Incidence, risk and survival outcomes of second primary malignancy among renal cell carcinoma survivors: A nested case-control study

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Research

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Abstract

Background: Second primary malignancy (SPM) challenges survival and surveillance protocols among renal cell carcinoma (RCC) survivors. The incidence, temporal patterns, survival outcomes, and risk factors of SPM after T1-4N0-1M0 RCC diagnosis need to be investigated.

Method: A nested case-control study that was designed using the Surveillance, Epidemiology, and End Results database from 2004-15; A cohort of 6204 SPM were matched with a control group of 37224 non-SPM.

Results: SPM shortens the overall survival (hazard ratio [HR], 1.34; 95% confidence interval [CI]: 1.28-1.42, P< 0.001). The median time interval to SPM was 54.5 months. The adjusted standardized incidence ratio (SIR) of SPM increases by survival time (SIR<sub>12-35-month</sub>: 12.04; SIR<sub>35-59-month</sub>: 12.67; SIR<sub>60-19-month</sub>: 16.08; SIR<sub>120-years</sub>: 25.01, all P< 0.001), and decreased with age (SIR<sub>18-44-years</sub>: 86.68; SIR<sub>45-59-years</sub>: 26.95; SIR<sub>60-74-years</sub>: 12.43; SIR<sub>75+-years</sub>: 10.66, all P< 0.001). The second primary RCC onset, especially contralateral kidney, has the highest SIR (SIR: 54.6; 95%CI: 51.0~58.4) among all sites of SPM. Prostate cancer (29.8%) in male and breast cancer (23.5%) in female were the most common SPM site. Older age, black race, male gender, higher family income statues, papillary RCC, and lower TNM stage significantly increases the risk of SPMs diagnosis. A longer time to SPM interval positively associated with a higher tumor stage of a SPM onset (P<sub>trend</sub><0.001). The overall survival since the SPM diagnosis was associated with SPM's stages, site, and surgical treatment, but not associated with time-to-SPM.

Conclusion: Collectively, our study described the epidemiological characteristics of SPM among RCC survivors and identified the independent predictors of the SPM onset and its survival outcomes, which provides the clinicians for patients consulting and long-term individual, tailored site, and time-specific surveillance to improve survival outcomes.

Introduction

Renal cell carcinoma (RCC) is one of the top 10 most prevalent cancers and accounts for 3% and 5% of all malignancies in females and males, respectively. A previous report highlighted the fact that in 2019, approximately 73,820 new cases of kidney and renal pelvis cancer were diagnosed in the USA, and that an estimated 14,770 patients died from RCC and renal pelvis cancer [1]. Worldwide, there has been a 2% increase in the incidence of RCC over the past two decades; this increase is particularly evident in developed countries and has been associated with the increased application of abdominal imaging technology [2]. In 2016, there were an estimated 15.5 million survivors of cancer in the USA; this number is expected to increase to 20.3 million by 2026 [3]. Given the increased number of RCC patients surviving due to improvements in early detection technology, treatments, and supportive care [4–7], it follows that there will be a substantial increase in the number of survivors being diagnosed with second primary malignancy (SPM). Previous research has shown that SPM can develop as a result of the late effects of certain treatments, such as radiotherapy [8]. Furthermore, the risk of SPM could also be increased by the interactions of common etiological factors, particularly the long-term use of tobacco, excessive alcohol intake, genetic susceptibility, and environmental exposure [7, 9]. Sequelae associated with SPM, particularly highly malignant tumors, will inevitably reduce life expectancy as this occurrence is known to be one of the most serious life-threatening adverse effects experienced by cancer survivors.

How to improve overall survival (OS) is still an important topic in RCC survivorship, and it's crucial to identify the high-risk population for better individual long-term surveillance. However, current guidelines for the frequency and length of follow-up to detect new primary malignancy among survivors with previous primary kidney cancer are based on limited evidence. According to current guidelines, the implementation of routine surveillance following treatment for RCC can permit urologists to monitor or identify postoperative complications, kidney function, the occurrence of local or contralateral recurrence, and the development of metastases; these surveillances focus closely within 5 years following treatment[10]. Actually, tumor recurrence, complications were considerations for the prediction of prognosis, and most occur within 5yr after treatment [11], this might lead some RCC survivor to consider ending surveillance after this interval. Therefore, we should not only consider the risk of local or distant recurrence; we should also stratify the risk of SPM onset. It is necessary to formulate and carry out individualized follow-up programs for patients that are at high risk of SPM people so that we can detect SPM early and provide clinical interventions as soon as possible. By doing this, it will be possible to reduce the risk of death as a result of a second malignancy and thus improve the OS of RCC patients experiencing SPM.

In the current study, we screen the Surveillance, Epidemiology, and End Results (SEER) cancer database to assess the risk factors associated with SPM development (including classification of SPM in ipsilateral/contralateral kidney, SPM of none-kidney) and time-to-SPM. Besides, the survival outcomes and its risk factors were analyzed with consideration of the time to SPM and RCC, and SPM-related characteristics after the first primary RCC.

Patients And Methods

Study design and data source

This was a nested case-control study that was designed to investigate the standard incidence ratio (SIR) and survival outcomes of SPM and associated risk factors in patients who had been treated for primary RCC. Patient data were retrieved from the SEER database (https://seer.cancer.gov/) compiled by the United States National Cancer Institute, including demographic and clinical characteristics, the incidence of cancer, treatments, and survival outcomes, from each cancer registry. The SEER database features 18 registries; collectively, these registries represent approximately 28% of the population of the USA. The characteristics of the patients identified were comparable to the general population and were screened to identify all patients diagnosed with T1-4N0-1M0 RCC. During the period of 2004–2015, there was more detailed information in the database and were used it for analysis. All cases were identified and
selected by the SEER *Stat software (version 8.3.6). All data obtained from the SEER database were anonymized and were not associated with research studies. Consequently, the need for ethics approval was waived by the Institutional Review Board.

Patient identification and study variables

Using the SEER database, we prospectively identified and extracted patients who had been treated for primary RCC but then went on to develop SPM during follow-up. These patients were extracted from the MP-SIR session and were considered as the case group. Patients who did not develop SPM were considered as the control group. Figure 1 shows a flowchart that describes how patients and data were selected from the SEER database. If the selected individuals had experienced multiple incidences of SPM, we only retrieved data relating to the first occurrence of SPM. We ensured that the patients who had been treated for their first primary RCC did not have any other metastatic diseases, were aged ≥ 18 years, and had undergone surgical treatment involving cryosurgery/radiofrequency ablation (RX Summ–Surg Prim Site codes 13, 15, and 23, in the SEER database) and/or partial/radical nephrectomy (RX Summ–Surg Prim Site codes 30, 40, 50, 70, and 80, in the SEER database). Furthermore, all diagnoses of RCC needed to have been finalized by histology and not by autopsy or death certification only. Tumor diameter needed to be no greater than 15 cm and SPM needed to have been diagnosed within 6 months of the diagnosis of primary RCC. Patients with pre-existing or synchronous tumors at the diagnosis of RCC were excluded. The primary cancer site was identified by referring to The International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) [12]. RCC was identified by the ICD-O-3 code C64.9.

We collated a wide range of demographical and clinical variables, as follows: year of diagnosis, age at diagnosis, gender, race or ethnicity (White and Others [Black, American Indian/Alaska Native, Asian Native, and Asian/Pacific Islander]), marital status, family income quartile, population, and region. We also collated a range of data related to tumors, as follows: tumor size (cm), histological cell type for RCC (clear cell, and non-clear cell [papillary and chromophobe]); tumor grade (well-differentiated [grade I], moderately differentiated [grade II], poorly differentiated [grade III], and undifferentiated [grade IV]); and American Joint Committee on Cancer (AJCC) 6th tumor node metastasis (TNM) staging classification. The surgical intervention included partial or radical nephrectomy, cryosurgery, or radiofrequency ablation.

Outcomes for analysis

The primary objectives of this study were to investigate the risk factors and survival outcomes associated with SPM following a primary diagnosis of RCC. Therefore, the main outcomes of interest were (i) SPM diagnosis and the time duration for SPM to develop following a diagnosis of RCC, and the stratification of SPM as kidney cancer, including contralateral and ipsilateral kidney cancer and other non-kidney malignancies; and (ii) overall-mortality, RCC-mortality, and other causes of mortality in patients with RCC. From the SEER database, we were able to collect data relating to the sequence of multiple primary malignancies and the time duration associated with their occurrence; we could also identify the specific causes of death. Patients who died from RCC were identified as RCC-cause mortality, those who died from other causes were designated as ‘competing events’ prior to RCC-cause mortality. Any other cause of death was considered as all-cause mortality; this was considered as a competing event for the occurrence of SPM. The time interval between RCC diagnosis and SPM, and the duration of survival, were defined as the time elapsed from the date of RCC diagnosis to the date of SPM diagnosis, and death or last contact, respectively.

Statistical analysis

Continuous variables are described as means ± standard deviations (SDs) if normally distributed and compared with the Student’s t-test. Continuous variables that were not normally distributed are described as medians and interquartile range (IQR) and compared with the Wilcoxon rank-sum test. Categorical variables are presented as frequencies (%) and were compared with the chi-squared test. The reverse Kaplan-Meier method was used to calculate the median follow-up time. To control bias related to case selection between cases and control groups, we performed propensity score matching (1:5: cases: controls) using the ‘nearest-neighbor’ method and the ‘MatchIt’ package in R. The year in which the primary RCC diagnosis was made, and the first SEER registries of the primary RCC, were designated as adjusted covariables and a multivariable logistic regression model was used to calculate the propensity score for each patient so as to maintain the case and control cohorts diagnosed during the same latency period, and to control for differences across different registries. The adjusted standard incidence ratio (SIR), along with its 95% confidence interval (CI), was calculated as the ratio of SPM in patients diagnosed with primary RCC to the number of expected events in the general population. SEER*Stat version 8.3.6 software was used for this analysis as it could compare the relative risk of SPM for RCC patients as compared with the general population. Age, time interval, and tumor site, were adjusted for the SIR calculation and the statistical significance of SIR was assessed using a likelihood ratio test. Since all-cause mortality could prevent the occurrence of SPM and was considered as a competing event, we used a Fine and Gray competing risks regression model to evaluate the risk factors for the first occurrence of SPM (all SPM, contralateral- and ipsilateral-metachronous kidney cancer, and other non-kidney cancers), and calculated the hazard ratio (HR) with 95% CIs for all risk factors. For Fine and Gray competing risks regression analysis, we define the time interval as the date from the primary RCC diagnosis to the earliest date of the SPM diagnosis (event observed) or the last follow-up in December 2017 (censored). For each Fine and Gray competing risk regression analysis, we compared case and control groups after propensity score matching (using a 1:5 ratio). When investigating the risk factors associated with survival outcomes, we used Cox proportional hazards regression to analyze the risk factors for overall mortality from the first RCC diagnosis and the first SPM diagnosis. Subsequently, we included all variables in multivariate analysis. All analyses were conducted using the R statistical package (v.3.6.3; R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org). All p values are two-sided, and P < 0.05 indicates statistical significance.

Results

Patients and baseline characteristics
From 2004 to 2015, a total of 93,406 patients (aged over 18 years-of-age) were diagnosed with first primary T1-4N0-1M0 RCC in the 18 registries of the SEER database. During follow-up to December 2017, 13,347 of these patients (14.3%) reported two or more subsequent cancer diagnoses. After screening patients with our inclusion and exclusion criteria (Fig. 1), we were able to identify a case-control cohort (SPM vs. non-SPM) with 6,204 patients (16.7%) in the case group and 31,020 patients (83.3%) in the control group after propensity score matching (1:5) for the year of diagnosis and different registers. 

**Supplementary Table 1** lists the baseline characteristics prior to propensity score matching; comparisons of the case and control cohorts revealed several significant differences, although tumor laterality (P = 0.579) and population density (P = 0.394) were not significantly different. Table 1 shows the demographic and clinical characteristics of patients after propensity score matching; there was a good balance between the case and control cohorts with regards to the year of diagnosis (P = 1.000), and the data registries (P = 0.979). In comparison with non-SPM patients, those with SPM were older (mean age, 63.3 [10.7] vs. 59.4 [12.7] years, P < 0.001), male (68.9% vs. 60.9%, P < 0.001), were of black race (12.5% vs. 11.1%, P < 0.001), had a higher tumor grade of I/II (69.6% vs. 67.7%, P = 0.026), had papillary RCC (14.2% vs. 11.0%, P < 0.001), had lower levels of T3/4 (16.0% vs. 17.7%, P < 0.001), had lower levels of N1 (0.8% vs. 1.8%, P < 0.001), had a small tumor size (mean, 47.5 vs. 49.7 cm, P < 0.001), and were more likely to have been treated by cryosurgery/radiofrequency and partial neurectomy (33.5% vs. 30.9%, P < 0.001). In addition, the onset of SPM was more common in married patients (68.6% vs. 66.0%, P < 0.001), and less common in patients with a median family income that was less than a quartile of 1 (20.3% vs. 22.2%, P < 0.001). 

**Supplementary Table 2** lists the demographic and clinical characteristics of patients with RCC as a primary malignant tumor between 2004 and 2015 after 1:5 propensity score matching for different case-control groups (non-RCC SPM vs. non-SPM; contralateral RCC SPM vs. non-SPM; ipsilateral RCC SPM vs. non-SPM).
Table 1
Demographic and clinic characteristics for patients with renal cell carcinoma as the first primary malignant tumor between 2004–2015 after propensity score matching.

|                     | Overall       | None-SPM (Control) | With SPM (Case) | P-value |
|---------------------|---------------|--------------------|-----------------|---------|
| **Year at diagnosis** | (N = 37224)   | (N = 31020)        | (N = 6204)      |         |
| 2004                | 4068 (10.9%)  | 3382 (10.9%)       | 686 (11.1%)     | 1.000   |
| 2005                | 4139 (11.1%)  | 3448 (11.1%)       | 691 (11.1%)     |         |
| 2006                | 4432 (11.9%)  | 3708 (12.0%)       | 724 (11.7%)     |         |
| 2007                | 4251 (11.4%)  | 3535 (11.4%)       | 716 (11.5%)     |         |
| 2008                | 4216 (11.3%)  | 3513 (11.3%)       | 703 (11.3%)     |         |
| 2009                | 3836 (10.3%)  | 3199 (10.3%)       | 637 (10.3%)     |         |
| 2010                | 3150 (8.5%)   | 2625 (8.5%)        | 525 (8.5%)      |         |
| 2011                | 2562 (6.9%)   | 2135 (6.9%)        | 427 (6.9%)      |         |
| 2012                | 2202 (5.9%)   | 1835 (5.9%)        | 367 (5.9%)      |         |
| 2013                | 2070 (5.6%)   | 1725 (5.6%)        | 345 (5.6%)      |         |
| 2014                | 1470 (3.9%)   | 1225 (3.9%)        | 245 (3.9%)      |         |
| 2015                | 828 (2.2%)    | 690 (2.2%)         | 138 (2.2%)      |         |
| **SEER registries** |               |                    |                 | 0.979   |
| Atlanta (Metropolitan) | 1252 (3.4%)  | 1047 (3.4%)        | 205 (3.3%)      |         |
| California excluding SF/SJM/LA | 7512 (20.2%) | 6246 (20.1%)       | 1266 (20.4%)    |         |
| Connecticut         | 1752 (4.7%)   | 1473 (4.7%)        | 279 (4.5%)      |         |
| Detroit (Metropolitan) | 2139 (5.7%)  | 1792 (5.8%)        | 347 (5.6%)      |         |
| Greater Georgia     | 2891 (7.8%)   | 2414 (7.8%)        | 477 (7.7%)      |         |
| Hawaii              | 566 (1.5%)    | 463 (1.5%)         | 103 (1.7%)      |         |
| Iowa                | 1880 (5.1%)   | 1554 (5.0%)        | 325 (5.3%)      |         |
| Kentucky            | 3102 (8.3%)   | 2594 (8.4%)        | 508 (8.2%)      |         |
| Los Angeles         | 3279 (8.8%)   | 2742 (8.8%)        | 537 (8.7%)      |         |
| Louisiana           | 2668 (7.2%)   | 2226 (7.2%)        | 442 (7.1%)      |         |
| New Jersey          | 4231 (11.4%)  | 3494 (11.3%)       | 737 (11.9%)     |         |
| New Mexico          | 462 (1.2%)    | 385 (1.2%)         | 77 (1.2%)       |         |
| Rural Georgia       | 72 (0.2%)     | 60 (0.2%)          | 12 (0.2%)       |         |
| San Francisco Oakland SMSA | 1623 (4.4%) | 1363 (4.4%)        | 260 (4.2%)      |         |
| San Jose Monterey   | 820 (2.2%)    | 676 (2.2%)         | 144 (2.3%)      |         |
| Seattle (Puget Sound) | 2318 (6.2%) | 1946 (6.3%)        | 372 (6.0%)      |         |
| Utah                | 657 (1.8%)    | 545 (1.8%)         | 112 (1.8%)      |         |
| **Marital status**  |                |                    |                 | < 0.001 |
| Married             | 24730 (66.4%) | 20459 (66.0%)      | 4271 (68.8%)    |         |
| Single/unmarried    | 5458 (14.7%)  | 4685 (15.1%)       | 773 (12.5%)     |         |
| Widowed/Divorced/Separated | 7036 (18.9%) | 5876 (18.9%)       | 1160 (18.7%)    |         |
| **Population density** |            |                    |                 | 0.270   |
| Counties            | 32546 (87.4%) | 27103 (87.4%)      | 5443 (87.7%)    |         |
| Nested Case-Control |
|---------------------|
| Rural              |
| 603 (1.6%)         |
| 517 (1.7%)         |
| 86 (1.4%)          |
| Urban              |
| 4075 (10.9%)       |
| 3400 (11.0%)       |
| 675 (10.9%)        |
| Region             |
| 0.995              |
| East               |
| 15968 (42.9%)      |
| 13308 (42.9%)      |
| 2660 (42.9%)       |
| Northern Plains    |
| 4019 (10.8%)       |
| 3346 (10.8%)       |
| 673 (10.8%)        |
| Pacific Coast      |
| 16118 (43.3%)      |
| 13436 (43.3%)      |
| 2682 (43.2%)       |
| Southwest          |
| 1119 (3.0%)        |
| 930 (3.0%)         |
| 189 (3.0%)         |
| The median family income quartile |
| 0.016              |
| 1 or less          |
| 8158 (21.9%)       |
| 6882 (22.2%)       |
| 1276 (20.6%)       |
| 1~2                |
| 9753 (26.2%)       |
| 8135 (26.2%)       |
| 1618 (26.1%)       |
| 2~3                |
| 9782 (26.3%)       |
| 8079 (26.0%)       |
| 1703 (27.5%)       |
| 3~4                |
| 9531 (25.6%)       |
| 7924 (25.5%)       |
| 1607 (25.9%)       |
| Age at diagnosis, years |
| < 0.001            |
| Mean (SD [Min-Max])|
| 60.0 (12.5 [18.0-100]) |
| 59.4 (12.7 [18.0-100]) |
| 63.3 (10.7 [26.0–93.0]) |
| Median (IQR)       |
| 60.0 (52.0, 69.0)  |
| 60.0 (51.0, 68.0)  |
| 64.0 (56.0, 71.0)  |
| Age group at diagnosis, years |
| < 0.001            |
| (~44]             |
| 4193 (11.3%)       |
| 3908 (12.6%)       |
| 285 (4.6%)         |
| [45–59]           |
| 13487 (36.2%)      |
| 11590 (37.4%)      |
| 1897 (30.6%)       |
| [60–74]            |
| 14648 (39.4%)      |
| 11591 (37.4%)      |
| 3057 (49.3%)       |
| (>75)             |
| 4896 (13.2%)       |
| 3931 (12.7%)       |
| 965 (15.6%)        |
| Race               |
| < 0.001            |
| White              |
| 31001 (83.3%)      |
| 25855 (83.3%)      |
| 5146 (82.9%)       |
| Black              |
| 4212 (11.3%)       |
| 3438 (11.1%)       |
| 774 (12.5%)        |
| Other              |
| 2011 (5.4%)        |
| 1727 (5.6%)        |
| 284 (4.6%)         |
| Sex                |
| < 0.001            |
| Female             |
| 14050 (37.7%)      |
| 12123 (39.1%)      |
| 1927 (31.1%)       |
| Male               |
| 23174 (62.3%)      |
| 18897 (60.9%)      |
| 4277 (68.9%)       |
| Grade              |
| 0.026              |
| Grade I            |
| 5179 (13.9%)       |
| 4317 (13.9%)       |
| 862 (13.9%)        |
| Grade II           |
| 20141 (54.1%)      |
| 16687 (53.8%)      |
| 3454 (55.7%)       |
| Grade III/IV       |
| 11904 (32.0%)      |
| 10016 (32.3%)      |
| 1888 (30.4%)       |
| Tumor side         |
| 0.501              |
| Left               |
| 18188 (48.9%)      |
| 15132 (48.8%)      |
| 3056 (49.3%)       |
| Right              |
| 19036 (51.1%)      |
| 15888 (51.2%)      |
| 3148 (50.7%)       |
| Histological type  |
| < 0.001            |
| ccRCC              |
| 22652 (60.9%)      |
| 18976 (61.2%)      |
| 3676 (59.3%)       |
| chRCC              |
| 1758 (4.7%)        |
| 1513 (4.9%)        |
| 245 (3.9%)         |
| paRCC              |
| 4294 (11.5%)       |
| 3414 (11.0%)       |
| 880 (14.2%)        |
| RCC (undefined)    |
| 6465 (17.4%)       |
| 5440 (17.5%)       |
| 1025 (16.5%)       |
| Other type RCC     |
| 2055 (5.5%)        |
| 1677 (5.4%)        |
| 378 (6.1%)         |
| AJCC stage group   |
| < 0.001            |
| I                  |
| 26326 (70.7%)      |
| 21790 (70.2%)      |
| 4536 (73.1%)       |
The anatomical distribution of SPM

Supplementary Fig. 1 shows the proportion (%) of each type of SPM. Within the all-SPM cohort, the top 10 sites for SPM were the prostate (20.5%), contralateral kidney (11.8%), lungs and bronchi (11.3%), female breast (7.3%), bladder (6.0%), colon/rectum (5.2%), thyroid (3.8%), skin (melanoma) (3.7%), NHL/Hodgkin (3.6%), and pancreas (27%). Within gender and race subgroups, we found that breast cancer was the top site for SPM in females (23.5%). The prostate was the most common site for SPM in males; the prostate accounted for 19.5%, 26.2%, and 19.9% of SPM sites in white, black, and other races, respectively.

It is noteworthy that contralateral RCC was a common malignancy following the primary RCC diagnosis in several different subgroups, accounting for 12.2% of males, 10.9% of females, 10.3% of white patients, 22.1% of black patients, and 9.8% of other races. When considering different follow-up periods (<1 year, 1–2 years, 3–5 years, and >5 years), there were no obvious changes with regards to the proportion (%) of each type of SPM (Supplementary Fig. 2). We observed clear histological changes associated with SPM in the kidney when compared with the primary RCC (Supplementary Fig. 3): 29.4% of cases with clear cell RCC, 40.1% of cases with papillary RCC, and 60.0% of cases with chromophobe RCC showed histological changes between the first primary RCC and the occurrence of SPM in the kidney. With regards to SPM in the contralateral kidney, 27.2%, 36.4%, and 59.6% of cases with clear cell, papillary, and chromophobe RCC, respectively, presented with histological changes. Histological changes were also evident in cases with SPM in the ipsilateral kidney; such changes were observed in 41.2% of cases with clear cell RCC, 73.3% of cases with papillary RCC, and 62.5% of cases with chromophobe RCC.
The time interval to SPM

Figure 2A and Supplementary Fig. 4 present the distribution of the time taken to diagnose SPM in all cohorts stratified by gender and different SPM sites. For the entire cohort, the median time to SPM onset after the first primary diagnosis was 54.5 months, 53.0 months, and 61.0 months, in all sex, male and female patients, respectively. With regards to different SPM sites, we found that SPM of the ipsilateral and contralateral kidneys had the shortest median time interval to SPM: 48.0 and 49.0 months, 41 and 46.5 months, and 21 and 31 months, in the entire cohort, the male cohort, and the female cohort, respectively. SPM of the ovary (79.5 months) and bladder (69 months) was associated with the longest median time interval to SPM. Another interesting finding was that tumor stage, tumor size, and TNM stage of SPM were significantly associated with the time interval to SPM (Fig. 2B). A larger tumor size ($P_{\text{trend}}<0.001$), more regional and distant metastasis ($P_{\text{trend}}=0.012$), and stage III/IV tumors ($P_{\text{trend}}<0.001$) were significantly associated with an increase by the time interval to SPM.

The age-, time interval-, and site-specific SIR for SPM

Next, we accessed the risk of SPM diagnosis after primary RCC as compared with the general population. To do this, we calculated the adjusted SIR for different anatomic sites, the time interval to SPM, and age. The adjusted SIRs showed that younger patients with RCC tended to have a significantly higher risk of developing SPM and presented a downwards trend for SPM incidence with increasing age ($\text{SIR}_{12−35\text{−month}}$: 12.04; $\text{SIR}_{36−59\text{−month}}$: 12.67; $\text{SIR}_{60−19\text{−month}}$: 16.08; $\text{SIR}_{120+\text{−years}}$: 25.01, all $P<0.001$). We also found that an increased postoperative time was associated with an increased incidence of SPM ($\text{SIR}_{12−35\text{−month}}$: 12.04; $\text{SIR}_{36−59\text{−month}}$: 12.67; $\text{SIR}_{60−19\text{−month}}$: 16.08; $\text{SIR}_{120+\text{−years}}$: 25.01, all $P<0.001$) (Fig. 2C). When considering all SPM sites, we found that the SIR was 13.60 (95% CI: 13.27–13.95; Fig. 2D). When considering the risk for each anatomical site, we found that several sites had a significantly higher risk for SPM after primary RCC treatment: kidney (both ipsilateral and contralateral; SIR: 54.62; 95% CI: 51.01–58.42), thyroid (SIR: 41.70; 95% CI: 36.55–47.37), and liver (SIR: 15.93; 95% CI: 13.37–18.84).

Risk factors for SPM following primary RCC diagnosis

Table 2 shows the results of our analyses relating to risk factors for all SPM sites, SPM in non-RCC, contralateral RCC, and ipsilateral RCC, after the primary diagnosis of RCC. Based on multivariate Fine and Gray competing risks regression, the risk of SPM was significantly associated with increasing age at the diagnosis of primary RCC (45–59 years vs. 18–44 years: sub-distribution hazard ratio [sHR] 2.13, 95% CI: 1.88–2.41, $P<0.001$; 60–74 years vs. 18–44 years, sHR, 3.40, 95% CI: 3.01–3.85, $P<0.001$; $\geq 75$ vs. 18–44, sHR, 3.30, 95% CI: 2.88–3.78, $P<0.001$). Black patients had a higher risk of developing SPM than white patients (sHR: 1.21; 95% CI: 1.12–1.31; $P<0.001$), and patients of other races had a lower risk of developing SPM (sHR: 0.86; 95% CI: 0.76–0.97; $P=0.012$). Compared with females, males had an increased risk of SPM (sHR: 1.41; 95% CI: 1.33–1.49; $P<0.001$). Patients with a high family income were associated with a higher risk of SPM (quartile 3–4 vs. 1 or less: sHR, 1.09; 95% CI: 1.00–1.18, $P=0.041$). In addition, the papillary and chromophobe forms of RCC were associated with a higher (sHR: 1.10; 95% CI: 1.02–1.19; $P=0.013$) and lower (sHR: 0.85; 95% CI: 0.74–0.96; $P=0.011$) risk of SPM, respectively, when compared with clear cell RCC. Furthermore, T3/4 diseases were associated with a lower risk of SPM compared with T1 (sHR: 0.89; 95% CI: 0.83–0.96; $P=0.004$). Patients with lymph node invasion were associated with a reduced risk of SPM (sHR: 0.51; 95% CI: 0.39–0.68; $P<0.001$). Patients undergoing any form of nephrectomy (sHR: 0.71; 95% CI: 0.56–0.90; $P=0.006$), partial nephrectomy (sHR: 0.78; 95% CI: 0.67–0.90; $P=0.008$), and radical nephrectomy (sHR: 0.64; 95% CI: 0.55–0.74; $P<0.001$) were associated with a higher risk of SPM diagnosis compared with those undergoing cryosurgery/radiofrequencies. Further analysis for the predictors of SPM in non-RCC patients showed that the risk factors were similar to those for any type of SPM (Table 2).
| Nested Case-Control: | Nested Case-Control group 1: | Nested Case-Control group 2: | Nested Case-Control group 3: |
|----------------------|-----------------------------|-----------------------------|-----------------------------|
| All SPM vs. none-SPM | Non-RCC SPM vs. Non-SPM #   | Contralateral RCC SPM vs. Non-SPM # | Ipsilateral RCC SPM vs. Non-SPM # |
| Unadjusted sHR (95%CI) | Unadjusted sHR (95%CI) | Unadjusted sHR (95%CI) | Unadjusted sHR (95%CI) |
| Adjusted sHR (95%CI) | Adjusted sHR (95%CI) | Adjusted sHR (95%CI) | Adjusted sHR (95%CI) |

### Age at diagnosis, years

| (~44) | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference |
|-------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| 2.12  | (1.88–2.40) | 2.72  | (2.34–3.17) | 1.08  | (0.86–1.36) | 2.09  | (0.90–4.85) | 2.46  | (1.01–6.00) |
| 3.92  | (2.94–3.75) | 4.61  | (3.97–5.34) | 0.97  | (0.77–1.22) | 1.04  | (0.82–1.33) | 1.98  | (0.84–4.67) |
| 3.05  | (2.67–3.48) | 4.38  | (3.74–5.13) | 0.62  | (0.44–0.87) | 0.79  | (0.56–1.12) | 2.44  | (0.87–6.85) |

### Race

| White | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference |
|-------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| 1.15  | (1.07–1.25) | 1.09 (1.00–1.18) | 1.16 (1.06–1.27) | 2.24 (1.88–2.66) | 2.22 (1.84–2.67) | 0.96 (0.41–2.24) | 1.24 (0.48–3.19) |
| Black | 1.21 (1.12–1.31) | 0.85 (0.75–0.97) | 0.87 (0.78–0.99) | 0.87 (0.60–1.25) | 0.83 (0.57–1.21) | 2.41 (0.97–5.97) | 1.51 (0.59–3.83) |
| Other | 0.86 (0.76–0.97) | 0.86 (0.76–0.97) | 0.87 (0.75–0.99) | 0.87 (0.60–1.25) | 0.83 (0.57–1.21) | 2.41 (0.97–5.97) | 1.51 (0.59–3.83) |

### Sex

| Female | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference |
|--------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| 1.39  | (1.31–1.46) | 1.35 (1.32–1.49) | 1.52 (1.30–1.78) | 1.34 (1.13–1.58) | 1.71 (1.06–2.76) | 1.29 (0.77–2.17) |
| Male   | 1.41 (1.33–1.49) | 1.40 (1.32–1.49) | 1.52 (1.30–1.78) | 1.34 (1.13–1.58) | 1.71 (1.06–2.76) | 1.29 (0.77–2.17) |

### Marital status

| Married | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference |
|---------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| 0.84 (0.78–0.91) | 0.81 (0.75–0.88) | 0.97 (0.89–1.06) | 1.10 (0.90–1.34) | 0.97 (0.79–1.24) | 0.53 (0.25–1.10) | 0.80 (0.38–1.68) |
| Single/unmarried | 0.96 (0.89–1.04) | 0.99 (0.93–1.07) | 0.99 (0.92–1.06) | 0.69 (0.56–0.85) | 0.75 (0.60–0.94) | 0.70 (0.37–1.33) | 0.71 (0.35–1.44) |
| Widowed/Divorced/Separated | 0.95 (0.89–1.01) | 0.96 (0.90–1.03) | 0.99 (0.93–1.07) | 0.99 (0.92–1.06) | 0.69 (0.56–0.85) | 0.75 (0.60–0.94) | 0.70 (0.37–1.33) | 0.71 (0.35–1.44) |

### Population

| Counties | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference |
|----------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Rural    | 0.85 (0.68–1.05) | 0.88 (0.70–1.10) | 0.91 (0.72–1.14) | 0.80 (0.42–1.52) | 0.96 (0.49–1.85) | 0.70 (0.10–4.79) | 0.66 (0.12–3.56) |
| Urban    | 0.99 (0.92–1.07) | 0.98 (0.90–1.07) | 1.00 (0.92–1.10) | 0.90 (0.71–1.15) | 1.05 (0.81–1.36) | 1.45 (0.76–2.77) | 1.35 (0.69–2.63) |

### Region

| East | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference |
|------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|

*Table 2: Univariate and multivariate Fine and Gray competing risks regression of risk factors for second primary malignancy (SPM) among renal cell carcinoma patients.*
| Nested Case-Control: | Nested Case-Control | Nested Case-Control | Nested Case-Control |
|----------------------|---------------------|---------------------|---------------------|
| All SPM vs. none-SPM | group 1: Non-RCC SPM vs. Non-SPM | group 2: Contralateral RCC SPM vs. Non-SPM | group 3: Ipsilateral RCC SPM vs. Non-SPM |
| Northern Plains      | 0.99 (0.91–1.08)    | 0.96 (0.88–1.05)    | 0.97 (0.77–1.21)    | 1.11 (0.54–2.26) |
| Pacific Coast        | 0.99 (0.94–1.04)    | 1.01 (0.95–1.07)    | 1.00 (0.94–1.06)    | 0.99 (0.85–1.16) |
| Southwest            | 1.01 (0.87–1.17)    | 1.07 (0.92–1.24)    | 1.02 (0.87–1.19)    | 0.93 (0.57–1.53) |

The median family income quartile

| 1 or less | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference |
|-----------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| 1 – 2     | 1.05 (0.97–1.13) | 1.05 (0.98–1.13) | 1.05 (0.97–1.13) | 1.06 (0.98–1.15) | 0.98 (0.79–1.21) | 0.96 (0.77–1.20) | 1.42 (0.76–2.66) | 1.38 (0.71–2.65) |
| 2 – 3     | 1.10 (1.03–1.19) | 1.11 (1.03–1.20) | 1.10 (1.02–1.19) | 1.11 (1.03–1.21) | 1.09 (0.89–1.34) | 1.14 (0.92–1.41) | 1.23 (0.65–2.34) | 1.22 (0.64–2.35) |
| 3 – 4     | 1.07 (0.99–1.15) | 1.09 (1.00–1.18) | 1.07 (0.99–1.16) | 1.09 (1.00–1.19) | 1.07 (0.87–1.32) | 1.16 (0.92–1.46) | 0.89 (0.45–1.77) | 1.27 (0.60–2.72) |

Grade

| Grade I | Grade II | Grade III/IV |
|---------|----------|--------------|
| 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference |
| 1.07 (1.00–1.16) | 1.10 (1.01–1.19) | 1.06 (0.98–1.15) | 1.13 (0.90–1.41) | 1.12 (0.90–1.40) | 1.97 (1.08–3.60) | 1.47 (0.76–2.85) |
| Grade I | Grade II | Grade III/IV |
| 1.00 (0.93–1.09) | 0.98 (0.91–1.07) | 1.02 (0.94–1.12) | 0.98 (0.90–1.07) | 1.28 (1.01–1.62) | 1.34 (1.06–1.71) | 1.54 (0.69–3.45) | 1.43 (0.61–3.33) |

Histological type

| ccRCC | chRCC | paRCC | RCC (undefined) | Other type RCC | AJCC TNM stage group |
|------|------|------|----------------|--------------|---------------------|
| 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference |
| 0.92 (0.72–0.94) | 0.85 (0.74–0.96) | 0.83 (0.72–0.95) | 0.86 (0.75–0.99) | 0.75 (0.50–1.12) | 0.62 (0.41–0.94) | 0.52 (0.12–2.17) | 0.86 (0.19–3.82) |
| 1.29 (1.20–1.39) | 1.10 (1.02–1.19) | 1.23 (1.13–1.33) | 1.05 (0.97–1.14) | 1.81 (1.15–2.19) | 1.33 (1.09–1.62) | 0.65 (0.32–1.33) | 0.60 (0.28–1.30) |
| 0.89 (0.83–0.96) | 0.87 (0.81–0.94) | 0.89 (0.83–0.97) | 0.88 (0.82–0.95) | 0.88 (0.72–1.09) | 0.83 (0.67–1.03) | 0.50 (0.26–0.99) | 0.46 (0.22–0.96) |
| 1.10 (0.99–1.23) | 1.08 (0.97–1.20) | 1.12 (1.00–1.26) | 1.10 (0.98–1.23) | 1.02 (0.73–1.41) | 0.94 (0.68–1.29) | 0.99 (0.39–2.52) | 1.77 (0.65–4.76) |

AJCC TNM stage group

| I | II | III/IV |
|---|---|------|
| 1 reference | 1 reference | 1 reference |
| 0.88 (0.81–0.95) | 0.96 (0.88–1.05) | 0.90 (0.82–0.98) | 0.96 (0.88–1.05) | 0.91 (0.72–1.15) | 0.98 (0.76–1.25) |
| 0.87 (0.81–0.93) | 0.86 (0.80–0.93) | 0.88 (0.82–0.94) | 0.84 (0.77–0.91) | 0.84 (0.69–1.01) | 0.92 (0.74–1.13) |

Tumor size of first primary RCC
| Nested Case-Control: | Nested Case-Control group 1: | Nested Case-Control group 2: | Nested Case-Control group 3 ¶: |
|----------------------|-----------------------------|-----------------------------|-----------------------------|
| All SPM vs. none-SPM | Non-RCC SPM vs. Non-SPM #   | Contralateral RCC SPM vs. Non-SPM # | Ipsilateral RCC SPM vs. Non-SPM # |
| (~ 4] cm             | 1 reference                 | 1 reference                 | 1 reference                 |
|                      | (1 reference)               | (1 reference)               | (1 reference)               |
| (4.1–7] cm           | 0.99 (0.94–1.05)            | 1.04 (0.98–1.10)            | 1.02 (0.96–1.08)            |
|                      | 1.03 (0.96–1.10)            | 0.99 (0.84–1.17)            | 1.14 (0.95–1.37)            |
| (7.1–10] cm          | 0.83 (0.76–0.89)            | 0.91 (0.83–0.99)            | 0.82 (0.76–0.90)            |
|                      | 0.87 (0.79–0.95)            | 0.96 (0.78–1.19)            | 1.19 (0.93–1.52)            |
| (10–) cm             | 0.75 (0.67–0.84)            | 0.85 (0.75–0.96)            | 0.75 (0.66–0.86)            |
|                      | 0.82 (0.71–0.93)            | 1.09 (0.81–1.46)            | 1.30 (0.93–1.80)            |

AJCC T stage §

| T1       | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference |
|----------|-------------|-------------|-------------|-------------|-------------|
| T2       | 0.87 (0.80–0.94) | 0.96 (0.88–1.04) | 0.89 (0.82–0.97) | 0.96 (0.87–1.05) | 0.90 (0.72–1.13) |
| T3/T4    | 0.88 (0.82–0.94) | 0.89 (0.83–0.96) | 0.89 (0.83–0.96) | 0.87 (0.81–0.95) | 0.85 (0.70–1.03) |

AJCC N stage §

| N0       | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference |
|----------|-------------|-------------|-------------|-------------|-------------|
| N1       | 0.47 (0.36–0.62) | 0.51 (0.39–0.68) | 0.47 (0.35–0.63) | 0.50 (0.37–0.67) | 0.34 (0.14–0.81) |

Surgery for first primary RCC ¶

| Cryosurgery/Radiofrequency | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference | 1 reference |
|----------------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Nephrectomy                | 0.59 (0.46–0.75) | 0.71 (0.56–0.90) | 0.68 (0.53–0.87) | 0.82 (0.64–1.06) | 0.63 (0.24–1.62) | 0.55 (0.21–1.45) |
| Partial nephrectomy        | 0.67 (0.58–0.77) | 0.78 (0.67–0.90) | 0.67 (0.57–0.79) | 0.80 (0.68–0.94) | 1.59 (0.92–2.75) | 1.45 (0.84–2.52) |
| Radical nephrectomy        | 0.56 (0.48–0.64) | 0.64 (0.56–0.74) | 0.60 (0.51–0.70) | 0.70 (0.60–0.82) | 1.08 (0.63–1.86) | 1.00 (0.58–1.72) |

SPM, second primary malignancy; CI, confidence interval; sHR, Sub-distribution hazard ratio; AJCC, American Joint Committee on Cancer system; RCC, renal cell carcinoma; T, Tumor; N, lymph node; ccRCC, clear cell renal cell carcinoma; paRCC, papillary renal cell carcinoma; chRCC, chromophobe renal cell carcinoma

Bold type indicates that the P-value is significant (P < 0.05).

* Univariate Fine and Grey proportional risk regression analysis.

** Multivariate Fine and Grey proportional risk regression analysis.

Each comparison group was matched with 1:5 propensity score, the matched data was shown in the Supplementary Table 2.

First primary renal cell carcinoma with the AJCC stage of T1aN0M0 (number of cases with SPM in ipsilateral renal cell carcinoma vs. control group was 82 vs. 410) was included.

Results of multivariate fine and Grey proportional risk regression analysis with all variables adjusted.

Results of multivariate Fine and Grey proportional risk regression analysis with adjusting for the AJCC N stage and all variables of ‡ except the AJCC stage group.

Results of multivariate Fine and Grey proportional risk regression analysis with adjusting for all variables of ‡ except AJCC stage group and tumor size group.

We identified several independent predictors for SPM in the contralateral RCC: black race vs. white race (sHR: 2.22; 95% CI: 1.84–2.67; P < 0.001), male vs. female (sHR: 1.34; 95% CI: 1.13–1.58; P < 0.001), tumor grade III/IV vs. grade 1 (sHR: 1.34; 95% CI: 1.06–1.71; P = 0.016), papillary RCC vs. clear cell RCC.
(sHR: 1.33; 95% CI: 1.09–1.62; P < 0.001), widowed/divorced/separated vs. married (sHR: 0.75; 95% CI: 0.60–0.94; P = 0.011), and N1 vs. N0 (sHR: 0.32; 95% CI: 0.13–0.79; P = 0.009). Multivariable analysis identified that only age (45–59 years vs. ≤44 years; sHR: 2.46; 95% CI: 1.01–6.00; P = 0.048), histological type (undefined vs. clear cell RCC; sHR: 0.46; 95% CI: 0.22–0.96; P = 0.038) and surgery type (partial nephrectomy vs. cryosurgery/radiofrequency; sHR: 0.30; 95% CI: 0.17–0.55; P < 0.001), represented independent predictors for SPM in the ipsilateral RCC.

Survival and risk predictors following the diagnosis of primary RCC and SPM

At the final follow-up (crude median: 76 months), we found that 4.7% and 7.3% of patients had died from other forms of malignancy and RCC-specific malignancy, respectively (results from unmatched data; data not shown). Survival analysis showed that the 5-year OS for RCC patients who experienced SPM was 85.9% (95% CI: 84.9–87.2%) from the primary RCC diagnosis, and 58.9% (95% CI: 57.1–60.8%) from the SPM diagnosis (Fig. 3). The development of SPM in the pancreas, brain, gallbladder/bile duct, liver, miscellaneous tissues, esophagus/stomach, and lungs/bronchi, was associated with poor survival outcomes, with a 5-year OS of 13.4%, 13.5%, 17.7%, 18.0%, 19.6%, 22.8%, and 24.2%, from SPM diagnosis, respectively. Similar results were obtained for the female and male cohorts (Supplementary Fig. 5).

Following the adjustment of other covariables by multivariable Cox regression, we found that when compared with non-SPM patients, those with SPM were associated with a significant impact in terms of OS following the primary RCC diagnosis (HR: 1.26; 95% CI: 1.20–1.32; P < 0.001; Supplementary Table 3). Supplementary Table 3 shows that the time interval to SPM could also impact the OS after the primary RCC diagnosis. An early SPM diagnosis, a higher risk of mortality (6 < time ≤ 12 months vs. >120 months; HR: 5.75; 95% CI: 3.87–8.49; P < 0.001), and different SPM sites, had different impacts on survival outcomes. There was no significant difference in the risk of mortality for cases of SPM in the contralateral kidney compared with the ipsilateral kidney since the primary RCC (HR: 1.43; 95% CI: 0.74–2.76; P = 0.286) or since the diagnosis of SPM (HR: 1.53; 95% CI: 0.79–2.95; P = 0.206). Furthermore, there were no significant differences in the risk of mortality when compared between cases of SPM in the cecum/small intestine, female breast, and thyroid, when compared to ipsilateral cases. Interestingly, we found that male patients with SPM in the prostate were associated with a lower risk of mortality than those with SPM in the ipsilateral kidney (HR: 0.43; 95% CI: 0.22–0.83; P = 0.011). We also investigated the effects of SPM tumor stage and the site of SPM on OS. Table 3 shows that a higher SPM tumor stage significantly reduced the OS and that surgical treatment could improve the OS (adjusted HR: 0.40; 95% CI: 0.35–0.46; P < 0.001).
Table 3
Risk predictors of all-cause mortality after SPM diagnosis by the TNM stage or stage groups of SPMs and surgical treatment among all patients with solid SPM.

|                         | Unadjusted | P-value | Adjusted | P-value |
|-------------------------|------------|---------|----------|---------|
| **Invasion of SPM**     |            |         |          |         |
| Local                   | 1 reference|         | 1 reference|        |
| Regional                | 2.19 (1.92–2.50) | < 0.001 | 1.59 (1.37–1.84) | < 0.001 |
| Distant                 | 9.13 (8.06–10.33) | < 0.001 | 3.83 (3.28–4.47) | < 0.001 |
| **AJCC stage group of SPM** |          |         |          |         |
| I                       | 1 reference|         | 1 reference|        |
| II                      | 0.89 (0.77–1.04) | 0.129 | 1.32 (1.10–1.59) | 0.003 |
| III                     | 2.55 (2.16–3.00) | < 0.001 | 2.02 (1.70–2.41) | < 0.001 |
| IV                      | 7.03 (6.10–8.11) | < 0.001 | 3.95 (3.34–4.67) | < 0.001 |
| **AJCC T stage of SPM** |            |         |          |         |
| T1                      | 1 reference|         | 1 reference|        |
| T2                      | 1.46 (1.27–1.68) | < 0.001 | 1.45 (1.25–1.68) | < 0.001 |
| T3/T4                   | 3.44 (3.02–3.91) | < 0.001 | 1.66 (1.42–1.93) | < 0.001 |
| Ta/Tis                  | 0.91 (0.70–1.19) | 0.500 | 0.42 (0.29–0.60) | < 0.001 |
| **AJCC N stage of SPM** |            |         |          |         |
| N0                      | 1 reference|         | 1 reference|        |
| N1                      | 2.22 (1.91–2.60) | < 0.001 | 1.15 (0.97–1.38) | 0.112 |
| N2                      | 5.37 (4.57–6.30) | < 0.001 | 1.61 (1.33–1.95) | < 0.001 |
| N3                      | 8.19 (6.20-10.83) | < 0.001 | 2.06 (1.51–2.80) | < 0.001 |
| **AJCC N stage of SPM** |            |         |          |         |
| M0                      | 1 reference|         | 1 reference|        |
| M1                      | 7.50 (6.66–8.45) | < 0.001 | 2.41 (2.09–2.79) | < 0.001 |
| **Surgical treatment for SPM** |      |         |          |         |
| No                      | 1 reference|         | 1 reference|        |
| Yes                     | 0.35 (0.32–0.39) | < 0.001 | 0.40 (0.35–0.46) | < 0.001 |

SPM, second primary malignancy; CI, confidence interval; AJCC, American Joint Committee on Cancer system; RCC, renal cell carcinoma; T, Tumor; N, lymph node; M, Metastasis.

*All SPM in solid malignancy (n = 5008) exclude acute/chronic leukemia/myeloma, melanoma of the skin, NHL/Hodgkin, miscellaneous.

§ Univariate Cox proportional risk regression analysis.

#Multivariate analysis with covariables adjusted (age at the time of diagnosis of SPM, sex, race, marital status, population, region, family income, tumor grade, histological type of first primary RCC, tumor size of first primary RCC, tumor TNM stage [or stage groups], time-to-SPM, types of SPM, and treatment of RCC and SPM).

† Invasion of SPM and AJCC TNM stage groups were separately included in the multivariate Cox proportional risk regression with other covariables.

¶ AJCC T, N, M were together included in the Cox proportional risk regression.

Discussion
The three significant guidelines for the surveillance of RCC patients following surgery (National Comprehensive Cancer Network [NCCN], European Association of Urology [EAU], and American Urological Association [AUA]) differ in terms of their recommendations for imaging modalities and frequencies [12]. Although there is no consensus with regards to an optimal surveillance strategy for patients after RCC treatment, it is often recommended that patients are followed-up closely for 3–5 years after surgery since relapse is most commonly seen within the first 5 years of surgery. Another common recommendation is to select different examination modalities based on individual risk stratification. The number of follow-up assessments can be reduced after the first 3 years but should continue for at least 5 years [13, 14]. In our study, it suggested that it’s important that long-term follow-up should not be stopped; rather, the surveillance modality and frequency should be adjusted based on individual risk.
Interestingly, the contralateral kidney showed the highest SIR (54.6) and accounted for the largest proportion of SPM cases (11.8%) in survivors of primary RCC. This indicates that it is crucial to perform lifelong follow-up assessments for RCC survivors, and that we pay particular attention to contralateral kidney carcinoma. Furthermore, it is important to routinely screen general patients or RCC survivors for malignancies associated with the prostate, breast, lung, bladder, colon/rectum, and thyroid [1]; these types of tumors accounted for most of the SPM cases seen in our current study. Although our results indicated that the early occurrence of SPM can exert impact on the OS, it was evident that survival can be prolonged if new cases of SPM are detected and treated early. Moreover, we found that if SPM cases were detected later, or involved a higher stage of solid SPM, then curative surgical treatment would be difficult and threaten long-term OS. The early detection of a small local SPM in the contralateral kidney would benefit from PN, particularly in patients who experienced RN for their primary RCC. Conversely, considering the risk of contralateral kidney cancer following surgery for primary RCC, it is recommended that we perform PN for the first kidney surgery in order to retain renal function, even if a contralateral SPM occurs. The early detection of a local small RCC is critical and could benefit from PN, and this technique may protect the normal renal parenchyma [15–18].

With regards to the design of individual surveillance plans, the selection of patients at risk could help to balance follow-up benefits and save costs, thus allowing the close monitoring of high-risk patients while reducing the over-medical treatment of low-risk patients. In the present study, we identified a series of independent high-risk predictors for the occurrence of SPM: increased age at the primary RCC diagnosis, black race, male gender, patients with high family income, papillary types of cancer, small tumors, the absence of lymph node invasion, a lower T stage, and a lower AJCC TNM stage. Our results further suggest that although some patients, such as those with a low TNM stage of RCC, may represent a low-risk group for recurrence after RCC [19], further follow-up is still necessary because this group is at high risk of developing SPM. Furthermore, the emergence of SPM is related to gender and the pathological type of RCC, thus indicating that SPM may be related to certain genes or other exposure environmental. Interestingly, SPM is known to be related to economic factors, and may be more prevalent in patients with a certain financial status; some patients may pay more attention to their follow-up and general health status and also have the financial means to afford the costs associated with follow-up.

Age is an independent risk factor for the occurrence of SPM. Interestingly, when predicting non-RCC SPM, the risk of SPM increases with age. However, when considering contralateral kidney tumors, it is evident that the elderly patients do not have an increased risk. Our univariate analysis found that the risk of patients over 60 years-of-age was lower for contralateral kidney SPM than that of patients under 44 years-of-age; this was consistent with previous literature [20, 21]. Age itself is an independent risk factor for cancer [22], and because the risk of developing tumors increases with age. As long as patients survive long enough, they are likely to develop more than two types of malignant tumors in their lives. It has been reported that 33% of cancer survivors over the age of 60 will be diagnosed with another type of cancer [23]. For some patients, RCC is only one of the earliest malignant tumors that could develop; however, with improvements in the prognosis and survival of RCC patients, it is now possible to detect SPM during the follow-up period. In elderly patients with RCC as their first cancer, SPM may be recorded shortly after RCC diagnosis. In contrast, younger patients may need a longer follow-up time for SPM to be detected, perhaps because the follow-up time required is relatively longer (in other words, the patients need to reach a certain age for successful detection). It is therefore possible that SPM was not detected by the end of the follow-up period in this study, or that the occurrence of a variety of competitive events prevented the occurrence of SPM.

The increased risk of secondary SPM in RCC patients still needs further verification and in-depth research in order to identify the precise connection between these two conditions. Possible mechanisms include renal insufficiency, and even renal failure after RCC, thus leading to long-term metabolic disorders and an increased risk of cancer in patients surviving from RCC. Furthermore, RCC patients may have experienced frequent episodes of computer tomography to monitor the disease, thus causing increased levels of exposure to radiation, or changes in the complex immune microenvironment. The biological characteristics of RCC confer all patients with kidney cancer with a higher risk of SPM. Renal cell carcinoma is also related to smoking [24]; however, smoking does not just affect the kidney. There may be a higher risk of cancer in patients with RCC who did not give up smoking after treatment, or in patients who smoked frequently over a long period prior to RCC diagnosis. However, these are hypotheses that have yet to be confirmed.

Furthermore, we analyzed the survival function for patients with SPM. We found that the occurrence of SPM, and an early time interval to SPM, could significantly shorten the OS when compared with patients who did not have SPM. However, the same site of SPM was not significantly associated with outcomes; for example, SPM of thyroid cancer, ipsilateral RCC, and prostate cancer, all showed an excellent 5-year OS after the diagnosis of SPM was made. After adjusting for other risk factors, we also found that SPM of contralateral RCC, cecum/small intestine, female breast, thyroid, and prostate cancer, had a similar or significantly better OS when compared with ipsilateral RCC. A worse OS was associated with SPM of the brain, liver, gallbladder/bile duct, lungs/bronchi, pancreas, and esophagus/stomach; furthermore, these sites of SPM also had a higher SIR compared with the general population. Another interesting finding was that the stage of SPM was also significantly associated with OS following the diagnosis of SPM; an SPM of a local disease had a better OS than regional and distant SPM. In addition, patients with SPM also could benefit from surgical treatment. These results clearly suggested that SPM can influence the OS. However, early detection and surgical intervention for solid SPM tumors is of great significance and can influence outcomes; this emphasizes the need to establish lifelong follow-up strategies rather than performing surveillance over the short-term.

This study had same limitations that need to be considered. First, all analyses were carried out using a registry-based dataset with inherent limitations. For example, we did not have access to any detailed clinical information such as patient comorbidities or a poor performance that lead to mortality within a period of follow-up time. This represents a vital competing risk for the occurrence of SPM and could not be adjusted in our multivariate analysis for SPM prediction. In addition, when analyzing the prediction of SPM for ipsilateral and contralateral kidney cancer, we had no access to information relating to hereditary RCC, such as von Hippel Lindau (VHL), hereditary papillary renal carcinoma, Birt Hogg Dube´ syndrome, and hereditary leiomyomatosis RCC [25]; these factors have all been identified previously as significant predictors for the metachronous de novo development of RCC over a long-term follow-up period. We did not have access to information relating to environment exposure, lifestyle, family history, and genetic mutation, all of which are known to act as risk factors for SPM. Second, patients with primary RCC or other diseases would generally pay more attention to routine cancer screening or surveillance than the general population, thus increasing the chances of identifying the occurrence of SPM in RCC survivors. Therefore, it is possible that surveillance
bias may exist in our study. Third, after the first primary diagnosis of RCC, it is possible that the preexisting or concomitant malignancy, metastasis diseases, or relapse in the patients with RCC, may have confounded the subsequent detection of SPM. To control for confounding factors, we only included patients with SPM that had been diagnosed at least 6 months after the first primary RCC diagnosis as our study cohort. When using the SEER dataset, we maintained quality assurance by performing systematic and standardized data collection procedures. Finally, due to a lack of information relating to local recurrence, we included patients with ipsilateral kidney cancer; these cases may have just been recurrences rather than SPM. However, more than 90% of ipsilateral kidney tumors were diagnosed more than 3 years after RCC diagnosis; 50% were diagnosed after more than 5 years. Furthermore, 35.6% of patients with RCC showed histological changes between the first and second occurrence of ipsilateral kidney cancer.

**Conclusion**

Our analyses demonstrated a higher incidence of SPM among RCC patients surviving over the long-term when compared with the general population. We also found that age at the diagnosis of first primary RCC, race, gender, economic status, histological type of RCC, and tumor stage, were all significantly associated with the occurrence of SPM. Tumor stage and the site of SPM showed particularly strong associations with OS. Lifetime follow-up and cancer screening is therefore recommended for RCC survivors. Although the occurrence of SPM can threaten long-term survival, patients with low grade/early-stage SPM could benefit from aggressive surgical treatment for solid tumors. According to the patient age, and the time interval after RCC diagnosis, it is also worthwhile monitoring high-risk RCC patients by site- and time-specific surveillance strategies; however, needs of balancing cost-effectiveness and Lifelong surveillance.

**Abbreviations**

SPM: Second primary malignancy; RCC: Renal cell carcinoma; SIR: standardized incidence ratio; ICD-0-3: The International Classification of Diseases for Oncology, 3rd Edition; AJCC: American Joint Committee on Cancer; TNM: tumor node metastasis; SD: standard deviations; IQR: interquartile range; CI: Confidence interval; HR: Hazard ratios; OS: Overall survival; SEER: Surveillance, Epidemiology, and End Results; NCCN: National Comprehensive Cancer Network; EAU: European Association of Urology; AUA: American Urological Association.

**Declarations**

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**Authors' contributions**

ZXW had full access to all of the data in the study, and ZWX and XYZ took responsibility for the integrity of the data and the accuracy of the data analysis. ZWX and XYZ designed the study. ZWX, JW and YPZ conducted the analysis and interpreted the data. ZWX and JW drafted the manuscript. XYZ had guarantor. All authors critically revised the manuscript. All authors read and approved the final manuscript.

**Availability of data and materials**

All the data of this study are derived from the Surveillance, Epidemiology, and End Results database (https://seer.cancer.gov/), which is a publicly available database. All detailed data included in the study are available upon request by contact with the first author (ZXW, SEER Username: 10026-Nov2019).

**Ethics approval and consent to participate**

Not applicable. SEER data are anonymized and nonhuman subject research. Therefore, the need for institutional review board approval was waived.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no conflict of interest.

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