Second primary malignancies in renal cortical neoplasms: an updated evaluation from a single institution

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Abstract

Purpose—To examine the incidence of secondary primary malignancies in patients with renal cortical neoplasms.

Methods—Between January 1989 and July 2010, 3647 patients underwent surgery at our institution for a renal cortical neoplasm and were followed through 2012. Occurrence of other malignancies was classified as antecedent, synchronous, or subsequent. All patients with antecedent malignancies ($n = 498$) and a randomly selected half of those with synchronous malignancies ($n = 83$) were excluded. The expected number of second primaries was calculated by multiplying Surveillance, Epidemiology, and End Results Program incidence rates of renal cortical neoplasms by person-years at risk within categories of age, sex, and year of diagnosis. The standardized incidence ratio (SIR) was calculated as observed cancers divided by expected incidence of the cancer, with approximation to the exact Poisson test used to obtain confidence intervals (CI) and p values.

Results—Of 3066 patients with renal cortical neoplasms, 267 had a second primary cancer; the five most common in men were prostate, colorectal, bladder, lung, and non-Hodgkin's lymphoma; the five most common in women were breast, colorectal, lung, endometrium, and thyroid. Men demonstrated higher than expected thyroid cancer rate (SIR 5.0; 95 % CI 1.83–10.88, $p = 0.002$),

and women had higher than expected rates of stomach cancer (SIR 5.0; 95 % CI 1.61–11.67, $p = 0.004$) and thyroid cancer (SIR 4.62; 95 % CI 1.69–10.05, $p = 0.003$).

Conclusions—The incidence of certain types of second malignancies may be higher in patients after diagnosis of renal cortical neoplasms compared to the general population. These observations can inform clinical follow-up in kidney cancer survivorship and future research studies.

Keywords

Kidney neoplasms; Renal cell carcinoma; Second malignancy

Introduction

The incidence rate of cortical renal neoplasms has been increasing in the USA over the last 30 years and is predicted to continue to increase until at least 2025 [1, 2]. In 2015, there were over 61,000 new cases of kidney cancer and over 14,000 disease-related deaths [3]. Interestingly, the 5-year survival rate for renal cortical neoplasms has increased from approximately 50 % among patients diagnosed between 1975 and 1977 to approximately 74 % for patients diagnosed between 2004 and 2010 [3]. Higher incidence and survival rates expose patients with a renal cortical mass to the risk of developing other primary malignancy during their follow-up. However, data on the most common second primary malignancies in these patients are limited.

Prior population-based and hospital-based studies examining new malignancies following renal cortical neoplasms revealed a 1.10–1.19 ratio of observed-to-expected rates of second primary malignancies [4–11]. An analysis of the Surveillance, Epidemiology, and End Results (SEER) data among 36,835 renal cortical neoplasm patients found significantly higher than expected rates of prostate, bladder, and thyroid cancers, melanoma, and leukemia [12]. Significantly higher rates of prostate, colorectal, bladder, and breast cancers, and non-Hodgkin's lymphoma were also found among 551 surgical patients treated at our institution for renal cell carcinoma (RCC) [9]. After stratifying by histologic subtype, patients with papillary RCC were found to be at increased risk of developing bladder cancer and prostate cancer [8]. Assessing the incidence and prognostic significance of second primary cancers among 58,174 RCC patients from the SEER database between 1973 and 2006, Chakraborty et al. [4] found a significantly higher than expected number of second primary malignancies with an observed-to-expected ratio of 1.18. The site-specific risk varied according to age, gender, race, and size of primary renal tumor.

Herein, we present an update of prior investigations performed at our institution [8, 9], reporting on the occurrence of second primary cancers among more than 3000 surgical patients with renal cortical masses managed between 1989 and 2010.

Materials and methods

Following institutional review board approval, we queried our prospectively maintained institutional database for all patients with renal cortical neoplasms managed surgically between 1989 and 2010. A total of 3647 evaluable patients were identified. The date of

surgery was used as date of diagnosis. For patients with multiple renal cortical malignancies treated with multiple surgical procedures, the date of the earliest operation was selected for analysis purposes. Data on all other malignancies experienced by each patient before or after their date of kidney surgery were extracted from the electronic medical records through 2012.

Other malignancies occurring more than 90 days prior to the surgery date were considered *antecedent*. Malignancies occurring between 90 days before and 90 days after the surgery date were considered *synchronous*. Malignancies occurring more than 90 days after the surgery date were considered *subsequent*. Using the Begg methodology, half of the synchronous cancers were randomly selected to be included in the group of patients with subsequent cancers. The remaining half of the synchronous cancers and the antecedent cancers were excluded from the analysis [13].

Follow-up time was calculated from the date of surgery until the date of the first subsequent malignancy or last follow-up. Person-years were calculated within 5-year age groups from 10 to 14 years through 85+ years, within 5-year diagnosis year groups from 1989 to 1994 through 2005 to 2010, and stratified by gender. Within each gender, all second primary sites with at least five observed cases were examined.

Age-, diagnosis year-, and gender-specific incidence rates were extracted for each malignancy site from the SEER nine database using SEER*Stat software version 8.1.5. The expected number of cases of each second malignancy was obtained by multiplying these incidence rates by the person-years at risk in each category. The standardized incidence ratio (SIR) for a second malignancy was calculated as the observed number of cases divided by the expected number of cases. Statistical tests and 95 % confidence intervals (CIs) were calculated, assuming that the observed number of second malignancies follows a Poisson distribution. Statistical significance was defined as $p < 0.05$. All statistical analyses were conducted using the statistical analysis system (SAS) software version 9.4 (SAS Institute Inc., Cary, NC) and the R software version 3.1.1 (R Core Development Team, Vienna, Austria).

Results

Of 3647 surgical patients with a cortical renal mass, 848 experienced another malignancy. Malignancies were antecedent in 498 patients, synchronous in 166, and subsequent in 184. Prostate, breast, and colorectal cancers were the most common antecedent tumors ($n = 498$), while prostate, colorectal, and gynecological cancers were the most common types of synchronous tumors that were excluded ($n = 83$). After excluding all patients with an antecedent malignancy and half of those with a synchronous second primary malignancy, our cohort included 3066 patients. Demographic and clinical characteristics of the study cohort, which was 64.3 % male and 89.6 % Caucasian, are presented in Table 1. Median age was 60.9 years [interquartile range (IQR) 51.9–69.2). The majority (61 %) of patients had pathological T1 disease, and the predominant (63 %) subtype was clear-cell RCC.

A total of 267 patients (9 %) were considered as having a second primary malignancy in our cohort. For these patients, median time to development of second primary was 24.2 months (IQR: 2.0, 62.7). Among the 2799 patients who did not develop a second primary, median follow-up time was 62.8 months (IQR: 34.6, 107.4). The observed and expected numbers of second primary malignancies stratified by gender are listed in Table 2. Among men, the most common types of second primary cancers were prostate, colorectal, bladder, and lung cancer, non-Hodgkin's lymphoma, thyroid cancer, melanoma, and pancreatic cancer. Among women, the most common types of second primary cancers were breast, colorectal, lung, endometrial, thyroid, and gastric cancer. The median time to second primary in males was 21.0 months (IQR: 2.0, 54.8) and for females was 32.1 months (IQR: 2.8, 73.8).

The rate of thyroid cancer in men was significantly higher than expected (SIR 5.0; 95 % CI 1.83–10.88; $p = 0.002$). The rate of lung cancer in men was significantly lower than expected [SIR of 0.45 (95 % CI 0.25–0.75; $p < 0.001$)]. Although more prostate cancers were observed than expected (SIR 1.19; 95 % CI 0.95–1.47), the difference was not statistically significant ($p = 0.06$). A similar pattern was observed in women, who had significantly higher than expected rates of thyroid cancer (SIR 4.62; 95 % CI 1.69–10.050; $p = 0.003$) and a lower SIR of lung cancer, although it was not statistically significant. Women had significantly higher than expected rates of stomach cancer (SIR 5.0; 95 % CI 1.61–11.67; $p = 0.004$) and lower than expected rates of breast cancer (SIR 0.47; 95 % CI 0.24–0.83; $p = 0.003$). A higher than expected yet not statistically significant rate of colorectal cancer was also observed among women.

All six men who developed thyroid cancer as a second primary were Caucasian and were diagnosed with their kidney tumor and thyroid cancer between the ages of 50 and 77 years. Thyroid cancer was symptomatic in two patients (one with palpable nodule; one with hypothyroidism and discrete nodule on ultrasound) and was found incidentally on surveillance imaging in three patients. In the remaining patient, the medical record lacked details on thyroid cancer presentation. In three patients, thyroid cancer was diagnosed within the same year as their kidney surgery for renal cortical neoplasm, suggesting a detection bias. The remaining three patients were diagnosed with thyroid cancer up to 13 years later. The histology of the kidney tumors was varied, but all were pathologic stage T2 or greater.

The six female patients who experienced a second primary thyroid cancer were diagnosed with their kidney tumor and thyroid cancer between the ages of 43 and 63 years. One female patient was African-American, whereas the others were Caucasian. Five patients presented with a palpable thyroid nodule; one patient had thyroid cancer discovered incidentally on surveillance imaging. Similar to males, there was a wide range of time between diagnoses. Unlike males, however, renal cortical neoplasms in these six females were primarily pathologic stage T1.

Symptomatic stomach cancer developed 2 years up to 12 years after renal surgery in five Caucasian women, whose ages at diagnosis of their renal cortical neoplasm ranged from 47 to 75 years. Histology revealed clear-cell RCC in all but one patient with renal cortical neoplasms.

Discussion

Identifying cancers which patients with renal cortical neoplasms might be at higher risk of developing can inform surveillance practices and shed light on factors that may be common to both diseases. In our cohort of over 3000 surgically treated patients with renal cortical neoplasms, a second primary malignancy was diagnosed in 267 patients. Compared to the general population, significantly higher than expected rates for thyroid cancer were found in both males and females. Female patients in our cohort also had an elevated SIR for gastric cancer. Significantly lower than expected rates were observed for lung cancer in males and for breast cancer in females. Because primary treatment in localized kidney cancer patients is predominantly surgical, the observed associations are unlikely to be due to treatment-related effects (e.g., chemotherapy or radiation therapy).

Findings of the current study are consistent with prior reports of patients with kidney cancer patients who face an elevated future risk of thyroid cancer [4, 11, 12]. Interestingly, second primary studies among patients with thyroid cancer have shown higher than expected rates of RCC [14, 15], and a large SEER cohort of 30,000 patients with thyroid cancer reported a significant excess risk of kidney cancer with no particular variability in age, gender, time after diagnosis, or histologic subtype [16]. Considering that the risk of one malignancy in the presence of the second appears to be reciprocal, the two cancers may be driven by a common mechanism such as a common environmental or genetic factor [4]. None of the established risk factors for kidney cancer, such as cigarette smoking, obesity, and hypertension, are associated with an increased risk of thyroid cancer. However, both cancers are considered metabolic diseases [17], and genetic variants in *VHL* [18], *MET* [19], and *SDH* [20] increase the risk of both thyroid and kidney cancers. Moreover, both familial papillary carcinomas of the thyroid and papillary carcinomas of the kidney are linked to the chromosome locus 1q21 [21]. Although all of the second primary thyroid cases detected in our study were of the papillary subtype, papillary RCC was not the initial histology in any of these patients. Both the thyroid and the kidney are highly vascularized organs, and metastatic spread from one site to the other has been previously reported [22–24]. Of note, all thyroid cancers subsequent to renal cortical neoplasms in the current study cohort were de novo malignancies with no evidence of metastatic spread from the primary renal cortical neoplasm.

To our knowledge, no prior study has found a significantly increased risk of subsequent stomach cancer among female patients with renal cortical neoplasms. Although tobacco smoking has been shown to increase the risk of developing both malignancies, the strength of the association is modest for gastric cancer. Infection with Helicobacter pylori, an established risk factor for gastric cancer, has not been associated with increased risk of developing renal cortical neoplasms. In the absence of replication of this finding in external populations, we interpret our finding of a higher than expected rate of stomach cancer in female patients with renal cortical neoplasms with caution.

The lower than expected rates of second primary lung cancer among patients included in this study are consistent with prior reports [10–12, 25]. Possible explanations for this finding could be that the survival of patients with an aggressive renal cortical neoplasm might be not

long enough to allow for the development of a second smoking-related primary malignancy, or that these patients died of a smoking-related comorbidity before developing lung cancer. Shiels et al. [26] recently found that among survivors of kidney cancer, current heavy smokers were more likely to die than never smokers. These findings might explain our inability to identify an elevated risk of second primary bladder cancer, which is also a smoking-related tumor.

The lower than expected rate of breast cancer in our cohort is supported by recent SEER data [12] and may relate to estrogen exposure. Recent meta-analyses of epidemiologic studies suggested that increasing parity and prior hysterectomy, both factors associated with decreased estrogen exposure, thus reducing the risk of breast cancer, increase the risk of RCC [27–29]. However, a recent study of second primaries among an international cohort of breast cancer patients found an excess risk of kidney cancer [30].

Findings of the current study are somewhat different from those observed with earlier evaluation of surgical patients with renal cortical neoplasms managed at our institution [8, 9]. In their study of 551 patients with RCC, Rabbani et al. [9] found significantly higher rates of prostate cancer, colorectal cancer, bladder cancer, and non-Hodgkin's lymphoma in men and higher rates of breast cancer, colorectal cancer, and non-Hodgkin's lymphoma in women. A later analysis of 763 RCC patients not stratified by gender confirmed higher than expected rates of prostate and bladder cancers limited to patients with papillary RCC [8]. Despite a cohort size more than four times larger than that of prior studies from our institution, the higher than expected rates of prostate cancer and non-Hodgkin's lymphoma cases in men and colorectal cancer in women detected by the current analysis did not reach statistical significance. Also, no difference between expected and observed number of patients with colorectal or bladder cancer was found in men, as confirmed by a SIR of 1.0. Of note, fewer than five bladder cancers were observed as second primaries among women in our analysis. These differences between our results from the prior findings at our institution [8, 9] or findings from large SEER cohorts [12] suggest that it is important for this subject to continue to be monitored for clinicians to understand trends, observations, and expectations.

Strengths of our study include a relatively large sample size, detailed clinical data, and long follow-up. Limitations are acknowledged and include potential loss to follow-up, which could have underestimated the number of second primary tumors, and lack of detailed information on second primaries such as mortality data and disease subtype. In addition, generalizability of our findings is limited primarily to Caucasians, which is consistent with the demographic of patients who are treated at our center. Future studies that systematically collect detailed exposure history and features of second primary malignancies from diverse patient populations with renal cortical tumors are needed.

Conclusions

Our findings are broadly similar to those derived from large, nationwide population-based registries such as SEER and suggest that the incidence of certain types of second malignancies may be higher in patients with renal cortical neoplasms compared to the

general population. These observations can inform clinical follow-up of kidney cancer survivors and future research studies that explore possible genetic links between renal cortical neoplasms and thyroid cancer.

Acknowledgments

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Table 1

Demographic and clinical characteristics of the 3066 surgical patients with renal cortical neoplasms

Variable	
Age, median years (IQR)	60.9 (51.9–69.2)
Gender, *n* (%)	
Male	1972 (64)
Female	1094 (36)
Race, *n* (%)	
Caucasian	2747 (90)
African-American	166 (6)
Asian	90 (3)
Other	36 (1)
Unknown	27 (1)
Stage, *n* (%)	
pTX	19 (1)
pT0	74 (2)
pT1	1866 (61)
pT2	269 (9)
pT3	807 (26)
pT4	31 (1)
Renal cortical histology, *n* (%)	
Clear cell RCC	1920 (62.6)
Papillary RCC	371 (12.1)
Chromophobe RCC	292 (9.5)
Oncocytoma	272 (8.9)
Unclassified RCC	80 (2.6)
Angiomyolipoma	71 (2.3)
Multilocular cystic carcinoma	18 (0.6)
Clear-cell papillary RCC	13 (0.4)
Metanephric adenoma	5 (0.2)
Translocation tumors	4 (0.1)
Granular RCC	4 (0.1)
Others	16 (0.5)

Table 2

Observed and expected number of second malignancies in patients with renal cortical neoplasms

Site	No. of observed	No. of expected	SIR (95 % CI)	*p* value
Male (*n* = 1972)				
Prostate	87	73.2	1.19 (0.95–1.47)	0.063
Colorectal	20	20.1	1.0 (0.61–1.54)	0.450
Bladder	16	16.0	1.0 (0.57–1.62)	0.434
Lung	15	33.1	0.45 (0.25–0.75)	<.001
Non-Hodgkin's lymphoma	13	8.4	1.55 (0.82–2.65)	0.085
Thyroid	6	1.2	5.0 (1.83–10.88)	**0.002**
Melanoma	5	8.8	0.57 (0.18–1.33)	0.128
Pancreas	5	5.0	1.0 (0.32–2.33)	0.383
Female (*n* = 1094)				
Breast	12	25.3	0.47 (0.24–0.83)	0.003
Colorectal	10	6.5	1.54 (0.74–2.83)	0.122
Lung	9	12.5	0.72 (0.33–1.37)	0.201
Endometrium	6	5.4	1.11 (0.41–2.42)	0.453
Thyroid	6	1.3	4.62 (1.69–10.05)	**0.003**
Stomach	5	1.0	5.0 (1.61–11.67)	**0.004**

Types of cancers with incidence *n* < 5 in men or women are not shown

Bold numbers include those with significantly higher observed than expected rates

SIR standard incidence ratio