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Incidence and Prognostic Significance of Second Primary Cancers in Renal Cell Carcinoma

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Abstract

Background—The survival of patients with renal cell carcinoma (RCC) has improved in recent years. However, data on the risk of developing a second cancer after a diagnosis of RCC is limited. We used the data available in the Surveillance Epidemiology and End Results (SEER) database to estimate the risk of second metachronous primary cancers in patients diagnosed with RCC between 1973 and 2006. Further, we also investigated the effect of the second primary cancers on the survival of RCC patients.

Results—3,795 cases of second primary cancers (SPCs) were registered in SEER between 1973–2006. The ratio of observed/expected number of SPCs in RCC was 1.18 which was significantly greater than expected. Solid tumors comprised 90% of all second malignancies in RCC patients, with the most second cancers reported in the prostate gland and the digestive and respiratory systems. The overall risk of second primaries was highest in patients aged <30 years at the time of diagnosis. The site-specific risk of second cancers varied with the age at diagnosis, gender, race of the patient, size of the primary renal tumor and history of radiation therapy. Patients with second primaries had a significantly longer overall survival than those without second malignancies. An interval of <1 year between the diagnosis of RCC and the second primary was the strongest predictor of poor OS in RCC patients with a second malignancy.

Conclusion—Patients with RCC are at a significantly higher risk of developing a second malignancy suggesting the need for careful surveillance for their early detection and management.

Keywords

Renal cell carcinoma; SEER; second primary; prognosis

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DISCLOSURE

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I. INTRODUCTION

Malignancies of the kidney (including the renal pelvis) are the seventh and eighth leading cause of cancer among men and women in the United States respectively. They are also among the top ten causes of cancer related deaths among men in the country¹. Globally, they are more common in developed rather than developing countries and in males rather than females². About 85% of all kidney cancers arise from the renal parenchyma (termed as renal cell carcinomas or RCCs) while the remaining arise from the urothelium lining the renal pelvis³. It is estimated that nearly 58,240 cancers of the kidney and renal pelvis were diagnosed in the United States in 2010, and about 13,040 patients died from these malignancies in the same period. Males accounted for more than 61% of all newly diagnosed cases and about 63% of all deaths from the malignancy¹. An interesting statistic is that there are an estimated 148,840 survivors of kidney and renal pelvis cancers in the United States alone⁴. The growing population of cancer survivors (both in case of RCC and other malignancies) has resulted in the emergence of a new area of cancer research, i.e. the study of second primaries arising in patients with an existing malignancy. Understanding the epidemiology of second primary cancers is an important first step in studying the molecular and genetic mechanisms underlying their development.

According to the National Cancer Institute, a second primary cancer (SPC) is defined as a new primary malignancy that occurs in a patient with a prior history of cancer (www.cancer.gov). Metachronous SPCs (i.e. SPCs that were diagnosed after a certain period of time following diagnosis of the first primary cancer) have been reported in association with several malignancies including male breast cancer⁵, colon cancer⁶, gastric cancer⁷, esophageal cancer and other head and neck cancers^{8;9}. In some of these malignancies, SPCs have also been reported to influence survival. For instance, patients with squamous cell carcinoma of the head and neck who developed a SPC had a 24% lower mortality after 15-years compared to those who did not develop a second tumor¹⁰. Liu and co-workers reported that patients who developed a lung cancer first followed by a second primary cancer had a significantly longer median survival than patients who had a non-lung primary tumor followed by a second primary cancer in the lungs¹¹. Data on the incidence of SPCs in patients with a prior diagnosis of RCC however is very limited, restricted only to a few European studies. One population-based study in Norway for instance, noted that the incidence of multiple primary malignancies in patients with a prior diagnosis of RCC was nearly 47%¹². Other smaller studies have reported that between 16%–18.5% of RCC patients develop a second primary malignancy^{13;14}.

Given that newer treatments are improving survival of patients with RCC^{15;16}, understanding the incidence and prognostic significance of second primary cancers in RCC survivors becomes an important question, both from the perspective of cancer treatment and the quality of life of the patient. Hence, the aim of our present study was to investigate the risk of second malignancies in patients with RCC using data from the Surveillance, Epidemiology and End Results (SEER) database. Further, we also sought to examine the effect of second primary cancers on the survival of RCC patients.

II. METHODS

2.1 Population selection

The SEER database (9 registries limited use, updated: November 2008) was queried for patients with RCC (ICD code: 8312/3) who were diagnosed between January 1973 and December 2006 with RCC and a second primary cancer (SPC). Only cases where RCC was the first of two or more cancers were considered for the analysis. Patients in whom the diagnosis of RCC was made at autopsy or mentioned in the death certificate only were

excluded as were any SPCs diagnosed within 1 month following the detection of RCC. De-identified information about individual patients with either RCC alone or RCC with SPC was also obtained from the SEER database (17 registries limited use, updated November 2008, containing information of cases between 1973–2006) and was used to analyze the effect of SPCs on survival of RCC patients and the effect of individual factors on the survival of RCC patients with SPCs.

2.2 Statistical analysis

Statistical analysis was performed using the PASW Statistics 18 software program (Release 18.0, SPSS Inc, IL, USA). The SEER*Stat version 6.5.2 was used to stratify the cases by age, gender, race, radiation therapy, site of SPC and latency period and to obtain the de-identified information about individual cases. The risk of an SPC was calculated by determining the standardized incidence ratio (SIR) which is defined as the ratio of the numbers of observed cases (O) of subsequent primary cancers (i.e. 2nd, 3rd etc.) at a given site (in patients with a pre-existing primary cancer) to the number of expected (E) subsequent cancers at the same site in the general population. Age, size of the primary RCC and the time elapsed between RCC and the second primary were considered as continuous variables, while gender, race, marital status, stage, grade and laterality of RCC, history of radiation therapy and history of radiation sequence with surgery were considered as categorical variables. A two-tailed Student's t-test was used to compare the mean values for continuous variables. Z-test was applied to compare the proportion of patients between two categories. Kaplan Meier survival analysis was used to examine the effect of individual risk factors on the overall survival (OS) of patients. A Cox proportional hazards test was used for multivariate analysis of factors affecting survival. All tests were conducted with 95% confidence intervals. A p-value <0.05 was considered significant.

III RESULTS

3.1 Study population

3,795 patients with RCC who were subsequently diagnosed with one or more second primary cancers were registered in the multiple primary (MP-SIR) section of the SEER database (comprising information from 9 registries in the United States) between 1973 and 2006. The expected number of second primary cancers in the population during the same period was estimated to be 3,208. Thus, the ratio of observed to expected number of second primaries (i.e. the SIR) was 1.18 (95% C.I. 1.15–1.22), which was significantly higher than expected ($p < 0.05$).

Solid tumors were the most common type of second malignancy in patients with RCC, accounting for over 90% of all SPCs. About 8% of second malignancies arose in the lymphatic and hematopoietic system and in about 2% cases the sites did not fit either classification. The most common sites of occurrence of second malignancies in RCC patients were the male genital system (n=896, 23.6%), the digestive system (n=718, 18.9%) and the respiratory system (n=562, 14.8%) (Table 1).

3.2 Relationship of patient and tumor related factors on the risk of second primary cancers in renal cell carcinoma

We first sought to investigate whether patient and/or tumor related factors had an effect on the risk of second primary cancers in patients with RCC. For this, the risk of SPCs was estimated from the actual number of second primaries reported during a follow-up period of >20 years (range: 1 month to >20 years) from the time of diagnosis of RCC. Two types of risks were examined: a) risk of a second cancer at all sites combined (termed as “overall

risk”) and b) risk of a second cancer at a specific site (termed as “site-specific risk”). The following factors were investigated:

A. Age at diagnosis of renal cell carcinoma—Patients with RCC followed by a second cancer were divided into three groups based on their age at the time of diagnosis of the RCC: <30 years, 30–59 years, and ≥60 years. As shown in Table 1, the overall risk of SPCs was significantly increased in all three age groups with patients younger than 30 years nearly 4 times more likely to develop a second malignancy than their older counterparts.

Analysis of the risk at specific sites revealed that in patients <30 years old, the risk of a SPC was highest in the kidney (SIR:170). Among hematologic malignancies, the risk was highest (23-fold) for Non-Hodgkin lymphoma (NHL). For patients between 30–59 years old, the risk was highest for Acute monocytic leukemia (SIR:7.3) followed by colon and thyroid cancer (SIR: 2.4 and 3.5 respectively). Among patients aged 60 years or more, the risk of a second malignancy was highest in the endocrine glands, particularly in the thyroid (SIR: 27) and adrenal glands (SIR: 7).

B. Age attained at the time of detection of the second primary cancer—We next investigated whether the age attained by the patient at the time of detection of the second cancer had an effect on their risk of developing the second malignancy at a specific site.

Only five RCC patients were younger than 30 years at the time of their second malignancy and all were diagnosed with a second primary in the kidney. This translated into a >1,000 fold higher risk of developing SPCs in the kidney (Table 1).

Among patients aged 30–59 years, the risk of a SPC was highest in the kidney (SIR: 13.6) followed by the thyroid gland and liver (SIR: 4.5 and 2.6 respectively).

Patients 60 years or older at the time of diagnosis of the second primary were at the highest risk of a second malignancy in the endocrine system, specifically in the thyroid and adrenal glands (SIR: 3 and 6.6 respectively)

C. Race—The overall risk of a second cancer was significantly increased in whites and blacks but not in other racial groups (Table 2). The risk was higher in blacks compared to whites (SIR: 1.38 vs. 1.15 respectively). The adrenal gland was the site with the highest risk of a second malignancy among whites (SIR:7.3), while the kidney, thyroid gland, small intestine and colon were at the highest risk of a second primary among blacks (SIR: 9.9, 4.7, 3.4 and 3 respectively). Notably, the risk of a second cancer in the kidney, prostate, urinary bladder and the thyroid gland were increased in all racial groups.

D. Gender—Although the overall risk of second malignancies was similar in both males and females (SIR: 1.2), it was significantly elevated only in the former. Significantly, males had a statistically higher risk of solid cancers while the risk of hematologic malignancies was significantly elevated in females. In males, the risk of a second primary was highest in the adrenal glands (SIR:6.6) followed by the kidneys and thyroid gland (SIR: 4.4 and 3.4 respectively) (Table 3). In females, the risk of a second malignancy was highest in the kidneys (SIR: 5.6) followed by the thyroid gland (SIR: 3.2). Significantly, the risk of a second cancer in both the sexes was highest in the first 6 months after the diagnosis of RCC but declined thereafter (Supplementary Tables 1 and 2).

E. Size of the kidney tumor—We next examined if there was a relationship between the size of the first primary cancer (i.e. RCC) and the risk of a second malignancy at a specific

site. For this, the RCC patients were divided into three groups based on the maximum diameter of the renal tumor: <5cm, between 5 and 10cm and 10cm.

As shown in Table 3, the risk of a second malignancy was significant in cases for renal tumors less than 10cm in diameter, but not for larger tumors. For tumors <10cm in size, the risk of a second malignancy was highest in the kidney (SIR:5) and endocrine glands (SIR: 3.8–4.1), particularly in the thyroid gland and adrenals. Interestingly, the risk of a second malignancy in the urinary bladder and prostate was strongly increased within the first 6 months after diagnosis of RCC, with a decline thereafter (Supplementary Table 3 and 4). Among hematologic malignancies, the risk of lymphocytic leukemias, specifically chronic lymphocytic leukemia was significantly elevated (SIR: 1.94) only for tumors <5cm in diameter but not for larger tumors. The only site with a significant risk of a second malignancy for tumors 10cm in size was the kidney (SIR:5.3).

G. History of radiation therapy—Therapeutic radiation is well known to increase the risk of cancers in general^{17–19}. We sought to investigate whether RCC patients who received radiation therapy had a difference in the risk of a second malignancy compared to those who had not received any form of radiation (including radioisotopes) therapy.

We found that the overall risk of a second malignancy was slightly higher in those patients who had not received radiation therapy compared to those who did (SIR: 1.18 and 1.11 respectively). The increased risk extended to both solid and hematologic malignancies in the former as summarized in Table 3. Among patients who received radiation therapy, the sites with the highest risk of a second malignancy were the adrenal glands and the thyroid (SIR: 201 and 32 respectively), with the risk being significant only within 6months and 1 year of diagnosis of RCC respectively (Supplementary Table 5). A similar increase in risk of thyroid cancer, although of a much lower magnitude (about 2-fold lower) was observed in patients who did not receive any radiation therapy (Supplementary Table 6). The risk of leukemias was specifically increased (by about 3-fold) in those who received radiation (SIR: 3.1). Conversely, the sites with an increased risk of a second malignancy specific to those who did not receive radiation were the skin and urinary bladder (SIR: 1.2 each).

3.3 Prognostic significance of Second primary cancers in Renal cell carcinoma

Having determined the sites with a differential risk of a second malignancy, we next sought to investigate the effect of second malignancies on the survival of RCC patients.

For this, we retrieved de-identified information on all RCC patients registered with the SEER database. A total of 58,174 patients with RCC were registered in 17 registries of the SEER database. Of these, 42,314 (72.7%) had RCC as the only primary tumor. This group was designated as “Only primary cancer” or OPC. In 5,769 cases (9.9%) RCC was the first of two or more primary malignancies. This group was designated as “second primary cancer” or “SPC”. In the remaining cases, RCC was diagnosed as the third or later of multiple primary cancers. Comparison of demographic characteristics of patients belonging to the OPC or SPC group (summarized in Supplementary Table 7) revealed that SPC patients were significantly older at the time of diagnosis and were more likely to be male, black and married, and less likely to have received radiation compared to the OPC group.

To determine the prognostic significance of SPCs in RCC, we first analyzed the effect of patient and tumor-related factors (including presence of second primaries) on the overall survival (OS) of patients (with RCC±SPC) by the Kaplan Meier method. As shown in Figure 1 and summarized in Table 4, patients in the SPC group had a significantly better survival than those in the OPC group. The other factors that predicted a longer OS in RCC patients included age 60 years at the time of diagnosis of RCC, non-white non-black race,

female gender, marital status (married/single), a well-differentiated, localized, unilateral renal tumor 5cm in diameter, and the absence of radiation therapy (with/without subsequent surgery) (Supplementary Figure 1).

Upon multivariate analysis, age <60 years at the time of diagnosis of RCC, female gender, married status, localized stage, well or moderate degree of differentiation (of RCC), tumor size 5cm, absence of radiation therapy and an unilateral RCC were significant independent predictors of a longer OS (Table 5). Presence of second primary cancers and race however, were not retained as significant predictors of OS in the multivariate analysis.

3.4 Factors influencing prognosis of RCC patients with one or more second primary cancers

Patients with multiple primary malignancies may be affected by prognostic factors unique from those with single primary cancers. Hence, we also investigated the factors that influence the OS of patients with RCC and one/more second cancers.

As summarized in Table 6 and illustrated in Supplementary Figure 2, age <60 years at the time of diagnosis of either RCC or the second malignancy, white or non-white non-black race, married status, a localized, well-differentiated, right sided renal tumor, lack of a history of radiation and an interval of 60 months between diagnosis of RCC and the second malignancy were associated with longer OS in patients with RCC and one/more second malignancies. Gender of the patient and size of the primary renal tumor however did not affect the OS significantly.

Upon multivariate analysis (Table 7), only age <60 years at the time of diagnosis of the second primary cancer, lack of a history of radiation therapy and an interval of 1 year between the diagnosis of RCC and the second malignancy were significant predictors of longer survival in RCC patients with second malignancies.

IV DISCUSSION

The present study represents the first comprehensive analysis of the risk of second primary cancers (SPCs) in patients diagnosed with renal cell carcinoma from data available in the SEER database. We observed that about 10% of all patients with RCC had one or more new primary tumors. The largest number of second cancers arose in the male genital system (particularly the prostate gland) and in the digestive and respiratory system. The overall risk of a second malignancy was highest in patients <30 years old at the time of diagnosis of either RCC or the second primary malignancy. Further, patients with a second cancer had a significantly longer overall survival than those without a second malignancy. The incidence of second cancers among RCC patients reported in our study is much lower than that reported in other non-US populations. For instance, a study by Beisland and co-workers in Norway had reported that the incidence of second malignancies in RCC was 47%¹². Other studies have reported an incidence between 16%–18.5%^{13;14}. A possible explanation for the lower incidence of second malignancies in the registries registered with SEER could be international difference in registration procedures used by various cancer registries²⁰. The completeness of data in a cancer registry is determined by several factors particularly the guidelines for screening and diagnosis of cancer. Differences in these guidelines could potentially influence the reported incidence of cancer in a given population²¹. Further, genetic differences (including polymorphisms) and differences in the environment (e.g. food habits, exposure to environmental carcinogens and lifestyle) might contribute to a higher or lower risk of second primary cancers in a given population.

In terms of the total number, the sites with the most second primary tumors in the SEER database were in the male genital system (24% of total), digestive system (19% of total) and respiratory system (15% of total). These three systems together accounted for 58% of all second malignancies. Specifically, the prostate gland, colon and the lung and bronchus were the sites in these systems with a consistent increase in risk of second malignancies in nearly all patient and treatment groups. This finding is similar to a report by Thompson et al., who observed that the risk of a second malignancy in RCC patients was highest in the prostate and colon¹⁴. Rabbani et al. also reported that the papillary type of RCC is associated with a significantly increased risk of second cancers in the prostate and bladder¹³. Other smaller studies have reported that the most common sites for second primary cancers in RCC are the prostate, colon and urinary bladder^{22;23}. While second cancers in the bladder accounted for 6.4% of all SPCs in our study (Table 1), the risk was significant only in patients aged 60 years or more (at time of diagnosis of either RCC or the SPC), with RCCs ≥ 5 cm in size and in patients without a history of radiation therapy (Table 3). There was no difference in incidence of second cancers in the bladder with either gender or race of the patient.

Among hematological malignancies, lymphomas were the most common second malignancies in RCC patients with 143 (3.8% of total) observed in the SEER population. Specifically, the risk of Non-Hodgkin lymphoma was increased, being significantly elevated in those < 30 years old at the time of diagnosis of RCC and within 6 months after the diagnosis of RCC in both genders (Supplementary Tables 1 and 2). Beisland et al. had also reported in their aforementioned study that NHL (together with melanoma) was the most common second malignancy in patients with an existing RCC¹².

The occurrence of two primary cancers in the same patient is, however, by itself not sufficiently strong to support the hypothesis that a common underlying mechanism may be driving both malignancies. However, if the risk of development of one malignancy in presence of the second is reciprocal (i.e. presence of either malignancy as the first increases the risk of the second in the same patient), the chance that the two are driven by a common mechanism would be significantly increased. Using this principle of reciprocal risk, we noted that solid tumors with a mutually increased risk of occurrence (with RCC) were the skin (excluding basal and squamous cell carcinomas), urinary bladder, prostate, thyroid and adrenal glands (Supplementary Table 8). Among the lymphatic and hematopoietic malignancies, the risk of leukemias was reciprocally increased in RCC patients. Several other studies have also reported (using the principle of reciprocal risk), that significant reciprocal associations exist between RCC and malignancy at another site. For instance, a study using data from the New South Wales Central Cancer Registry (Australia) reported that cancer of the renal parenchyma was associated with a significant increase in the risk of prostate cancer, and that the reciprocal was also true. A similar reciprocal risk relationship was reported by McCredie and co-workers for RCC and cancer of the urinary bladder. However, the enhanced risk was confined only to women²⁴. An analysis of the Danish Cancer Registry (1943–1980) revealed that patients with a primary malignancy in the kidney were at a significantly elevated risk of a second primary in the bladder (SIR: 7.1, 95% C.I. 6.0–8.4) and the reciprocal was true for patients with a primary malignancy of the bladder (SIR for SPC in the kidney being 3.2, 95% C.I. 2.7–3.8)²⁵. Although the exact mechanism for this reciprocal risk phenomenon is not known, a few possibilities can be suggested. These include a common environmental (e.g. cigarette smoking and/or alcohol are linked to cancers of the urinary system, respiratory system, oral cavity, pharynx, esophagus, pancreas and cervix, and benzidene for RCC and bladder cancer) or genetic risk factor (co-occurrence of familial papillary carcinoma of thyroid and papillary carcinoma of the kidney linked to the chromosome locus 1q21)^{25–27}. Familial RCC has also been shown to increase the risk of a second primary cancer in the urinary bladder and endocrine glands by nearly 3-fold²⁸.

The exact mechanism by which these factors induce oncogenic transformation at two separate anatomic sites however remains to be elucidated.

A significant observation in our analysis was a prominent increase in the risk of endocrine cancers, specifically thyroid and adrenal gland malignancies in patients with RCC. While the exact mechanism underlying the co-occurrence of RCC with thyroid cancer is unknown, one possibility is the occurrence of common genetic alterations that drive the development of tumors at the two sites. Missense mutations in *CHEK2*, a gene encoding the human analogue of the yeast checkpoint kinases Cds1 and Rad53 have, for instance, been associated with a significant increase in the risk of thyroid, prostate, colon breast and kidney cancer²⁹. On the other hand, the best known condition associated with an inherited risk of clear cell carcinoma of the kidney together with cancers in the adrenal glands, is the von Hippel-Lindau (VHL) syndrome, an autosomal dominant disease characterized by hemangioblastomas in the brain, spinal cord and retina and tumors in the kidney, adrenal glands and lymphatics³⁰. Sporadic cases of RCC with adrenal malignancies are however quite rare, limited to a handful of case reports³¹. Future studies in patients with these inherited syndromes could help elucidate the molecular mechanism underlying the development of multiple primaries including RCC.

An important focus of oncologic research from the standpoint of public health is the impact of cancers (in this case second primary cancers) on the survival of patients. Once the predictors of survival are identified, these could be utilized to guide therapeutic interventions and surveillance strategies to improve survival. We observed that patients who had both an RCC and a second primary cancer had a significantly longer survival than those with RCC alone (Table 4). However, this difference did not remain significant on multivariate analysis suggesting that, while the presence of second primaries may improve survival, they were not an independent predictor of overall survival in these patients. A similar observation (i.e. better survival in patients with one/more second primary cancers) has previously been reported in a study of 80 patients with cancers of the renal pelvis. Median survival was significantly better in those patients who had a history of a prior urothelial malignancy (42 months) compared to those in whom it was the only malignancy (19 months)³². Notably, RCC patients who received radiation therapy had a dramatic reduction in OS (26±1 months vs. 119±0.9 months in those who did not receive radiation). This concurs with previous reports in literature that suggested that radiation therapy does not improve survival in patients with RCC³³. Recent clinical trials have also not found any significant benefit with radiation therapy in RCC except in patients with brain metastasis, and even in them it has not been shown to produce a significant improvement in the progression free interval^{34;35}. It is possible that the lower survival in patients who received therapeutic radiation was due to the adverse effects of radiation itself including bone marrow depression and the resulting morbidity. Our finding of a longer overall survival in female RCC patients agrees with a recent study by Aron et al. which found that females presented with smaller tumors which were of a lower histologic grade compared to males who most often presented with regional or distant metastasis³⁶. While it is not clear how being married improved survival in RCC patients, one possible explanation is that these patients were more likely to receive emotional and psychological support that might have contributed to their longer survival.

When we examined the factors that affect survival in RCC patients with one/more second primaries (SPCs), we noted that they were very similar to those that predicted longer survival in patients with RCC alone. Thus, age <60 years at the time of diagnosis of RCC (or the second primary), white or non-black race, married status, localized and well-differentiated primary renal tumors arising from the left side and absence of a history of therapeutic radiation were predictors of a longer survival on univariate analysis (Table 6).

An additional factor that specifically predicted a better survival in patients with second primaries was a longer interval between diagnosis of RCC and the second primary (patients diagnosed with a second primary 5 years or later after the diagnosis of RCC had the longest OS). Upon multivariate analysis, time elapsed between the diagnosis of RCC and the second primary was an independent predictor of survival with, patients diagnosed with a second malignancy less than 1 year after being diagnosed with RCC having a significantly poorer OS compared to those diagnosed >1 year later (Hazards ratio 2.1, $p < 0.001$, Table 7). In order to validate the results of our multivariate survival analysis in patients with second primaries, we searched the literature for actual case studies on survival in patients with RCC and a second malignancy. Studies wherein a second primary was diagnosed <1 month after diagnosis of the RCC were excluded. We identified a study by Choueiri et al., wherein they had reported a series of four patients with RCC who subsequently developed multiple myeloma (MM) (summarized in Supplementary Table 9)³⁷. Of the four patients, the shortest survival time (9 months from the time of diagnosis of RCC) was noted for a 66yr old male patient (patient #3) who was diagnosed with MM 1 month after being diagnosed with RCC, while the longest survival (11 yrs) was observed for a 61 yr old male diagnosed with MM 108 months after being diagnosed with RCC (patient #1). Based on our multivariate analysis, patient #3 would be expected to have the shortest survival as he had two adverse prognostic factors- age >60 years at presentation with RCC and time elapsed between the diagnosis of RCC and the second primary <1 month. Patient #1 with one adverse factor (age >60 years) would be predicted to have a longer survival. A comparison of the predicted and actual survival for the four patients in this series is presented in Supplementary Table 9.

A key observation in our analysis was the significantly higher risk of developing a SPC (nearly 5-fold) in younger patients (age <30 years at the time of diagnosis of RCC) than in older patients with an antecedent RCC (Table 1). Hartley et al. had reported in a series of 218 patients diagnosed with renal tumors in childhood that the excess risk of developing a second malignancy was significantly higher than expected ($N=8$, SIR: 14.7)³⁸. The authors also suggested that development of bony exostoses might predict the development of a subsequent malignancy in patients with childhood renal tumors. It is possible that the elevated risk of SPCs in younger patients observed in our study could be at least partly due to an inherited predisposition to develop multiple tumors. However, this would need to be confirmed by detailed genetic analysis in a separate study.

In conclusion, we have conducted the first comprehensive analysis of SPCs in patients with RCC as the first primary malignancy using data from the SEER database. We have also examined the prognostic significance of factors influencing OS of patients with RCC with/without SPCs. Our results suggest that several patient, tumor and treatment related factors can affect the risk of SPCs at specific sites and influence the prognosis of RCC patients. By comparing our findings with published studies, we have demonstrated the correlation of database based studies with incidence and prognosis of RCC patients in actual hospital based settings. The results from the study have important implications in investigating the mechanisms underlying the occurrence of multiple primary tumors and in planning surveillance strategies for patients with newly diagnosed renal cell carcinoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

FPC	First primary cancer
OS	Overall survival
RCC	renal cell carcinoma
SPC	Second primary cancer

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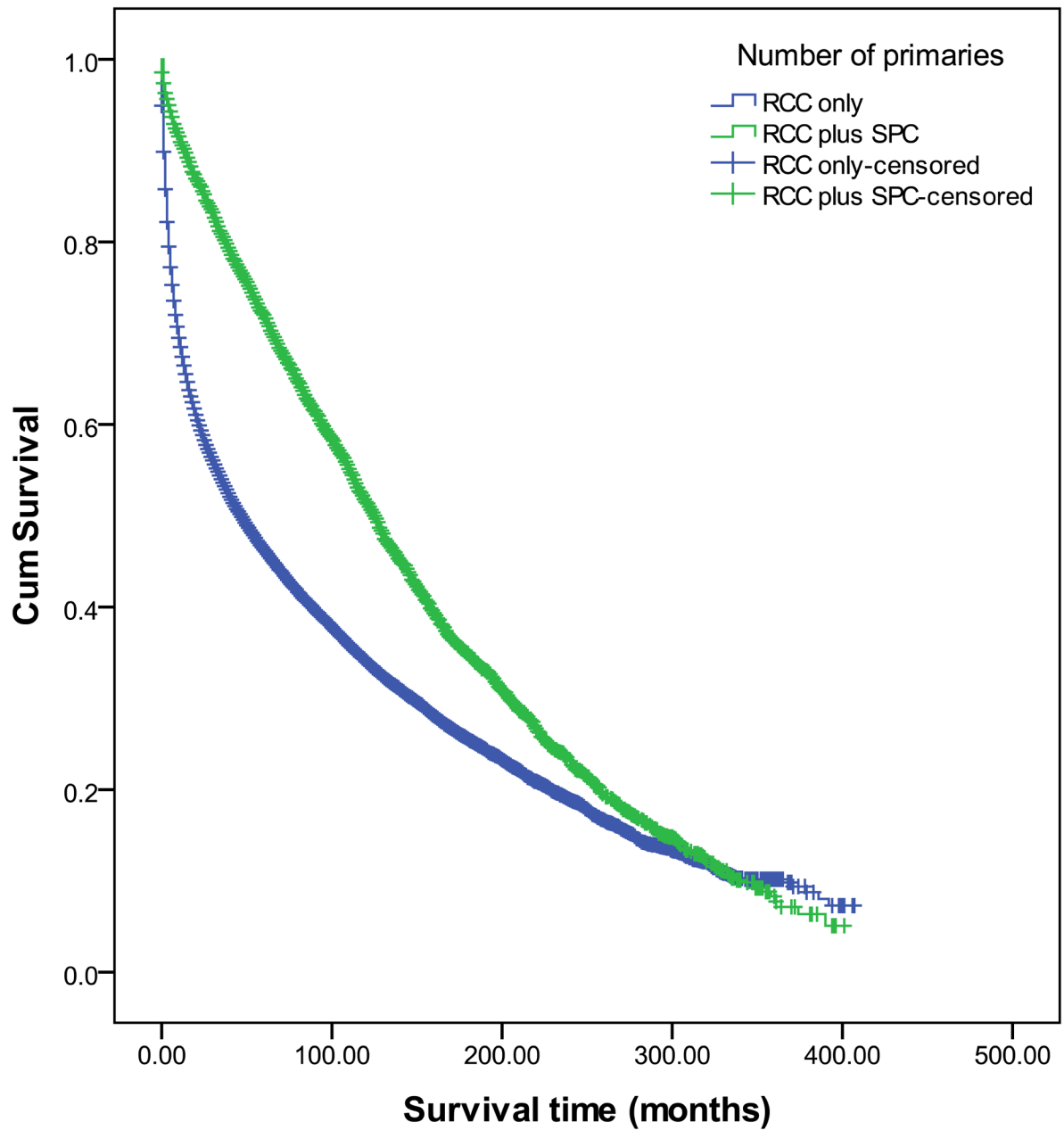


Figure 1. Kaplan Meier analysis to analyze the effect on second primary cancers (SPCs) on overall survival in patients with renal cell carcinoma (RCC)

Univariate analysis revealed that the survival of patients with RCC and one/more second primary cancers was significantly greater (151 ± 2 months) than that of patients where RCC was the only primary cancer (111 ± 1 months, $p < 0.001$ by Log Rank test)

Table 1

Effect of age on the risk of second primary cancers in renal cell carcinoma

Site of second malignancy	Age at diagnosis of RCC						Age attained at diagnosis of second primary cancer					
	0-29 yrs.		30-59 yrs.		60 yrs.		0-29 yrs.		30-59 yrs.		60 yrs.	
	O	(SIR)	O	(SIR)	O	(SIR)	O	(SIR)	O	(SIR)	O	(SIR)
All sites	23 (6.6) [*]	1,232 (1.3) [*]	1,143 (1.32)	2,540 (1.13) [*]	5 (12.02) [*]	574 (1.72) [*]	3,216 (1.12) [*]					
All solid tumors	19 (6.4)	1,143 (1.32)	2,258 (1.13)	2,258 (1.13)	5 (16.0)	533 (1.78) [*]	2,882 (1.12) [*]					
All lymphatic and Hematopoietic diseases	3 (7.1) [*]	72 (1.01)	223 (1.25) [*]	223 (1.25) [*]	0 (0)	33 (1.23)	265 (1.2) [*]					
Oral cavity and pharynx	0 (0)	22 (0.8)	32 (0.7) [*]	32 (0.7) [*]	0 (0)	14 (1.04)	40 (0.63) ^{*p}					
Digestive system	0 (0)	200 (1.2) ^b	518 (1.05)	518 (1.05)	0 (0)	81 (1.4) ^{*k}	637 (1.04) ^q					
Liver, GB IHBD, EHBD, other biliary	0 (0)	22 (1.4) ^c	35 (0.93) ^h	35 (0.93) ^h	0 (0)	12 (2.1) ^{*l}	45 (0.94) ^r					
Respiratory system	0 (0)	188 (1.14) ^d	374 (0.97)	374 (0.97)	0 (0)	74 (1.42) ^{*m}	488 (0.98)					
Bones and Joints	0 (0)	1 (1.0)	3 (1.9)	3 (1.9)	0 (0)	0 (0)	4 (1.9)					
Soft tissue including heart	0 (0)	3 90.7	12 (1.32)	12 (1.32)	0 (0)	2 (1.0)	13 (1.13)					
Skin excluding BCC and SCC	1 (2.9)	43 (1.2)	77 (1.24)	77 (1.24)	0 (0)	24 (1.42)	97 (1.2)					
Breast	1 (1.4)	79 (0.8)	172 (1.05)	172 (1.05)	0 (0)	45 (0.95)	207 (0.96)					
Female Genital system	0 (0)	31 (0.8)	65 (0.98)	65 (0.98)	0 (0)	16 (0.91)	80 (0.92)					
Male Genital system	1 (3.7)	273 (1.2) ^{*e}	622 (1.2) ^{*f}	622 (1.2) ^{*f}	0 (0)	81 (1.5) ^{*n}	815 (1.17) ^{*s}					
Urinary bladder	0 (0)	44 (0.9)	198 (1.4) [*]	198 (1.4) [*]	0 (0)	15 (1.2)	227 (1.3) [*]					
Kidney	14 (170.0) [*]	197 (7.6) [*]	123 (2.7) [*]	123 (2.7) [*]	5 (1,101) [*]	139 (13.6) [*]	190 (3.1)					
Renal pelvis	0 (0)	4 (2.3)	1 (0.2) [*]	1 (0.2) [*]	0 (0)	2 (4.2)	3 (0.4)					
Ureter	0 (0)	2 (1.8)	8 (2.0)	8 (2.0)	0 (0)	1 (4.2)	9 (1.8)					
Eye and Orbit	0 (0)	3 (2.0)	2 (0.7)	2 (0.7)	0 (0)	2(3.0)	3 (0.8)					
Brain and other Nervous system	0 (0)	14 (1.21)	18 (0.91)	18 (0.91)	0 (0)	9 (1.7)	23 (0.9)					
Endocrine system	2 (8.1)	37 (3.4) ^{*f}	31 (2.9) ^{*j}	31 (2.9) ^{*j}	0 (0)	27 (4.3) ^{*o}	43 (2.8) ^{*t}					
Lymphoma	3 (9.9) ^{*a}	38 (1.0)	102 (1.2)	102 (1.2)	0 (0)	18 (1.15)	125 (1.15)					
Myeloma	0 (0)	11 (0.95)	39 (1.3)	39 (1.3)	0 (0)	7 (1.8)	43 (1.1)					
Leukemia	0 (0)	23 (1.1) ^g	82 (1.31) [*]	82 (1.31) [*]	0 (0)	8 (1.1)	97 (1.3) [*]					

Site of second malignancy	Age at diagnosis of RCC					
	0-29 yrs.		30-59 yrs.		60 yrs.	
	O(SIR)	O(SIR)	O(SIR)	O(SIR)	O(SIR)	O(SIR)
Mesothelioma	0 (0)	4 (1.7)	7 (0.93)	0 (0)	2 (3.1)	9 (0.97)
Kaposi Sarcoma	1 (10.3)	0 (0)	2(1.3)	0 (0)	1 (0.5)	2 (1.1)
Miscellaneous	0 (0)	15 (0.8)	50 (0.8)	0 (0)	6 (0.98)	59 (0.8)

* $P < 0.05$, O-observed number of cases; SIR- Standardized incidence ratio (ratio of observed to expected number of second malignancies);

^a Significant increase in the risk of non-lymphocytic lymphomas (SIR:15.1) specifically for nodal type of NHL (SIR: 23.2);

^b Significant increase in the risk of an SPC in the hepatic flexure of the colon (SIR: 2.4);

^c Significant increase in the risk of liver cancer (SIR: 1.9);

^d Significant increased risk of developing cancer of the lung and bronchus (SIR: 1.2);

^e Significant increase in the risk of cancer of the prostate (SIR: 1.2);

^f Significant increase in the risk of thyroid cancer (SIR: 3.5);

^g Significantly increased risk of developing Acute Monocytic leukemia (SIR: 7.3);

^h Significant increase in risk of pancreatic cancer (SIR: 1.34);

ⁱ Significant increase in risk of prostate cancer (SIR: 1.2);

^j Significant increase in the risk of thyroid cancer (SIR: 27) and malignant neoplasms of the adrenal gland (SIR: 7.2);

^k Significant increase in the risk of SPC in the colon (excluding rectum) (SIR: 1.5);

^l Significant increase in the risk of an SPC in the liver (SIR: 2.63);

^m Significant increase in the risk of SPC in the lung and bronchus (SIR: 1.54);

ⁿ Significant increase in risk of prostate cancer (SIR: 1.5);

^o Significant increase in the risk of SPC in the thyroid gland (SIR: 4.3);

^p Significant decrease in the risk of an SPC in the pharynx (SIR: 0.4) and hypopharynx (SIR: 0.16);

^q Significant increase in the risk of SPC in the hepatic flexure of the colon (SIR: 1.66) ;

^fSignificant increase in the risk of pancreatic cancer (SIR: 1.31);

^gSignificant increase in the risk of prostate cancer (SIR: 1.17);

^jSignificant increase in the risk of thyroid cancer (SIR: 2.9) and cancer of the adrenal gland (SIR: 6.6).

Table 2

Race and the site-specific risk of second primary cancers in renal cell carcinoma

Site of second malignancy	Whites (O, SIR)	Blacks (O, SIR)	Others (O, SIR) [†]
All sites	3,230 (1.15) [*]	382 (1.38) [*]	182 (1.7)
All solid tumors	2,897 (1.15) [*]	355 (1.4) [*]	167 (1.73)
All lymphatic and Hematopoietic diseases	263 (1.17) [*]	20 (1.14)	15 (2.01) [*]
Oral cavity and pharynx	50 (0.74) ^{*a}	3 (0.44)	1 (0.4)
Digestive system	605 (1.06) ^b	59 (0.96) ^h	54 (1.7) ^{*l}
Liver, GB IHBD, EHBD, other biliary	51 (1.2) ^c	3 (0.6)	3 (0.55)
Respiratory system	474 (0.99) ^d	69 (1.3) ⁱ	19 (1.1) ^m
Bones and Joints	4 (1.7)	0 (0)	0 (0)
Soft tissue including heart	12 (1.0)	3 (3.0)	0 (0)
Skin excluding BCC and SCC	120 (1.23) ^{*e}	0 (0)	1 (1.5)
Breast	216 (0.93)	0 (0)	10 (1.4)
Female Genital system	88 (0.96)	5 (0.6)	3 (0.98)
Male Genital system	751 (1.16) ^{*f}	102 (1.3) ^{*j}	43 (1.9) ^{*n}
Urinary bladder	217 (1.22) [*]	15 (2.0) [*]	10 (2.53) [*]
Kidney	251 (4.01) [*]	65 (9.9) [*]	18 (8.1) [*]
Renal pelvis	4 (0.6)	1 (3.1)	0 (0)
Ureter	10 (2.1)	0 (0)	0 (0)
Eye and Orbit	4 (0.91)	0 (0)	0 (0)
Brain and other Nervous system	30 (1.03)	1 (0.7)	1 (1.4)
Endocrine system	57 (3.1) ^{*g}	6 (3.9) ^k	7 (5.3) ^{*o}
Lymphoma	125 (1.1)	10 (1.55)	8 (1.9)
Myeloma	45 (1.3)	4 (0.6)	1 (0.8)
Leukemia	93 (1.21)	6 (1.2)	6 (.9) ^{*p}
Mesothelioma	11 (1.2)	0 (0)	0 (0)
Kaposi Sarcoma	3 (0.93)	0 (0)	0 (0)
Miscellaneous	58 (0.84)	7 (0.98)	0 (0)

*
 $p < 0.05$ [†] American Indian, Alaskan Native, Native American, Asian and Pacific Islander^a Risk of SPC in the hypopharynx significantly decreased (SIR, 0.16);^b Risk of SPC in the hepatic flexure of the colon (SIR: 1.7) significantly increased;^c Risk of SPC in the pancreas significantly increased (SIR: 1.33);^d Risk of SPC in the larynx significantly decreased (SIR: 0.16);^e Risk of melanoma of the skin significantly increased (SIR: 1.22);^f Risk of SPC in the prostate significantly increased (SIR: 1.16);

^gRisk of SPC in the thyroid gland (SIR: 3.01) and adrenal gland (SIR: 7.3) significantly increased;

^hRisk of SPC in the small intestine and transverse colon significantly increased (SIR: 3.4 and 3.05 respectively);

ⁱRisk of SPC in the lung and bronchus significantly increased (SIR: 1.4);

^jRisk of SPC in the prostate gland significantly increased (SIR: 1.3);

^kRisk of SPC in the thyroid gland significantly increased (SIR: 4.7);

^lRisk of SPC in the colon (excluding the rectum, SIR:2.25), specifically in the hepatic (SIR:5.2) and splenic flexures (SIR: 7.7) and the sigmoid colon (SIR:2.3), rectum and rectosigmoid junction (SIR:2.22) is significantly increased;

^mRisk of SPC in the trachea (SIR: 84.3) significantly increased;

ⁿRisk of SPC in the prostate significantly increased (SIR: 1.87);

^oRisk of SPC in thyroid gland significantly increased (SIR: 6.0);

^pRisk of ALL (SIR: 17.6) significantly increased;

Table 3
Effect of gender, size of primary renal tumor and radiation on the risk of second primary cancers in renal cell carcinoma (RCC)

Site of second malignancy	Gender		Size of RCC				H/O of radiation?	
	Males	Females	5cm	>5 to <10cm	10cm	Yes	No	
	O(SIR)	O(SIR)	O(SIR)	Total (O, SIR)	Total (O, SIR)	Total (O, SIR)	Total (O, SIR)	
All sites	2,712 (1.2) [*]	1,083 (1.2)	971 (1.3) [*]	914 (1.2) [*]	226 (1.05)	110 (1.11)	3,666 (1.18) [*]	
All solid tumors	2,458 (1.2) [*]	962 (1.2)	873 (1.3) [*]	819 (1.2) [*]	207 (1.08)	99 (1.12)	3,304 (1.19) [*]	
All lymphatic and Hematopoietic diseases	203 (1.2)	95 (1.3) [*]	77 (1.29) [*]	77 (1.3)	13 (0.77)	11 (1.5)	286 (1.18) [*]	
Oral cavity and pharynx	39 (0.6) ^{*a}	15 (0.9)	9 (0.54)	13 (0.7)	6 (1.2)	1 (0.4)	53 (0.71) ^{*t}	
Digestive system	489 (1.1)	229 (1.12)	186 (1.23) ^{*g}	152 (0.98)	38 (0.9) ^p	18 (0.9) ^q	695 (1.08) ^u	
Liver, GB IHBD, EHBD, other biliary	45 (1.2)	12 (0.8)	18 (1.37) ^h	16 (1.2)	3 (0.8)	0 (0)	57 (1.1)	
Respiratory system	401 (0.96)	161 (1.2) ^e	129 (1.03)	135 (1.1)	39 (1.1)	20 (1.1)	540 (1.02)	
Bones and Joints	3 (1.7)	1 (1.2)	1 (1.67)	1 (1.6)	0 (0)	0 (0)	4 (1.6)	
Soft tissue including heart	10 (1.04)	5 (1.3)	7 (2.11)	4 (1.2)	0 (0)	0 (0)	15 (1.140)	
Skin excluding BCC and SCC	93 (1.2)	28 (1.21)	41 (1.61) ^{*i}	28 (1.1)	9 (1.2)	2 (0.7)	119 (1.23) ^{*v}	
Breast	6 (1.3)	246 (0.95)	80 (1.22)	48 (0.77) ^{*m}	14 (0.8)	4 (0.7)	245 (0.96)	
Female Genital system	-	96 (0.92)	16 (0.64)	24 (0.98)	5 (0.8)	4 (1.7)	92 (0.91)	
Male Genital system	896 (1.2) ^{*b}	-	215 (1.21) ^{*j}	222 (1.2) ^{*n}	54 (1.01)	33 (1.3) ^f	860 (1.9) [*]	
Urinary bladder	203 (1.2) [*]	39 (1.5) [*]	71 (1.63) [*]	60 (1.33)	12 (0.96)	5 (0.8)	236 (1.3) [*]	
Kidney	241 (4.4) [*]	93 (5.6) [*]	88 (5.0) [*]	92 (5.0) [*]	29 (5.3) [*]	7 (3.2) [*]	325 (4.7) [*]	
Renal pelvis	4 (0.7)	1 (0.5)	0 (0)	0 (0)	2 (4.3)	0 (0)	5 (0.7)	
Ureter	8 (2.0)	2 (1.8)	2 (1.74)	2 (1.7)	0 (0)	0 (0)	10 (2.0)	
Eye and Orbit	4 (1.2)	1 (0.8)	2 (1.96)	2 (1.9)	0 (0)	0 (0)	5 (1.2)	
Brain and other Nervous system	22 (0.9)	10 (1.1)	4 (0.56)	12 (1.6)	1 (0.5)	1 (1.0)	30 (0.99)	
Endocrine system	36 (3.3) ^{*c}	34 (3.2) ^{*f}	23 (4.07) ^{*k}	22 (3.8) ^{*o}	2 (1.2)	3 (5.2) [*]	67 (3.2) ^{*w}	
Lymphoma	93 (1.1)	50 (1.3)	32 (1.06)	33 (1.1)	9 (1.05)	2 (0.6)	141 (1.2) ^x	
Myeloma	30 (1.01)	20 (1.6)	10 (0.99)	22 (2.2) [*]	1 (0.4)	1 (0.8)	49 (1.2)	

Site of second malignancy	Gender		Size of RCC			H/O of radiation?	
	Males		>5 to <10cm		Yes		No
	O(SIR)	O(SIR)	O(SIR)	Total (O, SIR)	Total (O, SIR)	Total (O, SIR)	Total (O, SIR)
Leukemia	80 (1.3) ^{*d}	25 (1.1)	35 (1.80) ^{*f}	2 (1.1)	3 (0.5)	8 (3.1) ^{*g}	96 (1.2)
Mesothelioma	10 (1.1)	1 90.98)	5 (2.17)	2 (0.8)	0 (0)	1 (3.1)	10 (1.0)
Kaposi Sarcoma	3 (0.9)	0 (0)	1 (1.36)	1 (1.2)	0 (0)	0 (0)	3 (0.84)
Miscellaneous	39 (0.8)	26 (0.9)	14 (0.81)	16 (0.9)	0 (0)	0 (0)	64 (0.84)

* $p < 0.05$, O-observed number of cases; SIR- Standardized incidence ratio (ratio of observed to expected number of second malignancies);

^a Significant decrease in the risk of SPC in the pharynx (SIR: 0.3) and the hypopharynx (SIR: 0.15);

^b Significantly increased risk of prostate cancer (SIR: 1.2);

^c Significantly increased risk of thyroid (SIR: 3.4) and adrenal gland cancer (SIR: 6.6);

^d Significantly increased risk of non-lymphocytic leukemias (SIR: 1.4);

^e Significant increase in the risk of SPC in the lung and bronchus (SIR: 1.22);

^f Significant increase in the risk of thyroid cancer (SIR: 3.2);

^g Significant increase ($p < 0.05$) in the risk of cancer of the hepatic flexure of the colon (SIR: 2.68);

^h Significantly increased risk of pancreatic cancer (SIR: 1.84);

ⁱ Significantly increased risk of cutaneous melanoma (SIR: 1.5) and other non-epithelial skin cancers (SIR: 2.7);

^j All the cases comprise cancer of the prostate whose risk is significantly increased (SIR: 1.22);

^k Significantly ($p < 0.05$) increased risk of cancer of the thyroid gland (SIR: 3.9) and adrenal gland (SIR: 9.6);

^l Significantly increased risk of chronic lymphocytic leukemia (CLL, SIR: 1.94), Non-lymphocytic leukemias (SIR: 1.81) and Myeloid and Monocytic leukemia (SIR: 2.0);

^m Significantly decreased risk of cancer in the female breast (SIR: 0.73);

ⁿ Significantly increased risk of prostate cancer (SIR: 1.2);

^o Significantly increased risk of thyroid cancer (SIR: 3.84);

^p Significant increase in the risk of cancer of the hepatic flexure of the colon (SIR: 3.9);

^q Significantly increased risk of second cancer in the descending colon (SIR: 6.5);

- ^rSignificantly increased risk of penile cancer (SIR: 17.6);
- ^sSignificantly increased risk of other leukemias (excluding lymphocytic leukemias and MAML) was significantly increased (SIR: 9.8);
- ^tSignificant reduction in the risk of cancer of the pharynx (SIR: 0.41), specifically the hypopharynx (SIR:0.14);
- ^uSignificant increase in risk of cancer of the hepatic flexure of the colon (SIR: 1.81);
- ^vSignificantly increased risk of melanoma of the skin;
- ^wSignificant increase in the risk of thyroid cancer (SIR: 3.3) and cancer of the adrenal glands (SIR: 5.6);
- ^xSignificant increase in the risk of NHL.

Table 4

Kaplan Meier analysis of factors affecting overall survival in patients with renal cell carcinoma

Factor tested	Patient group	Total N	Mean survival (±SE)	95% C.I.	χ ²	Log Rank test (Mantel-Cox)
Number of primary tumors	OPC	42,314	111±1 months	109–113 months	691.4	P<0.001
	SPC	5,769	151±2 months	147–155 months		
Age at diagnosis of RCC	<60 years	20,243	173±1.7 months	170–176 months	4,007.7	P<0.001
	60 years	37,931	76±0.6 months	74.6–77 months		
Race	White	49,317	110±0.8 months	108–111 months	18.3	P<0.001
	Black	5,903	106±2.5 months	101–111 months		
	Others	2,761	115±3.5 months	108.5–122 months		
Gender	Male	36,630	104±1 months	102–106 months	75.7	P<0.001
	Female	21,544	119.5±1.4 months	117–122 months		
Marital status at time of diagnosis of RCC	Married	36,410	121±1 months	119–123 months	1562.0	P<0.001
	Widowed	8,754	62±1.2 months	60–64 months		
	Divorced	4,307	103±2.6 months	118–130 months		
	Single	5,955	124±3 months	118–129.5 months		
	Separated	590	91±5.6 months	80–102 months		
	Localized	15,112	81±0.4 months	80.5–82 months	14,845.0	P<0.001
	Regional spread	3,966	58.5±0.8 months	57–55 months		
	Distant spread	6,328	13±0.3 months	12–14 months		
	Well differentiated	4,911	179±3.5 months	172–186 months	2385.0	P<0.001
	Moderately differentiated	10,631	154±2.9 months	148–159 months		
Size of tumor	Poorly differentiated	5,882	98.5±3 months	93–104 months		
	Undifferentiated	1,591	67±3.8 months	59.5–74 months		
	5cm	12,948	124±1 months	122–126 months	1955.3	P<0.001
	>5cm- 10cm	13,410	97±0.9 months	96–99 months		
Unilateral or Bilateral RCC	>10cm	5,561	66±1.2 months	63–68 months		
	Unilateral	56,308	113±0.8 months	111–114 months	3052.3	P<0.001
Radiation therapy given?	Bilateral	1,866	22±1.6 months	19–25 months		
	Yes ^c	4,898	26±1 months	24–27 months	5057.4	P<0.001
	No	52,214	119±0.9 months	117–121 months		

Factor tested	Patient group	Total <i>N</i>	Mean survival (\pm SE)	95% C.I.	χ^2	Log Rank test (Mantel-Cox)
Radiation sequence with surgery	Received both	2,092	45 \pm 1.8 months	41.5–49 months	727.3	<i>P</i> <0.001
	Received neither	56,078	113 \pm 0.8 months	111–114 months		

Number of patients (*N*), only primary cancer (OPC), Secondary primary cancer (SPC), Well differentiated (WD), moderately differentiated (MD), poorly differentiated (PD),

^aBlack, American Indian, Alaskan Native, Asian, Pacific islander

^bRegional or distant spread of tumor

^cReceived either radiation or radioisotope therapy

Table 5

Multivariate analysis of factors that influence overall survival in patients with renal cell carcinoma

Variable	Categories	N	H.R.	95% CI for H.R.		p-value
				Lower	Upper	
Age at diagnosis of RCC	<60	3,799	0.54	0.49	0.58	<0.001
	60 yrs	3,156	-			
Gender	Male	2,593	1.22	1.12	1.33	<0.001
	Female	4,362	1.00			
Race	Others	5,858	1.23	1.10	1.37	<0.001
	Whites	1,097	1.00			
Marital status	Others ^a	4,710	1.34	1.23	1.46	<0.001
	Married	2,245	1.00			
Summary stage	Regional or Distant	4,739	2.94	2.68	3.22	<0.001
	Localized	2,216	1.00			
Grade	PD or UD	4,592	1.83	1.68	1.99	<0.001
	WD or MD	6,718	-			
Size of tumor	5cm	3,586	0.69	0.63	0.75	<0.001
	>5cm	3,369	-			
Radiation therapy	No	302	0.39	0.34	0.45	<0.001
	Yes	6,653	-			
Laterality	Unilateral	6,952	0.31	0.14	0.71	0.001
	Bilateral	6				

Hazards ratio (H.R.), confidence interval (CI), only primary cancer (OPC), second primary cancer (SPC), well differentiated (WD), moderately differentiated (MD), poorly differentiated (PD)

Variables not in the final model: Sequence of RCC (OPC vs. SPC).

Table 6
Kaplan Meier analysis of factors influencing overall survival in renal cell carcinoma patients with second primary cancers

Factor tested	Patient group	N	Mean survival (±SE)	95% C.I.	χ ²	Log Rank test (Mantel-Cox)
Age at diagnosis of RCC	<60 years	1,119	222±4.5 months	213.5–221 months	356.7	P<0.001
	60 years	2,253	130±2.0 months	126–134 months		
Age at occurrence of SPC	<60 years	538	198.6±8 months	184–213.5 months	26.8	P<0.001
	60 years	2,834	158±2.4 months	153–162 months		
Race	White	2,871	164±2.5 months	159.5–169 months	8.7	P=0.013
	Black	340	141±6.3 months	129–154 months		
	Others ^a	160	164±9.5 months	145.6–183 months		
Gender	Male	2,395	162±4 months	154–170 months	0.005	P=0.95
	Female	977	163±2.8 months	157–168 months		
Marital status at time of diagnosis of RCC	Married	2,463	171±2.8 months	166–178.5 months	65.4	P<0.001
	Widowed	358	119±5 months	109–129 months		
	Divorced	188	150±8 months	133–166 months		
	Separated	244	155±8.5 months	1390172 months		
	Single (Never married)	25	155±19 months	118.5–192 months		
	Localized	404	79.5±1.8 months	76–83 months		
	Regional	82	74±4 months	66–82 months		
Distant	34	30.5±1.7 months	19.1–42 months			
Grade of RCC	Well differentiated	350	184±8 months	168.6–200 months	15.5	0.001
	Moderately differentiated	610	143.5±4.5 months	134.6–152 months		
	Poorly differentiated	194	149±10 months	129–169.5 months		
	Undifferentiated	31	143±23 months	99–188 months		
Size of primary renal tumor	5cm	989	131±2.5 months	126–136 months	0.78	0.67
	>5cm- 10cm	702	129±3.0 months	123–135 months		
	>10cm	157	124±6.5 months	112–137 months		
Laterality	Right origin of primary	1,712	158±3 months	152–164 months	3.9	0.048
	Left origin of primary	1,632	168±3.5 months	161.5–175 months		
Radiation therapy given?	Yes ^c	99	119±11 months	98–141 months	15.3	P<0.001
	No	3,255	164±2.4 months	159.5–169 months		

Factor tested	Patient group	N	Mean survival (±SE)	95% C.I.	χ ²	Log Rank test (Mantel-Cox)
Radiation sequence with surgery	Received both	80	131±12 months	108–154 months	6.7	0.01
	Received neither	3,291	163.6±2.4 months	159–168 months		
Months between diagnosis of FPC and SPC	0–11 months	613	92.6±4.7 months	83.5–102 months	756.1	P<0.001
	12–59 months	1,093	120±3.6 months	113–127 months		
	60 months	1,666	210±2.3 months	204–216 months		

Number of patients (N), only primary cancer (OPC), Secondary primary cancer (SPC), Well differentiated (WD), moderately differentiated (MD), poorly differentiated (PD),

^aBlack, American Indian, Alaskan Native, Asian, Pacific islander

^bRegional or distant spread of tumor

^cReceived either radiation or radioisotope therapy

Table 7

Multivariate analysis of factors influencing overall survival in renal cell carcinoma patients with second primary cancers

Variable	Categories	H.R.	95% CI for H.R.		p-value
			Lower	Upper	
Age at diagnosis of SPC	<60 years	0.46	0.27	0.82	0.006
	60 years	-			
Received radiation	No	0.16	0.07	0.38	0.006
	Yes	-			
Months elapsed between FPC and SPC	0–11 months	2.10	1.40	3.20	<0.001
	12 months	-			

Hazards ratio (H.R.), confidence interval (CI), only primary cancer (OPC), second primary cancer (SPC), well differentiated (WD), moderately differentiated (MD), poorly differentiated (PD) and undifferentiated (UD).

^aIncluding divorced, widowed, separated and never married (single) individuals Variables not included in the model: Age at diagnosis of SPC (<60 years vs. 60 years), Race (Whites vs. others), grade of tumor (well and moderately differentiated vs. undifferentiated), size of tumor (< 5cm vs. >5cm), Radiation sequence with surgery (given vs. not given), gender (male vs. female), radiation or radioisotope therapy (given vs. none) and laterality (right vs. left origin of the primary renal tumor).