Risk of Renal Cell Carcinoma After Hysterectomy

Daniel Altman, MD, PhD; Li Yin, PhD; Anna Johansson, MSc; Cecilia Lundholm, MSc; Henrik Grönberg, MD, PhD

Background: Hysterectomy is the most common gynecologic operation among women; study findings indicate that hysterectomy is associated with renal cell carcinoma.

Methods: To assess the effects of hysterectomy on the incidence and risk of renal cell carcinoma, we performed a population-based cohort study using data from 184 945 women who had undergone hysterectomy (hereafter referred to as women with hysterectomy) and from 657 288 matched women who had not undergone hysterectomy (hereafter referred to as women without hysterectomy) by linking nationwide Swedish health care registers, including the Swedish Inpatient Register and the Swedish Cancer Register (January 1, 1973, through December 31, 2003). Risk of renal cell carcinoma owing to hysterectomy status was assessed using Cox proportional hazards regression models with hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: The crude incidence rates of renal cell carcinoma were 17.4 cases per 100 000 person-years among women with hysterectomy and 13.1 cases per 100 000 person-years among women without hysterectomy. This corresponded to an adjusted overall HR of 1.50 (95% CI, 1.33-1.69) for renal cell carcinoma among women with hysterectomy vs women without hysterectomy. The risk of renal cell carcinoma was age dependent, and the highest risk was found within 10 years of surgery among women who underwent hysterectomy at age 44 years or younger (HR, 2.36; 95% CI, 1.49-3.75). The overall risk of renal cell carcinoma after hysterectomy was consistently increased and of similar magnitude over the time strata: HR, 1.50 (95% CI, 1.26-1.78) for years 0 to 10; 1.49 (1.22-1.82) for years 11 to 20; and 1.51 (1.05-2.16) for more than 20 years after surgery.

Conclusions: Hysterectomy for benign indications was significantly associated with renal cell carcinoma. Women undergoing the procedure at a young age were at particular risk.

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Author Affiliations:
Department of Medical Epidemiology and Biostatistics (Drs Altman, Yin, and Grönberg and Mss Johansson and Lundholm) and Division of Obstetrics and Gynecology, Department of Clinical Sciences, Danderyd Hospital (Dr Altman), Karolinska Institutet, Stockholm, Sweden.

RENAL CELL CARCINOMA COMposes the majority of the 30 000 new cases of renal parenchyma adenocarcinoma occurring each year in the United States.[1] Although kidney cancer mortality has declined in several European countries over the last decade, the overall incidence has remained stable.[2] Renal cell carcinoma is the eighth most common cancer among women in the United States.[3] Several environmental risk factors for renal cell carcinoma are well documented, but its relationship with reproductive factors remains poorly understood.[4]

Hysterectomy for benign indications is associated with increased risk of renal cell carcinoma.[5-8] However, the evidence is mostly derived from hospital-based series or retrospective studies lacking control of the temporal aspects of the relationship; therefore, the suggested association is contentious.[9,10] In the United States, more than 600 000 hysterectomies are performed annually,[11] which makes it one of the most common surgical procedures, corresponding to 1 in 3 US women who have their uterus removed.[12,13]

Most hysterectomies are performed based on relative indications for noncancerous conditions[11,14] and represent a preventable cause of renal cell carcinoma. Therefore, it is important to understand the role of hysterectomy in renal cell carcinogenesis, for which metastatic disease is present in 20% to 30% of patients at the time of diagnosis. We assessed the long-term risk of renal cell carcinoma after hysterectomy for benign indications in a large population-based cohort of women identified through linkage of high-quality nationwide Swedish health care registers.

METHODS

We used data from several nationwide registers for which reporting is mandatory, regulated by law, and supervised by the Swedish Board of Health and Welfare. Established in 1964, the Swedish Inpatient Register contains

data on individual hospital discharges. Each inpatient discharge record contains (1) the dates of hospital admission and discharge; (2) up to 8 discharge diagnoses, coded according to *International Classification of Diseases* (*ICD*) revisions 7 through 10; and (3) up to 12 operation codes from the Swedish Classification of Operations and Major Procedures. Correct coding for surgical procedures is achieved for 98% of records in the Swedish Inpatient Register, with less than 1% yearly loss to registration.[15] The Swedish Inpatient Register also includes information about the unique national registration number, assigned to all Swedish residents, which allows unambiguous record linkage across all nationwide registers in Sweden.

Established in 1958, the Swedish Cancer Register includes histologically verified incident cancers and is more than 95% complete (http://www.socialstyrelsen.se/english). To facilitate comparisons over time, registration of cancers has been classified according to *ICD*-7 codes, as well as codes based on later *ICD* versions. The Swedish Birth Register includes prospectively collected information on more than 99% of all births in Sweden. The Swedish Cause-of-Death Register includes information about the date and cause of death among all residents, with completeness exceeding 99%. The Swedish Register of Population and Population Changes includes information about dates of birth, death, emigration, and immigration among all residents.

Using the Swedish Inpatient Register, we identified all hysterectomy records from January 1, 1973, through December 31, 2003. For each woman who had undergone hysterectomy (n=227 389) (hereafter referred to as women with hysterectomy), we randomly selected 3 women from the Swedish Register of the Total Population who had not undergone hysterectomy (n=682 167) (hereafter referred to as women without hysterectomy), who were individually matched by year of birth and by county of residence during the year of hysterectomy. Using national registration numbers, women with and without hysterectomy were linked to the Swedish Birth Register, Swedish Cancer Register, Swedish Emigration Register, and Swedish Cause-of-Death Register.

Within the Swedish Cancer Register, we identified all women with and without hysterectomy who had a record of renal cell carcinoma. We also identified all cases of urinary tract cancer and bladder cancer. Women in both cohorts were excluded from analyses if the death or birth date was incorrect (n=4), if age at the time of hysterectomy was younger than 18 years (n=134), or if renal cell carcinoma, urinary tract cancer, or bladder cancer preceded hysterectomy (or the corresponding study enrollment date for women without hysterectomy) or hysterectomy was performed for malignant indications (n=67 185). Women with and without hysterectomy contributed person-years to the study from the date of hysterectomy or from the corresponding date for women without hysterectomy until death, emigration, the end of the observation period (December 31, 2003), or the occurrence of renal cell carcinoma, urinary tract cancer, bladder cancer, or other primary cancer, whichever occurred first. Women without hysterectomy were censored from analysis at the time of hysterectomy and otherwise contributed person-years by the same criteria as women with hysterectomy.

Specific codes from the Swedish Classification of Operations and Major Procedures for 1973 to 1996 and 1997 to 2003 were used to identify hysterectomy and types of hysterectomy in the Swedish Inpatient Register (operation codes 7210, 7211, 7261, 7262, and 7467 for 1973-1996 and operation codes LCD00, LCC10, LCD10, LCD11, LCD01-LCD04, and LEF13 for 1997-2003). Information about the following cancer diagnoses was derived from the Swedish Cancer Register using *ICD*-7 nomenclature: renal cell carcinoma (code 180.0), cancer of the renal pelvis (code 180.1), cancer of the ureter (code 181.1), bladder cancer (code 181.0), and lung cancer (codes 161-163). Data on the number of childbirths were collected from the Swedish Birth Register.

We calculated unadjusted incidence rates as the number of cases per 100 000 person-years with 95% confidence intervals (CIs) based on Poisson distribution. We used Cox proportional hazards regression models to compute hazard ratios (HRs) conditional for the following 3 matching variables: birth year, county, and calendar time. Cancer risk was determined separately for renal parenchyma, urinary tract (renal pelvis and ureters), and bladder. Hazard ratios for hysterectomy relative to nonhysterectomy were computed by stratification according to age at hysterectomy in population quartiles and time since hysterectomy in 10-year bands. The effects of various hysterectomy techniques were estimated relative to control subjects without hysterectomy. Compared with women without hysterectomy, women with hysterectomy are smokers at increased risk not only of renal cell carcinoma but also of lung cancer. Because we had no access to information about smoking from the registers, we investigated whether women after hysterectomy were at increased risk of lung cancer as a measure of smoking exposure.

Renal cell carcinoma is associated with leiomyomatosis, a hereditary disorder characterized by multiple benign cutaneous and uterine leiomyomas.[16,17] Because leiomyoma of the uterus accounts for approximately 50% of hysterectomy indications in our study population,[14] we put forth a secondary hypothesis that the risk of renal cell carcinoma may be attributable to the underlying uterine disorder (ie, leiomyoma) rather than the hysterectomy. This nested analysis was restricted to the cohort of women with hysterectomy, among whom we estimated the risk of renal cell carcinoma based on whether the preoperative indication for hysterectomy was categorized as uterine leiomyoma or as nonleiomyoma (reference group).

We also investigated the effects of parity, categorized as the number of deliveries (0, 1-2, or >2). Because information on the number of childbirths and delivery mode was available only from 1973 onward, we restricted the analysis to a subgroup of women born in 1952 or later and estimated the HRs for the childbirth categories relative to nonvaginal birth.

All statistical analyses were performed using commercially available software (SAS, version 9.1, SAS Institute, Cary, North Carolina). The study was approved by the research ethics committee at Karolinska Institutet, Stockholm, Sweden, and conforms to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for reporting observational studies (http://www.strobe-statement.org).

RESULTS

The final cohort that was eligible for analysis consisted of 184 945 women with hysterectomy and 657 288 women without hysterectomy, with accumulated follow-up times of 2 061 556 and 7 631 824 person-years, respectively. **Table 1** gives the incidence rates and HRs for cancer owing to hysterectomy for benign indications. The unadjusted incidence rate of renal cell carcinoma was higher among women with vs without hysterectomy, whereas the rates of urinary tract cancer and bladder cancer showed minor differences between the 2 cohorts. Conversely, compared with the nonhysterectomy cohort, hysterectomy significantly increased the overall risk of renal cell carcinoma (HR, 1.50; 95% CI, 1.33-1.69).

The effects of age at hysterectomy and of time since hysterectomy are given in **Table 2**. The excess risk of

Table 1. Unadjusted Incidence Rates per 100 000 Person-Years and Hazard Ratios (HRs) for Renal Cell Carcinoma, Urinary Tract Cancer, and Bladder Cancer Relative to Hysterectomy Statusa

Cohort	Renal Cell Carcinoma			Urinary Tract Cancerb			Bladder Cancer		
	Cases, No. (%)	Incidence Rate (95% CI)	HR (95% CI)	Cases, No. (%)	Incidence Rate (95% CI)	HR (95% CI)	Cases, No. (%)	Incidence Rate (95% CI)	HR (95% CI)
Nonhysterectomy (n=657 288)	995 (0.15)	13.04 (12.25-13.87)	1 [Reference]	149 (0.02)	1.95 (1.66-2.29)	1 [Reference]	1170 (0.20)	15.33 (14.48-16.23)	1 [Reference]
Hysterectomy (n=184 945)	357 (0.20)	17.32 (15.61-19.21)	1.50 (1.33-1.69)	42 (0.02)	2.04 (1.51-2.76)	1.24 (0.88-1.75)	324 (0.20)	15.72 (14.09-17.52)	1.21 (1.07-1.37)

Abbreviation: CI, confidence interval.
[a] Conditional analysis with HRs adjusted for year of birth and for county of residence during the year of hysterectomy by matching.
[b] Includes cancer of the renal pelvis and ureters.

Table 2. Hazard Ratios (HRs) for Renal Cell Carcinoma, Urinary Tract Cancer, and Bladder Cancer Over Time Relative to Hysterectomy Statusa

Age at Hysterectomy by Population Quartile, y	Hysterectomy Cohort vs Nonhysterectomy Cohort, HR (95% CI)			
	Time Since Hysterectomy, y			
	0-10	11-20	>20	Overall
Renal cell carcinoma				
≤44	2.36 (1.49-3.75)	2.09 (1.42-3.08)	1.40 (0.72-2.75)	2.03 (1.55-2.67)
45-49	1.60 (1.13-2.25)	1.32 (0.92-1.90)	1.55 (0.86-2.81)	1.47 (1.17-1.85)
50-57	1.25 (0.88-1.76)	1.23 (0.82-1.85)	1.62 (0.84-3.09)	1.29 (1.01-1.64)
≥58	1.40 (1.05-1.86)	1.53 (0.95-2.47)	1.37 (0.16-11.83)	1.43 (1.12-1.83)
Overall	1.50 (1.26-1.78)	1.49 (1.22-1.82)	1.51 (1.05-2.16)	1.50 (1.33-1.69)
Urinary tract cancer				
≤44	2.16 (0.36-12.91)	. . .	0.63 (0.07-5.43)	0.69 (0.20-2.39)
45-49	1.62 (0.65-4.01)	1.64 (0.62-4.37)	. . .	1.41 (0.74-2.71)
50-57	1.17 (0.38-3.58)	1.22 (0.40-3.75)	1.02 (0.22-4.83)	1.15 (0.57-2.34)
≥58	1.48 (0.80-2.72)	1.04 (0.30-3.59)	. . .	1.36 (0.79-2.34)
Overall	1.48 (0.95-2.31)	1.08 (0.60-2.05)	0.63 (0.18-2.14)	1.24 (0.88-1.75)
Bladder cancer				
≤44	1.75 (1.02-3.02)	1.58 (1.04-2.41)	1.58 (0.84-2.98)	1.63 (1.21-2.19)
45-49	1.42 (0.96-2.08)	0.79 (0.52-1.19)	1.55 (0.90-2.67)	1.14 (0.89-1.46)
50-57	1.59 (1.11-2.27)	0.71 (0.43-1.15)	0.65 (0.32-1.32)	1.05 (0.81-1.36)
≥58	1.37 (1.08-1.75)	0.82 (0.50-1.34)	1.61 (0.53-4.84)	1.23 (1.00-1.52)
Overall	1.45 (1.23-1.72)	0.92 (0.74-1.15)	1.22 (0.87-1.70)	1.21 (1.07-1.37)

Abbreviations: CI, confidence interval; ellipses, not applicable.
[a] Conditional analysis with HRs adjusted for year of birth and for county of residence during the year of hysterectomy by matching. Ellipsis indicates inadequate number of cases to calculate HR.

renal cell carcinoma following hysterectomy was consistent through the age strata but showed an inverse correlation with increasing age at hysterectomy: the highest overall risk of renal cell carcinoma was observed among the youngest women (HR, 2.03; 95% CI, 1.55-2.67), and risk attenuated with increasing age. Moreover, among the youngest group of women with hysterectomy, the risk diminished to a nonsignificant level over time. The overall risk of renal cell carcinoma after hysterectomy was consistently elevated over the time strata and was of similar magnitude throughout the observation period. We found no excess risk of lung cancer among women with vs without hysterectomy (HR, 1.05; 95% CI, 0.98-1.13), suggesting that the association between hysterectomy and renal cell carcinoma was not confounded by smoking.

The adjusted overall risk of bladder cancer after hysterectomy was of smaller magnitude (HR, 1.21; 95% CI, 1.07-1.37) but showed a similar age-related risk pattern as that seen for renal cell carcinoma (Table 2). For bladder cancer, the positive association was significant only during the first 10 years after hysterectomy, after which the association became weaker and nonsignificant, except for the youngest women, for whom the risk persisted up to 20 years after hysterectomy. No significant association was noted between hysterectomy and cancer of the renal pelvis and ureters regardless of age category, and only minor and nonsignificant variations were noted over time.

Table 3 gives cancer risk owing to various types of hysterectomy. Compared with women who underwent total abdominal hysterectomy, women who underwent vaginal hysterectomy had significantly lower risks of subsequent renal cell carcinoma (HR, 0.75; 95% CI, 0.45-1.23) and bladder cancer (0.55; 0.34-0.89). Subtotal abdominal hysterectomy did not convey a protective or detrimental effect on the association. Because of insuf-

Table 3. Risk of Renal Cell Carcinoma, Urinary Tract Cancer, and Bladder Cancer Relative to the Type of Hysterectomy[a]

	Renal Cell Carcinoma		Urinary Tract Cancer		Bladder Cancer	
Type of Hysterectomy	Cases, No.	HR (95% CI)	Cases, No.	HR (95% CI)	Cases, No.	HR (95% CI)
None (n=657 288)	995	1 [Reference]	149	1 [Reference]	1170	1 [Reference]
Total abdominal (n=118 687)	251	1.51 (1.31-1.74)	28	1.19 (0.79-1.79)	225	1.24 (1.07-1.43)
Subtotal abdominal (n=45 302)	89	1.79 (1.43-2.24)	8	1.24 (0.60-2.58)	81	1.54 (1.22-1.94)
Vaginal (n=19 767)	16	0.75 (0.45-1.23)	6	1.51 (0.66-3.47)	17	0.55 (0.34-0.89)
Laparoscopic and laparoscopy-assisted vaginal (n=1154)	0	. . .	0	. . .	1	3.06 (0.42-22.39)

Abbreviations: CI, confidence interval; ellipses, not applicable; HR, hazard ratio.
[a]Conditional analysis with HRs adjusted for year of birth and for county of residence during the year of hysterectomy by matching. Type of hysterectomy is according to the Swedish Classification of Operations and Major Procedures for 1973 to 1996 and for 1997 to 2003.

ficient numbers of observations, risk analysis was impossible or yielded imprecise risk estimates for laparoscopic and laparoscopy-assisted vaginal hysterectomy.

Next, we estimated risk owing to preoperative medical diagnosis categorized as leiomyoma of the uterus or nonleiomyoma. Other indications included menometrorrhagia without leiomyoma, adenomyosis, pelvic organ prolapse, and benign tumors. Compared with women who had no preoperative *ICD* diagnosis of leiomyoma (n=75 088), women who had a diagnosis of leiomyoma (n=109 857) had no increased risk of renal cell carcinoma (HR, 1.06; 95% CI, 0.83-1.35), urinary tract cancer (0.92; 0.45-1.88), or bladder cancer (0.84; 0.66-1.07).

To determine the influence of childbirth on renal cell carcinoma risk, we restricted our study population to a subsample of women born in 1952 or later (n=136 891). Compared with women who had not given birth, the adjusted risk estimates for renal cell carcinoma, urinary tract cancer, and bladder cancer showed no association with the number of childbirths among women with vs without hysterectomy (data available from the authors).

COMMENT

The results of this large population-based cohort study suggest that women with hysterectomy for benign indications are at increased short-term and long-term risk of renal cell carcinoma compared with women who have an intact uterus. In view of the many hysterectomies performed for benign indications in the United States and other industrialized countries, a 50% increased risk of renal cell carcinoma after hysterectomy may portend important public health consequences. Renal cell carcinoma is often diagnosed at an advanced stage, and one-third of patients with localized disease will have a recurrence. This may be of particular importance among women who have had their uterus removed at age 44 years or younger, who carry the highest risk of renal cell carcinoma diagnosis.

We do not completely understand the biologic mechanism by which hysterectomy for benign indications affects the risk of renal parenchyma cancer. It may result from iatrogenic kinking or narrowing of the distal ureters secondary to changes in posthysterectomy pelvic anatomy. Persistent hydronephrosis has been radiologically verified up to 6 months after hysterectomy without recognized injury to the ureters during surgery, and the prevalence of persistent hydronephrosis after radical hysterectomy has been estimated to be 15%.[18] Therefore, ureteropelvic junction obstruction and persistent subclinical hydronephrosis after hysterectomy may be involved in renal cell proliferation and cancer transition of the renal parenchyma.[7]

Risk of renal cell carcinoma owing to hysterectomy varied according to age at the time of enrollment in the cohort (ie, hysterectomy or the corresponding date for controls). The strongest association between hysterectomy and subsequent renal cell carcinoma was observed among women age 44 years or younger at the time of hysterectomy. In this age group, leiomyoma is the predominant medical condition necessitating a surgical intervention.[14] Mutations of the gene encoding for the tricarboxylic cycle enzyme fumarate hydratase have been shown to predispose to benign cutaneous and uterine leiomyomas, as well as to renal cell carcinoma among those affected by hereditary leiomyomatosis.[19] Therefore, we tested a theory that women undergoing hysterectomy because of leiomyoma of the uterus would be at particular risk of subsequent renal cell carcinoma. Under these suppositions, the observed association between hysterectomy and renal cell carcinoma would be a consequence of the underlying medical condition leading up to hysterectomy rather than of the operation per se. However, we found no positive association between a preoperative diagnosis of leiomyoma and renal cell carcinoma (or any other cancer of the urinary tract). The role of hormonal factors in the association cannot be ruled out altogether, but 2 large cohort studies[10,20] showed no clear association of hormone-related factors such as hormone therapy, oral contraceptive use, and menopausal status with the risk of renal cell carcinoma. The mechanisms underlying the strong association between hysterectomy and renal cell carcinoma among younger women in particular remain elusive, and the need for further research is highlighted by a 2009 study[21] showing that younger women are also at increased risk of bilateral renal cell carcinoma.

Classification of renal cell carcinoma in the Swedish Cancer Register is confirmed by histopathologic assessment, which differentiates between various cancers of the renal parenchyma and renal pelvis, which effectively mini-

mizes misclassification bias. We found no excess risk of cancer in the transitional epithelium of the renal pelvis or ureters related to hysterectomy. However, there was a significant (albeit weak) association between hysterectomy and bladder cancer during the first 2 decades after surgery. Detection bias may have contributed to an increased short-term cancer incidence relative to the surgical procedure, but this should not come into play decades after surgery. A unique feature of the present study is that we are able to distinguish not only between different cancers of the urinary tract but also between effects related to the various types of hysterectomy. Compared with total abdominal hysterectomy, vaginal hysterectomy was associated with a protective effect against renal cell carcinoma and bladder cancer. This could be explained by the age-dependent risk association in the present study, as younger women are more likely to undergo an abdominal procedure, whereas older women are more often selected for the vaginal approach.[14] The less invasive subtotal hysterectomy technique, in which dissection of the bladder is sparse, did not convey a protective effect against renal cell carcinoma or bladder cancer. Therefore, it seems unlikely that overt or occult intraoperative injury to the bladder has a role in cancer formation of the bladder or renal parenchyma.

The study observation period included more than 1300 cases of renal cell carcinoma, and almost 10 million person-years at risk were accumulated. The high-quality data and uniform classification of exposure and outcomes lend further strength to our findings. Selection bias was avoided by using population-based registers with negligible enrollment loss. We were unable to adjust the analysis for smoking and obesity because this information is not collected in any of the registers. However, the presence of obesity would tend to underestimate the risk of renal cell carcinoma attributed to hysterectomy because obese women are less likely to undergo elective gynecologic surgery.[22] Although smoking is a risk factor for bladder cancer and renal cell carcinoma, it has not been convincingly linked to benign gynecologic indications leading to hysterectomy, such as leiomyoma,[23] and women who underwent hysterectomy in previous cohort studies[24,25] were not more likely to be smokers than women who did not undergo the procedure. We found no increased risk of lung cancer among women with hysterectomy, which further supports the notion that smoking does not confound the association between hysterectomy and renal cell carcinoma.

There was no increased risk of renal cell carcinoma among parous vs nulliparous women regardless of hysterectomy status. Furthermore, we could not confirm that among parous women, renal cell carcinoma risk is positively associated with the number of childbirths, as has been suggested.[10] Because information on obstetric history was available only from 1973 onward, we assessed the association between childbirth and renal cell carcinoma in a subpopulation of women born in 1952 or later (ie, who were 51 years or younger at the end of the follow-up period). This poses a limitation in interpreting the long-term influence of childbirth on renal cell carcinoma among older women.

To summarize, our findings support the hypothesis that hysterectomy for benign indications increases the risk of renal cell carcinoma in the short term and in the long term. In addition, undergoing hysterectomy at a younger age was associated with a disproportionately increased risk of renal cell carcinoma. Given current trends in gynecologic surgery whereby women are offered hysterectomy at younger ages, this has important implications and may influence future occurrence of renal cell carcinoma. Further efforts are needed to identify groups of women at high risk of renal cell carcinoma in the aftermath of hysterectomy.

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Correspondence: Daniel Altman, MD, PhD, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, 171 77 Stockholm, Sweden (daniel.altman@ki.se).
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Images From Our Readers

From lake to lake: "This photograph was taken on the 5-Lakes Hike on Mount Pizol in Switzerland, July 2009."

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