations have generally failed to confirm these observations (12). Case-control studies that have examined use of replacement hormones and renal cell cancer have also typically observed either no association (5, 7, 11, 13, 14) or, at most, a very weak positive association (9, 15). A history of hysterectomy, on the other hand, has been consistently found to be positively related to renal cell cancer risk in previous case-control studies, although the authors were unclear as to its biological interpretation (5, 6, 11, 16).

As part of a large case-control study of renal cell carcinoma in Los Angeles, with a focus on prior medical conditions and medication use, 422 black and white women with renal cell carcinoma and an equal number of age- and race-matched female controls have given information via in-person interviews on their use of exogenous hormones, history of hysterectomy, and total number of pregnancies. This study reports these gender-specific findings.

Materials and Methods

Between April 1986 and December 1994, the Los Angeles County Cancer Surveillance Program (17), the population-based Surveillance, Epidemiology, and End Results cancer registry of Los Angeles County, identified 598 female patients with histologically confirmed renal cell carcinoma who were either African-American or white (including Hispanic) and between the ages of 25 and 74 years at the time of the cancer diagnosis. Among these, 104 patients died before we could contact them or were too ill to be interviewed. Permission to contact 16 patients was denied by their physicians. Twenty-eight patients refused to be interviewed. Thus, we interviewed 75% (450 of 598) of all eligible patients. There was no evidence of demographic differences between recruited patients and those who failed to participate in the study. For example, of the 148 patients who were not interviewed, 89% were non-Hispanic whites, and the mean age at cancer diagnosis was 59.8 years. The corresponding figures among interviewed patients were 84% and 58.9 years, respectively.

For each interviewed patient, we sought to recruit a control who was matched to the patient on sex, date of birth (within 5 years), race, and neighborhood of residence at the time of the cancer diagnosis. We attempted to identify the sex, age, and

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[2] To whom requests for reprints should be addressed, at Department of Preventive Medicine, University of Southern California/Norris Comprehensive Cancer Center, M/S #44, University of Southern California School of Medicine, 1441 Eastlake Avenue, Los Angeles, CA 90033-0800. Phone: (323) 865-0826; Fax: (323) 865-0136; E-mail: mgago@hsc.usc.edu.

race of all inhabitants of each housing unit on specified neighborhood blocks. When we failed to find any eligible resident after canvassing 150 housing units according to a standard algorithm, we excluded race from the matching criteria. If a matched control based on this relaxed criteria could not be found in a maximum of 300 housing units, the case was dropped from the study. Twenty-seven cases were excluded from the study because of a lack of matched controls. We completed in-person interviews on 423 female control subjects. There were 31 controls who were not matched on race to the index case. A total of 283 (67%) control subjects were the first eligible controls identified, whereas 84 (20%) and 56 (13%) control subjects were second and third eligible controls, respectively. Among 423 renal cell carcinoma cases who had matched controls, 1 who failed to answer whether her uterus was removed was excluded; thus, 422 case-control pairs were included in the present study.

In-person, structured interviews were conducted in subjects' homes. The questionnaire requested information up to 2 years prior to the diagnosis of cancer for cases and 2 years prior to the diagnosis of cancer of the index case for matched controls. The questionnaire included information on demographic characteristics, height and weight, lifetime use of tobacco and alcohol, usual adult dietary habits, lifetime occupational history, prior medical conditions, prior use of certain medications and, for women, history of hysterectomy, use of hormones, including oral contraceptives and replacement estrogens, and total number of pregnancies. For women who had a hysterectomy, age at which the operation was performed was recorded. For women who had used oral contraceptives, information on ages at first and last use, duration of use, and usual frequency and dosage of use was solicited. For women who had used replacement estrogens after menopause in the form of either pill, suppository, or injection, we recorded the brand names of the drugs, ages at first and last use, duration of use, and the usual frequency and dosage of use.

The case-control study of renal cell carcinoma in men and women of Los Angeles, of which the current data set is a part, has identified several strong risk factors for renal cell carcinoma. They include cigarette smoking, obesity, history of hypertension, regular use of analgesics and amphetamines, and as a protective factor, cruciferous vegetable intake (18–21). These variables were treated as both potential confounders and effect modifiers in the present investigation.

Data were analyzed by standard matched-pair methods (22). The associations of renal cell carcinoma with various exposures of interest were measured by ORs[3] and their corresponding 95% CIs. Conditional logistic regression models were used to examine the exposure-disease relationships of interest with and without adjustment for potential confounders. Possible effect modifications by confounders on the exposure-disease associations of interest were also examined by unconditional logistic regression methods. Pairs in which either the case or the control failed to answer the relevant questions were eliminated from the corresponding analysis. ORs with two-sided Ps < 0.05 are considered statistically significant. All Ps that are quoted are two-sided.

Results

The mean age of the patients at diagnosis of renal cell carcinoma was 58.8 years. Most (85%) cases were non-Hispanic whites ($n = 359$); there were 36 Hispanic white and 27 African-American cases. On average, renal cell carcinoma patients had a lower level of education than the controls. The OR for renal cell carcinoma was 0.6 (95% CI, 0.4–0.9) among those who had attended college (≥13 years of schooling) compared with those who had a high school education or lower. Thus, all ORs presented below were adjusted for level of education (high school or less, college or above).

Table 1 History of hysterectomy and risk of renal cell carcinoma

	Cases	Controls	OR[a] (95% CI)	OR[b] (95% CI)
Hysterectomy				
No	245	297	1.0	1.0
Yes	177	125	1.8 (1.3–2.5)	1.6 (1.1–2.3)
Age at hysterectomy				
<40	80	50	2.0 (1.3–2.9)	1.7 (1.1–2.7)
40–<50	60	47	1.6 (1.1–2.5)	1.4 (0.9–2.2)
50+	37	28	1.8 (1.04–3.2)	1.9 (1.03–3.5)
Time interval between hysterectomy and cancer diagnosis (yr)				
<10	36	22	2.2 (1.2–3.9)	2.2 (1.2–4.1)
10–<20	67	45	1.9 (1.2–3.0)	1.7 (1.1–2.8)
20–<30	44	38	1.4 (0.9–2.3)	1.1 (0.7–2.0)
30+	30	20	1.9 (0.98–3.7)	1.5 (0.7–3.3)

[a] Adjusted for level of education (high school or less, college or above).
[b] Adjusted for level of education, body mass index, history of hypertension, cigarette smoking, cruciferous vegetable intake, and regular use of analgesics and amphetamines.

A history of hysterectomy was a statistically significant risk factor for renal cell carcinoma (Table 1). Compared with women with an intact uterus, hysterectomized women experienced an 80% excess risk of renal cell carcinoma (95% CI, 1.3–2.5). This elevation in risk was not influenced by age at surgery; irrespective of the subject's age when the operation was performed, the increase in risk was 60–100% above the baseline. Similarly, there was no clear indication that risk either increased or decreased systematically by the time interval between hysterectomy and cancer diagnosis, although the risk estimate in women whose operations occurred within the last 10 years (OR, 2.2; 95% CI, 1.2–3.9) was higher than those in women whose operation occurred in the more distant past (OR, 1.9; 95% CI, 0.98–3.7). Results were similar after adjustment for the potentially confounding effects of other risk factors for renal cell carcinoma identified in this study (Table 1).

Among hysterectomized women, 12 renal cancer patients and 10 control subjects had the surgery due to the diagnosis of cancer in the pelvic region (uterus, cervix uteri, ovary, or vagina), thereby yielding an OR of 1.6 (95% CI, 0.6–4.2). These noted cancer diagnoses might represent metastases of an underlying renal cell cancer. Therefore, we repeated the analysis after excluding these 22 subjects. The results were similar (OR, 1.6; 95% CI, 1.1–2.3).

Table 2 presents the relationship between the use of replacement estrogens after menopause and risk of renal cell carcinoma. Ever use was associated with a statistically nonsignificant 20% excess risk ($P = 0.23$). There was an indication that risk increased with increasing levels of exposure such that women with a lifetime cumulative dose of about 2 g of replacement estrogens experienced a statistically significant 80% increase in renal cell carcinoma risk. However, this association was substantially attenuated and was no longer statistically significant after adjustment for a history of hysterectomy (Table 2).

Table 3 presents the relationship between use of birth control pills and risk of renal cell carcinoma. There was no

[3] The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 2 Use of replacement estrogens and risk of renal cell carcinoma

	Cases[a]	Controls[a]	OR[b] (95% CI)	OR[c] (95% CI)
Ever used replacement estrogens				
No	227	241	1.0	1.0
Yes	192	179	1.2 (0.9–1.6)	1.0 (0.7–1.3)
Oral estrogens only	170	154	1.2 (0.9–1.7)	1.0 (0.7–1.4)
Usual monthly dose of estrogen pills (mg)[d]				
<15	40	33	1.4 (0.8–2.5)	1.2 (0.6–2.1)
15–<25	37	33	1.3 (0.9–2.2)	1.1 (0.6–1.9)
25+	51	43	1.4 (0.9–2.2)	1.0 (0.6–1.6)
Cumulative lifetime dose of estrogen (mg)[d]				
<473	33	37	1.0 (0.6–1.7)	0.8 (0.5–1.4)
473–<1980	40	35	1.5 (0.9–2.5)	1.2 (0.7–2.1)
1980+	55	37	1.8 (1.1–3.0)	1.3 (0.7–2.2)

[a] Three cases and two controls were excluded from the analysis due to unknown status of estrogen replacement use.
[b] Adjusted for level of education.
[c] Adjusted for level of education and history of hysterectomy.
[d] The sum was less than the total number of users due to the exclusion of subjects with a missing dose in the analysis.

evidence that use of birth control pills had any influence on subsequent risk of renal cell carcinoma.

We investigated the possible association between parity and renal cell carcinoma. Relative to women who never had a pregnancy, those with up to four pregnancies exhibited no increase in risk (OR, 1.1; 95% CI, 0.7–1.6), whereas women with five or more pregnancies showed a statistically nonsignificant 40% elevation in risk (95% CI, 0.8–2.4). This modest association was further attenuated after adjustment for a history of hysterectomy (OR, 1.2; 95% CI, 0.7–2.1).

We examined the possible confounding or risk-modifying effects of other risk factors on the hysterectomy-renal cell carcinoma association. Results showed that the effect of a history of hysterectomy on the risk of renal cell carcinoma was independent of the effects of all other risk factors (Table 4).

There were 31 case-control pairs who were not matched on race. We repeated all analyses after excluding these 31 pairs, and the results were unchanged. We also repeated all analyses on the subset of 283 case-control pairs in which the control subjects were first eligible controls. Again, the results were similar to those based on the full data set.

Discussion

The major finding in this report is an increased risk of renal cell carcinoma among hysterectomized women relative to those who never had this surgical procedure. Previously, five case-control studies had examined the possible association between a history of a hysterectomy, with and without oophorectomy, and renal cell carcinoma risk (5, 6, 8, 11, 16). In all studies, more cases than controls reported a history of a hysterectomy (ORs ranging from 1.1 to 1.9), but only two of these hysterectomy-cancer associations were statistically significant (6, 16). Two of the studies also investigated the possible differential risk of renal cell carcinoma following a hysterectomy with and without oophorectomy (5, 6). Whereas Lindblad *et al.* (5) noted an increased cancer risk only in women who had a hysterectomy with an accompanying oophorectomy (either unilateral or bilateral), Chow *et al.* (6) observed an increased cancer risk among hysterectomized women without regard to their oophorectomy status. Both studies also examined cancer risk in women who had undergone an oophorectomy alone. No association was noted in either study. A history of an oophorectomy was not assessed in the current study. Therefore, we could not address whether or not risk varied between hysterectomized women with and without a history of an oophorectomy.

We considered the possibility that the excess hysterectomies observed among renal cancer cases were the result of metastatic renal cell carcinomas misdiagnosed as primary cancers of the female genital tract. The clear cell variant of renal cell cancer can metastasize to the female genital tract and be misdiagnosed as primary cancers of the uterus, cervix uteri, ovary, or vagina, which may show similar histological features (23). Among all hysterectomized women in our study, 22 subjects (12 cases and 10 controls) had the surgery due to cancer being diagnosed in the pelvic region (uterus, cervix uteri, ovary, or vagina). The hysterectomy-cancer association remained unchanged after we excluded these 22 subjects from the analysis.

It has been suggested that the lower incidence of renal cell carcinoma in women than in men in most populations (24) may be indicative of endocrine involvement in disease development. There is experimental data to support this hormonal hypothesis. Deguchi *et al.* (25) demonstrated that the incidence of carcinogen-induced renal cell carcinoma is directly affected by sex hormones. Specifically, testosterone treatment or ovariectomy increased the incidence of renal cell carcinoma in carcinogen-treated rats, whereas estradiol treatment or castration decreased the incidence. Therefore, the decrease in natural estrogens following hysterectomy, usually with accompanying oophorectomy (at least 50% of hysterectomies performed in the United States are accompanied by bilateral oophorectomy; Ref. 26), may be the reason for the increase in risk of renal cell carcinoma in hysterectomized women.

However, previous limited epidemiological data do not support a hormonal hypothesis, and our large study, by and large, is not supportive either. In the present study, there was no association between cancer risk and use of oral contraceptives, replacement estrogens, or parity after adjustment for history of hysterectomy, which is consistent with the overall findings on such factors from previous studies.

In this study, we found little evidence that use of oral contraceptives influences the risk of renal cell carcinoma. Our results are consistent with published cohort findings (12), although findings from case-control studies included both decreased (5–7) and increased risk (9, 11) associated with oral contraceptive use.

In the current study, we noted a significant increase in

Table 3 Use of oral contraceptives and risk of renal cell carcinoma

	Cases	Controls	OR[a] (95% CI)	OR[b] (95% CI)
Ever used oral contraceptives				
No	258	255	1.0	1.0
Yes	164	167	1.0 (0.7–1.4)	1.0 (0.7–1.4)
Age started (yr)				
<20	25	23	1.0 (0.5–2.2)	1.0 (0.5–2.2)
20–<30	71	82	0.8 (0.5–1.3)	0.8 (0.5–1.3)
30–<40	46	39	1.3 (0.7–2.1)	1.3 (0.7–2.2)
40+	20	18	1.2 (0.6–2.3)	1.2 (0.6–2.4)
Total duration (mo)				
<12	44	43	1.1 (0.7–1.8)	1.1 (0.7–1.8)
12–<60	50	61	0.9 (0.5–1.4)	0.9 (0.5–1.4)
60–<120	36	34	1.1 (0.6–1.9)	1.1 (0.6–1.9)
120+	34	26	1.3 (0.7–2.3)	1.3 (0.7–2.3)
Cumulative lifetime dose of estrogen (mg)[c]				
<8.9	59	56	1.1 (0.7–1.7)	1.1 (0.7–1.8)
8.9–<44.2	46	60	0.8 (0.5–1.3)	0.8 (0.5–1.3)
44.2+	59	48	1.2 (0.8–2.0)	1.2 (0.8–1.9)

[a] Adjusted for level of education.
[b] Adjusted for level of education and history of hysterectomy.
[c] The sum was less than the total number of users due to the exclusion of subjects with a missing value in the analysis.

Table 4 Hysterectomy and risk of renal cell carcinoma stratified by other risk factors

	Cases[a]	Controls[b]	OR[c] (95% CI)
Cigarette smoking			
Never	70	53	1.9 (1.2–3.1)
Ever	107	72	1.4 (0.9–2.2)
History of hypertension			
No	98	83	1.6 (1.1–2.5)
Yes	79	42	1.6 (0.97–2.7)
Body mass index (kg/m^2)			
Below median[d]	93	86	1.4 (0.96–2.2)
Above median	84	39	1.8 (1.1–3.0)
Cruciferous vegetable intake (times/yr)			
Below median[e]	94	59	1.6 (1.03–2.4)
Above median	83	66	1.6 (1.03–2.6)
Regular use of analgesics			
No	72	65	1.6 (1.1–2.5)
Yes	105	60	1.7 (1.1–2.6)
Regular use of amphetamines			
No	154	116	1.6 (1.2–2.2)
Yes	23	9	2.0 (0.4–9.4)

[a] Number of cases with a history of hysterectomy within the specified subgroup.
[b] Number of controls with a history of hysterectomy within the specified subgroup.
[c] Reference group, no history of hysterectomy. ORs were computed using unconditional logistic regression models that included age, level of education (high school or less, college or above), and all of the other risk factors listed in the table.
[d] Median, 24.4 kg/m^2.
[e] Median, 159.5 times/yr.

renal cell cancer risk in heavy users of replacement estrogens that was explicable by hysterectomy status because replacement estrogens are frequently prescribed to women who undergo hysterectomy.

Seven case-control studies have investigated the relationship between parity and renal cell cancer risk in women. Results are mixed. Three studies (5–7) reported a positive association, whereas four others (8–11) observed no association. In the present study, women who had five or more pregnancies experienced a 40% but not statistically significant increased risk of renal cell carcinoma relative to those with fewer pregnancies. This moderate, positive association between parity and risk was also partially explained by history of hysterectomy because hysterectomy is positively associated with high parity (27).

Alternatively, damage to the kidney as a result of unintentional ureteral injury during the operation may explain the elevated risk of renal cell cancer among hysterectomized women. The anatomical proximity of the pelvic portion of the ureter to the female reproductive organs renders it vulnerable to injury during hysterectomy (28). The incidence of ureteral injury as a result of hysterectomy is believed to be about 1–2% (29–33). This figure is likely to be a minimum estimate; there is some evidence that the majority of such injuries were undetected during surgery and in the postoperative period (30–32, 34). Such ureteral injuries (*e.g.*, complete or partial ligation or transection or even excision; Ref. 32) can result in the dilation of the renal pelvis (hydronephrosis) and eventual renal damage (32, 35).

One possible way to confirm that hysterectomized cases were more likely than female controls to incur ureteral injury during the operation is to review the surgical reports of both groups of hysterectomized women. One would hypothesize that the prevalence of ureter damage noted in surgical reports would be higher among female cases than among female controls. Unfortunately, this confirmatory exercise may not be feasible, given that many of these surgeries occurred decades ago. Many of the surgeons who performed these operations may have retired or died and thus may be difficult if not impossible to trace. Furthermore, even if the surgeon is still in practice and is reached, the relevant report may have been destroyed (in California, physicians are legally required to keep medical charts for only 7 years).

In rats, unilateral ureteral ligation and hydronephrosis lead to malignant renal cell tumors in the contralateral kidneys (36, 37). This surprising observation has been hypothesized to relate to a transient compensatory increase in DNA replication in the contralateral kidney, which is similar to what occurs in rodent models of hepatocarcinogenesis following partial hepatectomy (38, 39).

Hysterectomy is one of the most frequently performed surgeries in the United States, second only to the Caesarian section. During the 10-year period between 1965 and 1975, the number of hysterectomies performed each year in the United States increased from 427,000 to 725,000, but it has subsequently declined to <600,000/year (40, 41).

In summary, this study found a nearly 2-fold, statistically significant increased risk of renal cell carcinoma among women with a history of hysterectomy. Our study also clearly demonstrated a lack of association between renal cancer risk and hormone-related factors, such as use of oral contraceptives and replacement estrogens and parity, thus suggesting the possibility of a non-endocrine-related mechanism underlying the observed hysterectomy-renal cancer association. We conjecture that unintentional injury to the ureter during the surgical procedure, which results in renal cell damage and consequent renal cell proliferation, may be a cause of the increased cancer risk in hysterectomized women.

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