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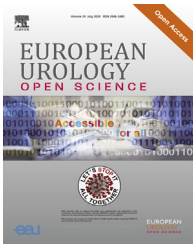

European Association of Urology

Kidney Cancer

# Second Primary Cancers After Kidney Cancers, and Kidney Cancers as Second Primary Cancers

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**Abstract**

***Background:*** Second primary cancers (SPCs) are increasing due to improving survival in first primary cancers. Previous studies on SPCs in renal cell carcinoma (RCC) have focused on treatment and other risk factors, but data of RCC as an SPC are scarce.

***Objective:*** In this study, we want to elucidate the risk for any SPC after RCC, and in reverse order, for RCC as an SPC after any cancer. We additionally consider how family histories influence the risks.

***Design, setting, and participants:*** Patient data were obtained from the Swedish Cancer Registry from years 1990 through 2015, and family data were obtained from the Multigeneration Register.

***Outcome measurements and statistical analysis:*** We employed standardized incidence ratios to estimate bidirectional relative risks of subsequent cancer associated with RCC.

***Results and limitations:*** We identified 17 587 RCCs (60% in male patients). The highest increases for SPCs were observed for nervous system hemangioblastoma (HB; 26.8), adrenal (12.09) tumors, and renal pelvic cancer (6.32). In the reverse order, RCC as an SPC, nervous system HB (17.01), and adrenal tumors (15.34) were associated with the highest risks. Risks for many other sites (12 sites and subsites) were increased bidirectionally. For women, a total of seven sites and subsites were increased bidirectionally, and many were shared with men. The only significant sex

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difference in SPCs was the higher lung cancer risk in women (2.41) than in men (1.28). Patients with a family history of HBs or of prostate, colorectal and lung cancers showed high risks of these cancers as SPCs after RCC. Family history accounted for 30% of prostate cancers after RCC.

***Conclusions:*** The bidirectional study design was able to suggest risk factors for SPCs and offered a clinical take-home message urging to consider strategies for early detection and prevention of SPCs. Readily available information on lifestyle (eg, smoking) and family history (eg, prostate cancer) may reveal targets for risk reduction with prognostic benefits.

***Patient summary:*** Close to 10% of kidney cancer patients develop another cancer. The cause for these other cancers may not depend on kidney cancer.



## 1. Introduction

Renal cell carcinoma (RCC; kidney cancer) is characterized by a male predominance, with men having a two- to four-fold higher risk than women. The incidence trend of RCC in Sweden reached a maximum in around 1990, which for men was about 10/100 000 and for women 5/100 000; after a decline, the incidence has increased again, after the year 2000, to the earlier peak level (http://www-dep.iarc.fr/NORDCAN/english/frame.asp). Early detection and improvements in treatment have contributed to positive trends in RCC survival [1]. Novel imaging technologies have resulted in frequent incidental detection of tumors that tend to be smaller than symptomatic tumors [1]. Standard treatment for RCC is surgery, and, during the past decade, antiangiogenic drugs have been introduced for metastatic cancer [1]. Improving survival implies that the likelihood of second primary cancers (SPCs) is increasing [2,3]. Survivors of RCC have an elevated risk of many SPCs, including bladder, prostate, colorectal, lung, and nervous system cancers; melanoma; and non-Hodgkin lymphoma (NHL) [4–6]. In a Korean study, excess risks of female breast cancer, thyroid cancer, and soft tissue tumors were additionally reported [7]. In our previous study, we showed that a family history of RCC influenced the risk of some SPCs, most notably that of nervous system hemangioblastoma (HB), a pathognomonic tumor for von Hippel-Lindau syndrome [8,9].

Plausible etiologies for SPCs are many, but probably the most important ones are intensive medical surveillance (surveillance bias) after the diagnosis of the first primary cancer (FPC), therapy for FPC, shared genetic or nongenetic risk factors between FPC and SPC, and immune dysfunction elicited by FPC, or interactions between these [10–12]. As data on the possible risk factors for SPCs are usually limited, we have devised a bidirectional analysis as a tool to help interpret the findings [11,13,14]. The objectives of the present study are to quantify and understand the risks for SPCs after RCC and the risks for RCC as an SPC after any FPC. This bidirectional analysis will help distinguish, at least to some extent, the influence of treatment and medical surveillance on the risk, because two different cancers are usually treated and diagnosed in different ways. As the previous literature has focused on SPCs after RCC, we hypothesized that the bidirectional analysis will be able to produce a novel association with interpretable mechanisms. We repeated the analyses for individuals who have a family history of RCC in order to unravel possible genetic mechanisms.

## 2. Patients and methods

This study was conducted with linkage to several Swedish national registers, including the Swedish Cancer Registry, the Multigeneration Register, the Cause of Death Register, and the Total Population Register. All incident tumors were registered in the Swedish Cancer Registry since 1958, with >90% coverage [15]. The Multigeneration Register recorded all the offspring born after 1931 with their biological parents. Place of residence and socioeconomic factors were retrieved from the Total Population Register. We considered RCCs found in the Swedish Cancer Registry using ICD-7 code 1800 or RCC codes in later ICD versions; all cases with these codes were included, irrespective of their histological confirmation. The renal pelvis included the calyces and the ureter. Other cancers include any of 21 common male and 22 female primary cancers, and for some cancers, histological subtypes were included. Excluded were cancers for which 1-yr survival was <50% (esophagus and pancreas). Cancer patients diagnosed after 1990 were included and followed for SPCs from the diagnosis of FPC until the end of 2015 or immigration or death, whichever occurred first. In analyses considering a family history, all the cancer patients registered in the Swedish Cancer Registry since 1958 with parental information in the Multigeneration Register were included, in order to boost statistical power. Only discordant (different) FPC-SPC pairs were included as concordant RCC had been investigated in previous studies, including ours [13]. Upper aerodigestive tract included the lips, oral cavity, pharynx, and larynx. For skin cancer, only squamous cell carcinoma was included. Among thyroid cancers, a specific code was applied for medullary thyroid cancer, but because only one male and one female patient were found among those with SPCs, no data were shown. In case of adrenal tumors, a specific code was used for pheochromocytoma, but no cases were found. In some analyses, family histories among first-degree relatives (parents or siblings) were considered.

Standardized incidence ratios (SIRs) were used to describe the risk of SPCs after RCC or risk of RCC as an SPC. Using the risk of SPCs as an example for the calculation of SIR, the observed number of SPC diagnoses after RCC was divided by the expected number of SPCs. The expected

number was obtained from the incidence of SPCs as first primary in the general population considering person-years at risk. The estimation was done separately for men and women, and adjusted for age (5-yr group), calendar year (5-yr group), place of residence (big cities, northern Sweden, southern Sweden, and unspecific), and socioeconomic factors (blue-collar workers, white-collar workers, farmers, private business owners, professionals, or other/unspecified). The risks were further stratified by the time after FPC diagnosis (1, 2–5, and >5 yr). Stratification of family history for the risk of a specific SPC (eg, breast cancer) was based on the concordant cancer (breast cancer) diagnosis in first-degree relatives (parents and/or siblings). However, for this analysis, genders were combined due to the limited number of cases. We used Poisson assumption while calculating the 95% confidence interval (95% CI).The statistical tests were two tailed, and $p < 0.05$ was regarded as significant. All the analyses were performed in SAS 9.4.

The study was approved by the by the Regional Ethical Review Board in Lund.

## 3. Results

During the follow-up period of 1990–2015, we identified 17 587 RCCs, with 60.0% in male patients having a median diagnostic age of 68 (interquartile range, 59–75) yr. The number of SPCs considered in the analysis was 1654. The total number of other cancers considered was 1 066 203.

SIRs for male SPCs are shown in Table 1. The overall risk for SPCs after RCC cancer was 1.28; the highest significant increases were observed for nervous system HB (26.8), renal pelvic cancer (6.32), and adrenal (12.09) and parathyroid (3.33) tumors, all of which were rare SPCs. Common SPCs, such as prostate, bladder, and lung cancers, were modestly increased, mostly for bladder (1.45) cancer. In the reversed order, RCC as an SPC, the overall SIR was increased to 1.61. Nervous system HB (17.01) and adrenal tumors (15.34) were associated with the highest risks also as FPCs. Risks for many other sites (12 sites and subsites) were increased bidirectionally, while some associations were significant only for cancers as FPCs, notably colorectal (2.15), testicular (3.61), ureter (6.47), and thyroid (5.14) cancers as well as hematological malignancies.

A similar analysis for female cancer is shown in Table 2. The overall risk for SPCs after RCC was 1.33, with case numbers barely over half of the male numbers. Only one patient presented with nervous system HB. Adrenal tumors (11.29) and renal pelvic cancer (3.94) showed the highest risks as SPCs. Notably, the risk for second lung cancer was significantly higher (with nonoverlapping CIs) for women (2.06) than for men (1.28); even second colorectal and bladder cancer risks were higher for women than for men (overlapping CIs). In the reversed order, for RCC as an SPC, the overall SIR was 1.69. Common cancers, such as colorectal, lung, and bladder cancers, showed an increased bidirectional association with second RCC; in

**Table 1 – Male risks of SPCs after renal cell carcinoma and this cancer as an SPC**

| Cancer site | SPC after renal cell carcinoma | | | | Renal cell carcinoma as SPC | | | |
|---|---|---|---|---|---|---|---|---|
| | *N* | SIR | 95% CI | | *N* | SIR | 95% CI | |
| Upper aerodigestive tract | 23 | 1.03 | 0.65 | 1.55 | 27 | 1.23 | 0.81 | 1.8 |
| Stomach | 23 | 0.97 | 0.61 | 1.45 | 19 | 1.33 | 0.8 | 2.07 |
| Small intestine | 9 | **2.23** | 1.01 | 4.26 | 11 | **3.37** | 1.67 | 6.05 |
| Carcinoid | 4 | 2.11 | 0.55 | 5.45 | 6 | **3.09** | 1.11 | 6.78 |
| Adenocarcinoma | 4 | 2.94 | 0.76 | 7.6 | 2 | 2.45 | 0.23 | 9.02 |
| Colorectum | 126 | 1.13 | 0.94 | 1.35 | 205 | **2.15** | 1.87 | 2.47 |
| Liver | 30 | **1.56** | 1.05 | 2.23 | 19 | **2.46** | 1.48 | 3.85 |
| Lung | 97 | **1.28** | 1.04 | 1.56 | 46 | 1.35 | 0.99 | 1.8 |
| Breast | 4 | 2.87 | 0.75 | 7.42 | 4 | 2.93 | 0.76 | 7.59 |
| Prostate | 413 | **1.13** | 1.03 | 1.25 | 519 | **1.27** | 1.16 | 1.39 |
| Testis | 3 | 2.26 | 0.43 | 6.68 | 17 | **3.61** | 2.1 | 5.8 |
| Male genital | 1 | 0.33 | 0 | 1.89 | 1 | 0.33 | 0 | 1.87 |
| Renal pelvis | 8 | **6.32** | 2.7 | 12.52 | 5 | 2.65 | 0.83 | 6.22 |
| Bladder | 100 | **1.45** | 1.18 | 1.76 | 149 | **2.28** | 1.93 | 2.67 |
| Melanoma | 46 | **1.39** | 1.01 | 1.85 | 57 | **1.55** | 1.17 | 2.01 |
| Skin | 80 | 1.2 | 0.95 | 1.49 | 53 | **1.34** | 1.01 | 1.76 |
| Nervous system | 29 | **2.01** | 1.35 | 2.89 | 30 | **2.09** | 1.41 | 2.98 |
| Hemangioblastoma | 4 | **26.8** | 6.98 | 69.34 | 5 | **17.01** | 5.37 | 40 |
| Others | 25 | **1.75** | 1.13 | 2.59 | 25 | **1.77** | 1.15 | 2.62 |
| Thyroid | 4 | 1.65 | 0.43 | 4.26 | 15 | **5.14** | 2.87 | 8.49 |
| Endocrine | 23 | **3.52** | 2.23 | 5.29 | 32 | **3.06** | 2.09 | 4.32 |
| Adrenal gland | 7 | **12.09** | 4.79 | 25.06 | 12 | **15.34** | 7.89 | 26.89 |
| Parathyroid gland | 9 | **3.33** | 1.51 | 6.36 | 13 | **2.69** | 1.43 | 4.62 |
| Pituitary gland | 3 | 1.25 | 0.24 | 3.71 | 4 | 1.02 | 0.27 | 2.64 |
| Connective tissue | 6 | 1.25 | 0.45 | 2.73 | 7 | 1.54 | 0.61 | 3.19 |
| NHL | 34 | 1.15 | 0.8 | 1.62 | 60 | **2.35** | 1.79 | 3.03 |
| Hodgkin lymphoma | 4 | 2.58 | 0.67 | 6.67 | 6 | **2.85** | 1.02 | 6.24 |
| Myeloma | 15 | 1.15 | 0.64 | 1.9 | 17 | 1.71 | 0.99 | 2.74 |
| Leukemia | 42 | **1.55** | 1.12 | 2.1 | 35 | **1.62** | 1.13 | 2.25 |
| All | 1193 | **1.28** | 1.21 | 1.35 | 1378 | **1.61** | 1.52 | 1.69 |

CI = confidence interval; *N* = observed number of cases; NHL = non-Hodgkin lymphoma; SIR = standardized incidence ratio; SPC = second primary cancer.
Bold type: 95% CI does not include 1.00.

**Table 2 – Female risks of SPCs after renal cell carcinoma and this cancer as an SPC**

| Cancer site | SPC after renal cell carcinoma | | | | Renal cell carcinoma as SPC | | | |
|---|---|---|---|---|---|---|---|---|
| | *N* | SIR | 95% CI | | *N* | SIR | 95% CI | |
| Upper aerodigestive tract | 13 | 1.71 | 0.91 | 2.94 | 12 | 1.89 | 0.97 | 3.31 |
| Stomach | 10 | 0.96 | 0.46 | 1.77 | 13 | **2.39** | 1.27 | 4.09 |
| Small intestine | 4 | 1.66 | 0.43 | 4.3 | 3 | 1.63 | 0.31 | 4.83 |
| Carcinoid | 0 | | | | 2 | 1.85 | 0.17 | 6.82 |
| Adenocarcinoma | 0 | | | | 1 | 1.93 | 0 | 11.07 |
| Colorectum | 95 | **1.39** | 1.12 | 1.7 | 98 | **1.84** | 1.49 | 2.24 |
| Liver | 14 | 1.05 | 0.57 | 1.77 | 13 | **2.68** | 1.42 | 4.6 |
| Lung | 77 | **2.06** | 1.62 | 2.57 | 37 | **2.41** | 1.69 | 3.32 |
| Breast | 139 | 1.15 | 0.97 | 1.36 | 228 | **1.4** | 1.22 | 1.59 |
| Cervix | 6 | 0.99 | 0.35 | 2.16 | 12 | 1.49 | 0.76 | 2.61 |
| Endometrium | 30 | 0.95 | 0.64 | 1.35 | 59 | **1.47** | 1.12 | 1.89 |
| Ovary | 16 | 0.97 | 0.55 | 1.57 | 22 | 1.35 | 0.85 | 2.05 |
| Female genital | 2 | 0.39 | 0.04 | 1.43 | 7 | 1.81 | 0.72 | 3.76 |
| Renal pelvis | 10 | **3.94** | 1.88 | 7.28 | 1 | 1.17 | 0 | 6.72 |
| Bladder | 33 | **2.21** | 1.52 | 3.11 | 29 | **2.3** | 1.54 | 3.31 |
| Melanoma | 26 | 1.45 | 0.95 | 2.13 | 30 | 1.4 | 0.94 | 1.99 |
| Skin | 25 | 0.74 | 0.48 | 1.1 | 20 | 1.05 | 0.64 | 1.62 |
| Nervous system | 28 | **2.48** | 1.64 | 3.58 | 26 | **1.93** | 1.26 | 2.84 |
| Hemangioblastoma | 1 | 18.8 | 0.01 | 107.5 | 3 | **24.9** | 4.7 | 73.76 |
| Others | 27 | **2.4** | 1.58 | 3.49 | 23 | **1.73** | 1.09 | 2.59 |
| Thyroid | 8 | **2.42** | 1.04 | 4.8 | 11 | **2.5** | 1.24 | 4.48 |
| Endocrine | 20 | **2.16** | 1.32 | 3.34 | 30 | **1.93** | 1.3 | 2.75 |
| Adrenal gland | 5 | **11.29** | 3.56 | 26.55 | 4 | **6.37** | 1.66 | 16.47 |
| Parathyroid gland | 11 | 1.52 | 0.75 | 2.72 | 23 | **1.82** | 1.15 | 2.74 |
| Pituitary gland | 2 | 1.95 | 0.18 | 7.18 | 3 | 1.81 | 0.34 | 5.36 |
| Connective tissue | 2 | 0.79 | 0.07 | 2.92 | 5 | 2.26 | 0.71 | 5.31 |
| NHL | 17 | 1.02 | 0.59 | 1.64 | 40 | **2.88** | 2.06 | 3.93 |
| Hodgkin lymphoma | 1 | 1.18 | 0 | 6.77 | 0 | – | – | – |
| Myeloma | 8 | 1.11 | 0.48 | 2.21 | 12 | **2.42** | 1.24 | 4.23 |
| Leukemia | 19 | 1.31 | 0.79 | 2.06 | 25 | **2.38** | 1.54 | 3.52 |
| All | 661 | **1.33** | 1.23 | 1.43 | 775 | **1.69** | 1.57 | 1.81 |

CI = confidence interval; *N* = observed number of cases; NHL = non-Hodgkin lymphoma; SIR = standardized incidence ratio; SPC = second primary cancer.
Bold type: 95% CI does not include 1.00.

total, seven sites and subsites were increased bidirectionally. However, breast and endometrial cancers, and hematological neoplasms were significant only as FPCs, and for NHL the difference in SIRs was significant. Men and women shared bidirectional associations for bladder, nervous system, and endocrine cancers, and among the latter for adrenal tumors.

Comparing SIRs for men and women in more detail (Tables 1 and 2) for SPCs after RCC, small intestinal and liver cancers and leukemia were increased only among men, while colorectal and thyroid cancers were increased only among women. RCC as an SPC was increased only for men after small intestinal and skin cancers and Hodgkin lymphoma; in women, second RCC was increased after stomach and lung cancers and after myeloma. Melanoma risk was increased bidirectionally for men, but female results also reached a borderline significance.

The dependence of results on the follow-up time is shown in Supplementary Tables 1 and 2 for men and women, respectively. All the overall SIRs were increased, with the highest risks within 1 yr after FPC and the lowest risks during the follow-up period of 2–5 yr.

Table 3 shows results for SPCs when a family history of an SPC was considered. The results are for men and women combined. Familial events were rare, and they reached statistical significance only for colorectal, lung, and prostate cancers and for leukemia. The difference between familial and sporadic prostate cancer was significant, and notably the latter SIR was not significant; 30% of second prostate cancers were familial.

Table 4 shows risks for RCC as an SPC depending on stratification by family history of RCC. Familial second RCC was increased to 9.17 after lung, 2.36 after prostate, and 10.11 after nervous system cancers, but none of the SIRs differed significantly from the results for sporadic second RCC. The only significant difference was for HB (SIR 278); notably, following HB, three or four of second RCCs were familial.

We also analyzed the risk for SPCs after RCC depending on the family history of RCC; however, only 37 discordant SPCs were found. The SIR for HB was 558 (*N* = 3; 95% CI 105–1654) and that of myeloma was 10.06 (3; 1.90–29.77).

## 4. Discussion

In applying the bidirectional analysis, the results showed significantly lower risks for all cancers as SPCs (~1.3) than for RCC as an SPC after any cancer (~1.65), and the results agreed for men and women. One obvious explanation is the

**Table 3 – Risks of SPCs after renal cell carcinoma stratified by the family history of the concordant cancer**

| Cancer site | With family history | | | | Without family history | | | |
|---|---|---|---|---|---|---|---|---|
| | *N* | SIR | 95% CI | | *N* | SIR | 95% CI | |
| Upper aerodigestive tract | 1 | 3.8 | 0 | 21.78 | 16 | 1.4 | 0.8 | 2.27 |
| Stomach | | | | | 9 | 1.25 | 0.57 | 2.38 |
| Small intestine | | | | | 8 | **3.31** | 1.41 | 6.55 |
| Carcinoid | | | | | 3 | 2.77 | 0.52 | 8.19 |
| Adenocarcinoma | | | | | 2 | 2.46 | 0.23 | 9.05 |
| Colorectum | 14 | **2.62** | 1.43 | 4.41 | 74 | **1.48** | 1.16 | 1.85 |
| Liver | | | | | 15 | 1.65 | 0.92 | 2.73 |
| Lung | 10 | **3.74** | 1.78 | 6.9 | 59 | **1.6** | 1.22 | 2.07 |
| Breast | 10 | 1.71 | 0.81 | 3.15 | 47 | 1.04 | 0.76 | 1.39 |
| Cervix | | | | | 0 | | | |
| Endometrium | 1 | 4.34 | 0 | 24.89 | 12 | 1.06 | 0.54 | 1.85 |
| Ovary | 1 | 7.23 | 0 | 41.42 | 7 | 1.2 | 0.48 | 2.48 |
| Female genital | | | | | | | | |
| Prostate | 50 | **2.37** | 1.76 | 3.13 | 120 | 0.95 | 0.78 | 1.13 |
| Testis | | | | | 3 | 3.16 | 0.6 | 9.36 |
| Male genital | | | | | 1 | 0.85 | 0 | 4.86 |
| Renal pelvis | | | | | 4 | 3.14 | 0.82 | 8.13 |
| Bladder | 4 | 3.17 | 0.83 | 8.2 | 24 | **1.83** | 1.33 | 2.46 |
| Melanoma | 3 | 4.21 | 0.79 | 12.46 | 30 | 1.29 | 0.87 | 1.84 |
| Skin | 3 | 3.78 | 0.71 | 11.19 | 35 | 1.42 | 0.99 | 1.98 |
| Nervous system | | | | | 17 | 1.45 | 0.84 | 2.32 |
| Hemangioblastoma | | | | | 4 | **37.29** | 9.7 | 96.43 |
| Others | | | | | 13 | 1.1 | 0.58 | 1.88 |
| Thyroid | | | | | 5 | 2.21 | 0.7 | 5.19 |
| Endocrine | 1 | 8.23 | 0 | 47.18 | 18 | **2.78** | 1.64 | 4.4 |
| Adrenal gland | | | | | 4 | 8.99 | 2.34 | 23.24 |
| Parathyroid gland | | | | | 8 | 2.19 | 0.94 | 4.34 |
| Pituitary gland | | | | | 2 | 1.17 | 0.11 | 4.3 |
| Connective tissue | | | | | 3 | 1.24 | 0.23 | 3.67 |
| NHL | 1 | 2.28 | 0 | 13.09 | 17 | 1.11 | 0.65 | 1.79 |
| Hodgkin lymphoma | 1 | 355.71 | 0.14 | 2038.96 | 4 | **4.04** | 1.05 | 10.45 |
| Myeloma | | | | | 9 | 1.41 | 0.64 | 2.69 |
| Leukemia | 3 | **7.94** | 1.5 | 23.51 | 22 | 1.58 | 0.99 | 2.39 |
| Any cancer except RCC | 503 | **1.51** | 1.38 | 1.65 | 238 | **1.25** | 1.10 | 1.42 |

CI = confidence interval; *N* = observed number of cases; NHL = non-Hodgkin lymphoma; RCC = renal cell carcinoma; SIR = standardized incidence ratio; SPC = second primary cancer.
Bold type: 95% CI does not include 1.00.

predominantly surgical treatment for RCC, while, for example, many hematological testicular neoplasms are treated with aggressive chemotherapy; RCC risk was increased 2.5-fold after lymphoma and 3.6-fold after testicular cancer. Treatment-related explanations may be partially valid also for colorectal and bladder cancers, but probably with additional contribution by skewed surveillance. In the analysis of SPCs by follow-up time, most cases of RCCs as SPCs were diagnosed within a year after first colorectal and bladder cancers, while second colorectal and bladder cancers after RCCs were diagnosed more evenly over the follow-up time. A number of other SPCs showed different follow-up patterns. An SPC of the renal pelvis was more common than RCC after first pelvic cancer, probably because of kidney-sparing surgeries and the direction of urinary flow, which is thought to play a role in recurring urothelial cancers [16,17]. In lung cancer, there was no large difference in the two bidirectional analysis, as tobacco smoking is a risk factor of lung cancer as well as of RCC [18]. Similarly, for nervous system and endocrine tumors, bidirectional results agreed largely, which will be discussed later.

In the overall analysis, we carried out four comparisons (bidirectional SPCs and both sexes) for the associations of RCC as FPC and SPC. Bladder, nervous system, and endocrine (including adrenal tumors) cancers displayed four positive associations; colorectal, lung, and thyroid cancers and leukemia had three positive associations; and small intestinal, liver, renal pelvic, and prostate cancers, and melanoma and NHL had two positive associations. As the case numbers of many associations were small, even two significant associations give credibility to the findings. Surveillance bias may be critical at sites of anatomic proximity, and it may further be suspected if a large proportion of cases and all significant associations are found in the 1st year of follow-up. Prostate, bladder, and colorectal cancers might have been influenced by surveillance bias, as pointed out above. Notably, 30% of patients with prostate cancer as an SPC were men with a family history of prostate cancer, and the risk disappeared in men without a family history.

While many SPCs were consistently increased for men and women (the overall SIRs for all cancers differed only by a few decimal points), there were however differences,

**Table 4 – Risks of renal cell carcinoma as an SPC stratified by the family history of renal cell carcinoma**

| Cancer site | With family history | | | | Without family history | | | |
|---|---|---|---|---|---|---|---|---|
| | *N* | SIR | 95% CI | | *N* | SIR | 95% CI | |
| Upper aerodigestive tract | 2 | 6.52 | 0.61 | 23.96 | 19 | **1.67** | 1.01 | 2.62 |
| Stomach | | | | | 12 | **2.85** | 1.47 | 5 |
| Small intestine | 1 | 16.14 | 0.01 | 92.54 | 5 | 2.48 | 0.78 | 5.84 |
| Carcinoid | | | | | 2 | 1.71 | 0.16 | 6.28 |
| Adenocarcinoma | | | | | 3 | **6.21** | 1.17 | 18.38 |
| Colorectum | 3 | 2.36 | 0.45 | 6.99 | 100 | **2.16** | 1.76 | 2.63 |
| Liver | | | | | 9 | **2.68** | 1.21 | 5.11 |
| Lung | 4 | **9.17** | 2.39 | 23.71 | 29 | **1.85** | 1.24 | 2.66 |
| Breast | 5 | 2.48 | 0.78 | 5.85 | 110 | **1.43** | 1.17 | 1.72 |
| Cervix | | | | | 6 | 1.51 | 0.55 | 3.32 |
| Endometrium | | | | | 19 | 1.2 | 0.72 | 1.88 |
| Ovary | 1 | 5.89 | 0 | 33.77 | 10 | 1.47 | 0.7 | 2.71 |
| Female genital | 1 | 24.02 | 0.01 | 137.66 | 2 | 1.67 | 0.16 | 6.14 |
| Prostate | 10 | **2.36** | 1.12 | 4.35 | 220 | **1.43** | 1.24 | 1.63 |
| Testis | | | | | 13 | **3.47** | 1.84 | 5.96 |
| Male genital | | | | | 1 | 0.76 | 0 | 4.34 |
| Renal pelvis | 1 | 38.49 | 0.02 | 220.62 | 3 | 3.49 | 0.66 | 10.33 |
| Bladder | 3 | 3.84 | 0.72 | 11.36 | 24 | **2.46** | 1.87 | 3.18 |
| Ureter | 1 | 114.66 | 0.05 | 657.23 | 2 | 6.57 | 0.62 | 24.16 |
| Melanoma | 2 | 2.48 | 0.23 | 9.13 | 43 | **1.41** | 1.02 | 1.9 |
| Skin | 1 | 2.27 | 0 | 13.01 | 26 | 1.51 | 0.99 | 2.22 |
| Nervous system | 4 | **10.11** | 2.63 | 26.14 | 28 | **1.99** | 1.32 | 2.87 |
| Hemangioblastoma | 3 | **2781.6** | 524.4 | 8233.8 | 5 | **20.36** | 6.43 | 47.9 |
| Others | 1 | 2.53 | 0.001 | 14.53 | 23 | **1.66** | 1.05 | 2.5 |
| Thyroid | 0 | | | | 11 | **3.21** | 1.6 | 5.77 |
| Endocrine | 1 | 3.16 | 0 | 18.1 | 21 | **1.94** | 1.2 | 2.97 |
| Adrenal gland | | | | | 3 | 3.99 | 0.75 | 11.82 |
| Parathyroid gland | 1 | 4.91 | 0 | 28.17 | 13 | **2.04** | 1.08 | 3.5 |
| Pituitary gland | | | | | 4 | 1.36 | 0.35 | 3.52 |
| Connective tissue | | | | | 5 | 1.82 | 0.57 | 4.27 |
| NHL | 1 | 2.66 | 0 | 15.27 | 36 | **2.32** | 1.62 | 3.21 |
| Hodgkin lymphoma | | | | | 4 | 2.44 | 0.63 | 6.3 |
| Myeloma | | | | | 9 | 1.84 | 0.83 | 3.51 |
| Leukemia | 2 | 5.36 | 0.51 | 19.71 | 24 | **1.97** | 1.26 | 2.94 |
| Any cancer except RCC | 45 | 3.28 | 2.39 | 4.39 | 852 | **1.70** | 1.59 | 1.82 |

CI = confidence interval; *N* = observed number of cases; NHL = non-Hodgkin lymphoma; RCC = renal cell carcinoma; SIR = standardized incidence ratio; SPC = second primary cancer.
Bold type: 95% CI does not include 1.00.

most notably significantly higher lung cancer risk for women than for men; the SIR for women was 2.41, which reminds of smoking control. The bidirectional associations for male small intestinal cancer were higher than the female associations, whereas for lung cancer, female associations exceed the male ones.

In analyses with familial cancers, a family history of cancer X increased the risk of X being an SPC, but with the exception of prostate, colorectal, and lung cancers for which the case numbers were few; yet for these three cancers, risks were substantial, warranting an inquiry about a family history in a clinical setting. A previous study on the interaction of familial risk and SPCs found a multiplicative interaction between RCC and endocrine gland, nervous system, and urinary bladder cancers [5]. In the bidirectional analyses, the contribution of von Hippel-Lindau syndrome emerged as a likely explanation, and for nervous system HB, it was reinforced in the analysis of familial patients. Nervous system HB is considered the prototypic lesion of von Hippel-Lindau syndrome, it has male predilection, and it is the main cause of death from the syndrome [8]. The findings on high risk of bidirectional adrenal tumors supported the von Hippel-Lindau etiology, although classification of tumors as pheochromocytomas was not confirmed. Using SNOMED codes for the 12 male and female second adrenal tumors, only one was malignant pheochromocytoma, seven were found as adenomas, one was undifferentiated, and three were missing (coding system started in 1993). Pheochromocytomas are usually benign and were not included in the present analysis. A curious SPC association, three myelomas diagnosed as SPCs in familial RCC patients, appeared fortuitous although the SIR was as high as 10, particularly as the association myeloma in von Hippel-Lindau syndrome is not described in the expert literature [8]. Nevertheless, it has been suggested earlier that proangiogenic stress response caused by hypoxia-inducible factor 1α, encoded by the von Hippel-Lindau gene, promotes myeloma progression [19].

Other associations with probably genetic contribution included melanoma and thyroid cancer. Melanoma associ-

ation with RCC was for men and of borderline for women. Germline mutations in the *BAP1* gene predispose to melanoma and RCC, and can be a common denominator of the present associations [20,21]. The consistent associations with thyroid cancer is also likely to be due to a familial predisposition, even though the underlying genes cannot be pointed out [22].

A US study on SPCs after kidney cancer, based on the Surveillance Epidemiology and End Results (SEER) database, reported the highest case numbers for second prostate, lung, and digestive tract cancer, which we could confirm here [23]. Using the same database, high risks for contralateral RCC were reported, in line with an earlier Swedish study [22,24]. In our recent study, among immune-responsive cancers, kidney cancer was associated with many individual cancers as FPCs and SPCs [25]. In a recent Swiss study, second kidney cancer was increased after lung cancers, as also found here [26].

The major limitation, in spite of using nationwide coverage, is the scarcity of data, particularly on rare and familial cancers. We had no data on treatment or personal habits, such as smoking. We decided not to apply any lag time between diagnoses of FPCs and SPCs because, in the Swedish Cancer Registry practically, all cancers are histologically verified and thus are true cancers [27]. The application of a lag time would have caused a bias because a large number of true SPCs would have been missed. On the contrary, some benign cancers were probably included; these could have remained nonsymptomatic during the patient's lifetime. This study has the foremost strength of having access to a high-level cancer registry data in which even rare urothelial tumors are well recorded [28,29]. The bidirectional and sex-specific design is another strength in helping both interpret the associations and reduce chance findings. Complete coverage of Swedish families is also a unique strength.

## 5. Conclusions

In conclusion, we showed that many common cancers have an increased risk as SPCs after RCC and vice versa. While the bidirectional study design was able to suggest some surveillance, treatment, environmental, and genetic risk factors to explain the associations, the clinical take-home message is to consider strategies for early detection or prevention of SPCs. Readily available information on lifestyle (eg, smoking) and family history (eg, prostate cancer) may reveal targets for risk reduction. For the urological clinic, the high bidirectional risks of RCC with bladder cancer are of note. Risk of RCC was also high in cancers for which chemotherapy is the main treatment (hematological and testicular cancers). Many SPCs have unwanted influence on survival, and early detection of SPCs is likely to alleviate the harmful sequelae.

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*Other:* None.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.euros.2020.12.007.

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